Protocol Amendment I6T-MC-AMCB (a)

A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution Using a 1-mL Autoinjector and an Investigational 2-mL Autoinjector in Healthy Participants

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Title Page

Protocol Title:

A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution Using a 1-mL Autoinjector and an Investigational 2-mL Autoinjector in Healthy Participants

Protocol Number: I6T-MC-AMCB

Amendment Number: [a]

Compound: Mirikizumab (LY3074828)

Brief Title: A bioequivalence study of subcutaneous injections of citrate-free mirikizumab solution using a 1-mL autoinjector and an investigational 2-mL autoinjector in healthy participants

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285

Manufacturer: Eli Lilly and Company

Regulatory Agency Identifier Number: IND: 125444

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	21-March-2024

Amendment [a]

Overall rationale for the amendment

The rationale for the amendment is to increase the approximate number of participants that may be enrolled.

Section # and Name	Description of Change
1.1 Synopsis	The approximate number of participants that may be enrolled overall has increased from 440 to 484.
4.1 Overall Design	
9.5 Sample Size Determination	
8.2.6.1 Hepatic Safety Monitoring and Evaluation	It was clarified that the actions taken for abnormal hepatic laboratory or clinical changes were based on participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN).
10.6 Liver Safety: Suggested Actions and Follow-up Assessments	It was clarified that if a lab did not offer total antibody testing, IgG and/or IgM were acceptable substitutes.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Bioequivalence Study of Subcutaneous Injections of Citrate-Free Mirikizumab Solution Using a 1-mL Autoinjector and an Investigational 2-mL Autoinjector in Healthy Participants

Brief Title: A bioequivalence study of subcutaneous injections of citrate-free mirikizumab solution using a 1-mL autoinjector and an investigational 2-mL autoinjector in healthy participants

Regulatory Agency Identifier Number: IND: 125444

Rationale:

Study I6T-MC-AMCB (AMCB) will assess the pharmacokinetics (PK) and safety of a 200-mg dose of citrate-free mirikizumab (LY3074828) solution formulation administered via an autoinjector (AI) as 2 × 1-mL subcutaneous (SC) injections or a single 2-mL SC injection. The study will provide bioequivalence data on delivery of the citrate-free mirikizumab solution via the 2-mL AI planned to be used as the investigational AI device for subsequent studies and patient use. Both administrations will be evaluated at 3 different injection sites (arm, thigh, and abdomen).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2-mL AI (test) compared to using 2 × 1-mL AI (reference)	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2-mL AI (test) compared to using 2 × 1-mL AI (reference)	• TEAEs and SAEs

Abbreviations: AI = autoinjector; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Overall Design:

Study AMCB is a Phase 1, open-label, randomized, 2-arm, parallel-design, single-dose multi-center study of citrate-free mirikizumab administered via AI in healthy participants.

Brief Summary:

Screening

All participants will be screened within 35 days prior to Day 1.

Treatment and Assessment Period

Eligible participants will be admitted to the clinical research unit on Day -1. Participants will be stratified by 1 of 3 weight categories based on their weight assessment measured on Day -1:

- less than 75.0 kg
- 75.0 to 85.0 kg
- more than 85.0 kg

Participants will be stratified by weight category and randomized 1:1 to either 1 × 2-mL SC injection of 100 mg/mL citrate-free mirikizumab (test) or 2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab (reference) with a computer-generated allocation code using an interactive web-response system. Injection-site location, either arm, thigh, or abdomen, will be assigned in an approximately equal distribution within each study arm using an interactive web-response system.

Approximately 484 participants may be enrolled so that approximately 400 participants, 200 in each test and reference group, complete the study. Approximately 242 participants will be randomized to the test arm and approximately 242 participants will be randomized to the reference arm, with approximately 80 participants for each injection site in each study arm.

A minimum of approximately 80 participants overall in each weight category should complete the study.

On Day 1, participants will receive assigned study intervention. Participants may be allowed to leave the clinical research unit after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion, and will return for PK sampling and safety assessments at predefined times up to 10 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety will be assessed through clinical chemistry, hematology, and urinalysis testing, vital signs measurements, recording of adverse events and product complaints, and physical examination.

Study Population:

Participants will

- be overtly healthy individuals assigned male at birth or assigned female at birth who are individuals of childbearing potential or not of childbearing potential
- be between 18 and 65 years of age, inclusive, at the time of signing the informed consent and of an acceptable age to provide informed consent, and
- have a body mass index within the range of 18.0 to 34.0 kg/m^2, inclusive.

Participants may have chronic, stable medical conditions that, in the investigator's opinion, will not place the participant at increased risk by participating in the study.

Number of Participants:

Approximately 484 participants, approximately 242 participants in each treatment arm, may be enrolled so that approximately 400 participants, 200 in each test and reference group, complete the study.

Intervention Groups and Duration:

All participants will be screened 35 days prior to Day 1. Mirikizumab will be administered into the arm, abdomen, or thigh as either:

- 1 × 2-mL SC injection of 100 mg/mL citrate-free mirikizumab (test), or
- 2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab (reference).

Participants will be followed through to Day 71 ± 3 days. Total study duration is up to 109 days.

Ethical Considerations of Benefit/Risk:

Mirikizumab-related risks

As with other immunomodulatory therapies, mirikizumab may increase the risk of developing an infection or may exacerbate an existing infection. These may include opportunistic infections and reactivation of latent infections, such as tuberculosis and hepatitis B, although such infections have not been reported in healthy participant clinical trials administering mirikizumab to date. Therefore, participants testing positive for hepatitis B/C, human immunodeficiency virus, or tuberculosis at screening will not be permitted to participate in this study. Immunomodulatory therapies may increase the risk of malignancies; however, due to the single dose of mirikizumab being administered in this study, it is not considered necessary to monitor for such effects.

Immediate hypersensitivity reactions, defined as anaphylactic reaction and infusion-related hypersensitivity reaction, including urticaria, angioedema, and anaphylaxis, have rarely been reported with the administration of mirikizumab.

No other clinically significant safety or tolerability concerns have been identified to date in healthy participants exposed to mirikizumab up to the highest single doses given of 2400 mg intravenously or SC.

There is no anticipated therapeutic benefit for the participants in this trial. However, participants may benefit from the screening procedures, through detection of unknown health issues, even if they receive no therapeutic benefit from the trial.

AI-related risks

As this study will use AIs, device-related safety risks will be evaluated. Possible device-related safety risks include local effects such as pain at the injection sites from either the needle or the solution entry into the SC tissue, swelling, erythema, bleeding, and bruising. These risks are mitigated by training of investigative site staff on proper injection techniques.

Data Monitoring Committee: No.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

	Screening	Study Day																Comments
Procedure	-35 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	ED	
Informed consent	X																	
Medical history and demographics	X																	
Review and confirm I/E criteria	X	X																
Admission to CRU		X																
Discharge from CRU			X															Participants may be discharged after completing the 4h safety assessments on D1, or later at the investigator's discretion.
Outpatient visit	X			X	X	X	X	X	X	X		X		X		X	X	
Telephone call											X		X		X			To check on the presence of any AEs and CMs.
Randomization		X	P															Randomization can occur on D-1 or D1; participants will be randomized as described in Section 4.1.
Height, weight, and BMI	X	X														X	X	Only weight will be measured on D-1 and D71 or ED.
Body temperature	X	X	P	X	X	X	X	X	X	X		X		X		X	X	
Physical examination	X	X														X	X	Complete physical examination at either screening or D-1. Symptom-directed examinations and assessments at D71 or ED, and as deemed necessary by the investigator or designee.

	Screening	Study Day																Comments
Procedure	-35 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	ED	
Vital signs (pulse rate and blood pressure) (sitting) (hours)	X	X	P, 2 to 4					X				X				X	X	D1: 2h to 4h to be conducted at least 2h after the last injection and prior to discharge at approximately 4h postdose. Time points may be added if warranted and agreed upon between Lilly and the investigator.
Hematology, clinical chemistry, urinalysis	X	X	P	X				X		X						X	X	See Section 10.2.
Serology	X																	See Section 10.2.
QuantiFERON®-TB Gold test	X																	See Section 10.2.
Breath or urine ethanol test and urine drug screen	X	X																May be repeated at additional time points at the discretion of the investigator. See Section 10.2.
FSH (participants who are AFAB only)	X																	See Section 10.2.
Pregnancy test (participants who are AFAB only)	X	X														X	X	Serum at screening and D-1. Urine at D71 or ED. See Section 10.2.
Single 12-lead ECG (supine)	X	X														X	X	May be obtained at additional times, when deemed clinically necessary.
Mirikizumab administration			X															
Mirikizumab PK sample			P	X	X	X	X	X	X	X		X		X		X	X	See Section 10.2.
Pharmacogenetic sample			P															See Section 10.2.

	Screening	**Study Day**															**Comments**
Procedure	-35 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	ED	
AE, PC, and CM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If an AE of *Injection-site reaction* is reported, the investigator or designee will complete a supplemental injection-site reaction AE form.

Abbreviations: AE = adverse event; AFAB = assigned female at birth; BMI = body mass index; CM = concomitant medication; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; h = hour; I/E = inclusion/exclusion; P = predose; PC = product complaint; PK = pharmacokinetics; TB = tuberculosis.

2. Introduction

2.1. Study Rationale

Study I6T-MC-AMCB (AMCB) will assess the PK and safety of a 200-mg dose of citrate-free mirikizumab (LY3074828) solution formulation administered via an AI as 2 × 1-mL SC injections or a single 2-mL SC injection. The study will provide bioequivalence data on delivery of the citrate-free mirikizumab solution via the 2-mL AI planned to be used as the investigational AI device for subsequent studies and patient use. Both administrations will be evaluated at 3 different injection sites (arm, thigh, and abdomen).

2.2. Background

Mirikizumab is a humanized immunoglobulin G4-variant monoclonal antibody that binds to the p19 subunit of IL-23 without binding to other members of the IL-12 cytokine family. Mirikizumab is being developed for the treatment of immune-mediated diseases in which the IL-23 pathway is thought to have a pathogenic role. Mirikizumab is approved for treatment of adults with moderately to severely active UC. Mirikizumab is also being developed for CD and was previously in development for psoriasis.

Mirikizumab has been studied at single doses of up to 2400 mg via both IV and SC administration and a citrate-free formulation was developed to lessen ISRs such as pain.

The recommended mirikizumab dose regimen for patients with UC has 2 stages:

- an induction period with dosing of 300 mg mirikizumab infused IV for at least 30 minutes at Weeks 0, 4, and 8, and
- maintenance dosing of 200 mg mirikizumab injected as 2 × 1-mL SC injections every 4 weeks, starting at Week 12.

Administration of a SC 200-mg dose of citrate-free mirikizumab solution via a single 2-mL SC dose AI would provide a more convenient option for patients; thus there is a need to demonstrate bioequivalence of this delivery compared to 2 × 1-mL SC AI.

2.2.1. Safety

As of 22 March 2022, a total of 4898 participants in completed and ongoing mirikizumab clinical trials have been exposed to at least 1 dose of mirikizumab and have contributed safety data to the integrated analyses presented here, including

- 1088 healthy adult participants
- 2170 adult participants with psoriasis
- 1454 adult participants with UC, and
- 186 adult participants with CD.

Phase 3 studies have been completed for psoriasis, UC, and CD.

In biopharmaceutic and clinical pharmacology Phase 1 studies, healthy participants have been exposed to mirikizumab dose levels ranging from 60 mg to 2400 mg. No clinically significant

dose-related safety or tolerability issues have been observed in completed or ongoing biopharmaceutic or clinical pharmacology studies.

A mirikizumab 1-mL and/or 2-mL AI has been used in 6 completed clinical studies in healthy participants, all containing the mirikizumab solution formulation, including the citrate-free solution, and has shown acceptable safety and performance.

Data from the mirikizumab trials that used the AI showed acceptable safety and usability based on the

- PK parameters
- TEAEs of *Injection-site pain*, and
- injection-site assessment.

Citrate-free Mirikizumab

Citrate-free mirikizumab has been assessed in 3 completed clinical trials in healthy participants.

Study I6T-MC-AMBV compared the safety and tolerability of mirikizumab solution formulation and mirikizumab citrate-free solution formulation following SC administration using PFS. The incidence of all TEAEs reported during the study was similar for the 2 formulations. The frequency of positive responses to the prospective ISR (erythema, edema, induration, pruritus, and pain) assessments was lower following administration of the mirikizumab citrate-free solution formulation (50.0%) compared to the mirikizumab solution formulation (76.7%). Participants who received the mirikizumab citrate-free solution formulation had a statistically significant lower mean VAS pain score at the 1-minute time point when compared to the mirikizumab solution formulation.

Study I6T-MC-AMBT was a bioequivalence study of mirikizumab solution and citrate-free solution using 2 × 1-mL SC injections of 100 mg/mL mirikizumab using an AI, where both were well tolerated. The incidence of all TEAEs reported during the study was similar following administration of mirikizumab solution and citrate-free solution and between injection-site locations. The incidence of ISRs was lower following administration of mirikizumab citrate-free solution compared to mirikizumab solution.

Study I6T-MC-AMBY was a bioequivalence study that investigated mirikizumab solution versus citrate-free mirikizumab SC solution in 1-mL and 2-mL PFS. A higher proportion of participants reported TEAEs of *Injection-site reaction* following administration of 300 mg mirikizumab solution when compared to mirikizumab citrate-free solution. Excluding *Injection-site reaction*, the incidence of all TEAEs reported during the study was similar between formulations and injection-site locations.

2.2.2. Deaths, Serious Adverse Events, and Discontinuations Due to an Adverse Event

No deaths have been reported in any of the completed or ongoing biopharmaceutic and clinical pharmacology studies.

One participant in the Phase 1 Study I9O-MC-AABC was discontinued due to an SAE of malignant brain tumor (preferred term *Brain neoplasm malignant*). The event was considered unrelated to the study treatment.

In the Phase 1 Study I6T-MC-AMBX, 1 participant who received mirikizumab by AI reported an SAE of *Spontaneous abortion*. The SAE was severe and considered unrelated to the study intervention by the investigator.

In Phase 2 and 3 studies in participants with psoriasis, UC, and CD, a total of 23 deaths have been reported. SAEs and discontinuations due to AEs are summarized in the IB.

2.2.3. Other Treatment-Emergent Adverse Events

Across the integrated dataset of Phase 1 studies, of the 851 healthy participants exposed to mirikizumab, 400 participants (47.0%) reported TEAEs. The most commonly reported TEAEs, reported by 5% or more of treated participants, include

- ISRs (22.2%)
- nasopharyngitis (7.3%), and
- headache (7.2%).

Administration of mirikizumab using either 1-mL or 2-mL AIs has previously shown to have an acceptable safety profile and usability in healthy participants, based on TEAEs and injection-site pain.

2.2.4. Pharmacokinetics

Studies in healthy participants and adult participants with UC found that mirikizumab exposure increased proportionally, and that mirikizumab has a half-life of approximately 9.3 days and SC absolute bioavailability of 44%.

Body weight was identified as a covariate on the clearance of mirikizumab and BMI was identified as a covariate on the SC bioavailability of mirikizumab, with participants with higher body weight or BMI having a lower mirikizumab exposure. Although the effect size of weight or BMI is not considered clinically relevant, it represents a potential confounding factor for the bioequivalence evaluation. Therefore, participants will be stratified by weight in the current study.

Citrate-free mirikizumab

In Study AMBV, no statistically significant differences in C_{max}, AUC(0-∞), and AUC(0-t_{last}) were observed following administration of the 200-mg mirikizumab solution formulation and mirikizumab citrate-free solution formulation as 2 × 1-mL SC injections into the arms, thighs, or abdomen overall nor at each injection site separately, with the 90% CIs for the ratios of geometric least squares means including unity. There was no statistically significant difference in the median t_{max} of mirikizumab between the formulations.

In Study AMBT, bioequivalence was observed between the 100-mg/mL mirikizumab solution and citrate-free solution using 2 × 1-mL SC injections via AI, as assessed by AUC(0-t_{last}), AUC(0-∞), C_{max}, and t_{max}.

In Study AMBY, bioequivalence was observed between the mirikizumab solution and citrate-free mirikizumab SC solution in 1-mL and 2-mL PFS as assessed by AUC(0-t_{last}), AUC(0-∞), and C_{max}.

2.3. Benefit/Risk Assessment

Mirikizumab-related risks

As with other immunomodulatory therapies, mirikizumab may increase the risk of developing an infection or may exacerbate an existing infection. These may include opportunistic infections and reactivation of latent infections, such as TB and hepatitis B, although such infections have not been reported in healthy participant clinical trials administering mirikizumab to date. Therefore, participants testing positive for hepatitis B/C, HIV, or TB at screening will not be permitted to participate in this study. Immunomodulatory therapies may increase the risk of malignancies; however, due to the single dose of mirikizumab being administered in this study, it is not considered necessary to monitor for such effects.

Immediate hypersensitivity reactions, defined as anaphylactic reaction and infusion-related hypersensitivity reaction, including urticaria, angioedema, and anaphylaxis, have rarely been reported with the administration of mirikizumab.

No other clinically significant safety or tolerability concerns have been identified to date in healthy participants exposed to mirikizumab up to the highest single doses given of 2400 mg IV or SC.

There is no anticipated therapeutic benefit for the participants in this trial. However, participants may benefit from the screening procedures, through detection of unknown health issues, even if they receive no therapeutic benefit from the trial.

Detailed information about the known and expected benefits, risks, SAEs, adverse drug reactions, and reasonably anticipated AEs of mirikizumab are described in the IB.

Autoinjector-related risks

As this study will use AIs, device-related safety risks will be evaluated. Possible device-related safety risks include local effects such as pain at the injection sites from either the needle or the solution entry into the SC tissue, swelling, erythema, bleeding, and bruising. These risks are mitigated by training of investigative site staff on proper injection techniques.

Detailed information about the known and anticipated risks and deficiencies of the AI, and related anticipated adverse device effects can be found in the device IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2-mL AI (test) compared to using 2 × 1-mL AI (reference)	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety of a 200-mg SC dose of 100 mg/mL citrate-free mirikizumab solution using a 1 × 2-mL AI (test) compared to using 2 × 1-mL AI (reference)	• TEAEs and SAEs
Exploratory	
• To evaluate the impact of injection-site location on PK	• C_{max}, AUC(0-∞), and AUC(0-t_{last})

Abbreviations: AI = autoinjector; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study AMCB is a Phase 1, open-label, randomized, 2-arm, parallel-design, single-dose multi-center study of citrate-free mirikizumab administered via AI in healthy participants.

Screening

All participants will be screened within 35 days prior to Day 1.

Treatment and Assessment Period

Eligible participants will be admitted to the CRU on Day -1. Participants will be stratified by 1 of 3 weight categories based on their weight assessment measured on Day -1:

- less than 75.0 kg
- 75.0 to 85.0 kg
- more than 85.0 kg

Participants will be stratified by weight category and randomized as shown in Table AMCB.1 1:1 to either 1 × 2-mL SC injection of 100 mg/mL citrate-free mirikizumab (test) or 2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab (reference) with a computer-generated allocation code using an IWRS as described in Section 6.3. Injection-site location, either arm, thigh, or abdomen, will be assigned in an approximately equal distribution within each study arm using an IWRS.

Approximately 484 participants may be enrolled so that approximately 400 participants, 200 in each test and reference group, complete the study. Approximately 242 participants will be randomized to the test arm and approximately 242 participants will be randomized to the reference arm, with approximately 80 participants for each injection site in each study arm.

A minimum of approximately 80 participants overall in each weight category should complete the study.

On Day 1, participants will receive assigned study intervention. Participants may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion, and will return for PK sampling and safety assessments at predefined times up to 10 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety will be assessed through clinical chemistry, hematology, and urinalysis testing, vital signs measurements, recording of AEs and PCs, and physical examination.

Table AMCB.1. Study Intervention Randomization Including Weight Stratification and Injection Site Assignment

Weight Category	Administration Method[a]	Subcutaneous Injection Site[a]
Low <75.0 kg	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Arm
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Abdomen
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Thigh
Medium 75.0 – 85.0 kg	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Arm
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Abdomen
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Thigh
High >85.0 kg	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Arm
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Abdomen
	2 × 1-mL AI (Reference) 1 × 2-mL AI (Test)	Thigh

Abbreviations: AI = autoinjector; SC = subcutaneous.

[a] Using an interactive web-response system, participants will be stratified by weight, assigned an injection site, and randomized 1:1 to 1 × 2-mL SC injection or 2 × 1-mL SC injections.

4.2. Scientific Rationale for Study Design

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications in participants. A population of healthy participants is frequently used in the assessment of the PK of both small and large molecules.

Single doses of citrate-free mirikizumab and the PK sampling time points have been selected to generate PK profiles sufficient to fulfill the study objectives.

The mirikizumab citrate-free solution formulation is being investigated as a potential replacement for the mirikizumab solution formulation and has been used in 3 Phase 1 clinical trials (Studies I6T-MC-AMBT, I6T-MC-AMBV, and I6T-MC-AMBY).

Due to the 5-day return of results for the QuantiFERON® TB Gold test, a 35-day screening period has been selected. The extension from the standard 28 days allows investigative sites more flexibility to screen, randomize, and dose a larger number of healthy participants.

Weight will be stratified into 3 categories, administration methods will be randomized, and injection site will be assigned. The number of participants randomized to each administration method and the number of participants assigned to each site of injection is desired to be balanced. Previous population PK analyses have shown that participants with a lower body weight tended to have a lower clearance, central volume of distribution, or both. While the

effects of body weight on these PK parameters were statistically significant, it was not considered to be clinically relevant. However, to mitigate these potentially confounding effects, weight is a stratification factor to ensure that an approximately equal number of participants in each weight category will be randomized to each reference and test administration methods.

A parallel-group design is chosen because a crossover design is impractical for mirikizumab, which has a half-life of approximately 9.3 days. Additionally, a crossover study could confound PK data if participants develop neutralizing anti-drug antibody.

4.3. Justification for Dose

The 200-mg dose of citrate-free mirikizumab chosen for this study is based on 200 mg mirikizumab being found to be effective in the completed Phase 3 UC development program and is the marketed SC dose for UC maintenance therapy.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed all visits in the study.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

Participants who are not enrolled within 35 days of screening may undergo additional medical assessments, clinical measurements, or both to confirm their eligibility. In such instances, the following screening tests and procedures will be repeated: vital signs, ECG, clinical laboratory tests, and pregnancy test for participants who are assigned female at birth only.

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

5.1. Inclusion Criteria

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

Age

1. are between 18 and 65 years of age, inclusive, at the time of signing the informed consent and of an acceptable age to provide informed consent.

Type of participant and disease characteristics

2. are overtly healthy as determined by medical evaluation including:
   - medical history
   - physical examination
   - clinical laboratory tests
   - ECG, and
   - vital signs.

Note: participants may have chronic, stable medical conditions that, in the investigator's opinion, will not place the participant at increased risk by participating in the study, and will not interfere with interpretation of the data, for example, treated controlled mild hypertension, hypercholesterolemia, gastroesophageal reflux disease.

3. have clinical laboratory test results at screening and Day -1
   - within normal reference range for the population, or
   - within normal reference range for the investigative site, or
   - results with acceptable deviations that are judged to be not clinically significant by the investigator.

Weight

4. have a BMI within the range of 18.0 to 34.0 kg/m^2, inclusive.

Sex assigned at birth and contraceptive/barrier requirements

5. are individuals assigned male at birth or assigned female at birth who are individuals of childbearing potential or individuals not of childbearing potential.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the definitions and additional requirements related to contraception requirements of this protocol, see Section 10.4.

Informed consent

6. are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

7. have venous access sufficient to allow for blood sampling as per the protocol.
8. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
9. agree not to donate blood or plasma until after the end of their participation in the study.

5.2. Exclusion Criteria

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

Medical conditions

10. have significant allergies to humanized monoclonal antibodies or known allergies to citrate-free mirikizumab, related compounds or any components of the formulation, or history of significant atopy.
11. have self-perceived dullness or loss of sensation in either arm or thigh or on either side of the abdomen.
12. have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data. Uncomplicated cholecystectomy, appendectomy, or hernia repair will not be exclusionary.
13. have known or ongoing psychiatric disorders deemed clinically significant by the investigator.
14. have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis.
15. have a diagnosis or history of malignant disease within 5 years prior to baseline, with the following exceptions:
    - basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
    - cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline.
    - history of breast cancer will be exclusionary.

Prior/concomitant therapy

16. intend to use over-the-counter or prescription medication, including herbal medications and traditional medications, within 7 days prior to dosing. Participants on stable doses of some medications, such as statins and antihypertensives, may be eligible for enrolment following discussion with the sponsor or designee. Specific medications listed in Section 6.8 may be allowed.
17. have received treatment with biologic agents, such as monoclonal antibodies, including marketed drugs, within 3 months or 5 half-lives, whichever is longer, prior to dosing.
18. have ever received anti-IL-12p40 antibodies, for example, ustekinumab (Stelara®), or anti-IL-23p19 antibodies, for example risankizumab (BI 655066), brazikumab (MEDI2070), guselkumab (CNTO 1959), or tildrakizumab (MK 3222), for any indication, including investigational use.
19. have received any live vaccine (that is, live attenuated) within less than 4 weeks or inactivated vaccine within less than 2 weeks before randomization, or intend to receive a live vaccine during the study or an inactivated vaccine 2 weeks postdose, and then they must be given at an injection site remote from mirikizumab administration.
20. have been treated with oral steroids within 1 month of screening or intend to during the study. Mild potency topical steroid creams or ointments are permitted, with the exception of ± 24 hours from injection of the study intervention as specified in Section 6.8.

Prior/concurrent clinical study experience

21. are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
22. have participated in a clinical study involving an investigational product within the last 30 days or 5 half-lives, whichever is longer, prior to screening. If the clinical trial involved treatment with biologic agents, such as monoclonal antibodies, including marketed drugs, at least 3 months or 5 half-lives, whichever is longer, should have elapsed prior to dosing.
23. have previously completed or withdrawn from this study or any other study investigating mirikizumab, and have previously received mirikizumab.

Diagnostic assessments

24. have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.
25. have clinically significant blood pressure, pulse rate, or body temperature as determined by the investigator.
26. have HIV infection.
27. have a current infection with hepatitis C virus, that is, positive for hepatitis C virus RNA.
28. have a current infection with hepatitis B virus, that is, positive for hepatitis B surface antigen or polymerase chain reaction positive for hepatitis B virus DNA.

29. have a current or recent acute, active infection. For at least 30 days before screening and up to randomization, participants must have no symptoms or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.
30. have had any of the following types of infection within 3 months prior to screening or develops any of these infections before the randomization:
    a. Serious: Requiring hospitalization, or IV or equivalent oral antibiotic treatment, or both.
    b. Opportunistic: As defined in Winthrop et al. 2015. Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
    c. Chronic: Duration of symptoms, signs, and/or treatment of 6 weeks or longer.
    d. Recurring: Including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis.
31. show evidence of active or latent TB, as documented through medical history, examination, and TB testing (positive [not indeterminate] QuantiFERON TB Gold test; if a repeat test is also indeterminate, the participant will not be eligible); or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been completed at least 3 months prior to treatment. Participants with any history of active TB are excluded from the study, regardless of previous or current TB treatments. Participants that have or have had latent TB infection that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization and the United States Centers for Disease Control and Prevention, unless such treatment is underway, are excluded as described in Section 8.2.8.

Other exclusion criteria

32. are pregnant, or intend to become pregnant or to breastfeed during the study.
33. regularly use known drugs of abuse or show positive findings on drug screening.
34. have donated blood of more than 500 mL within 1 month of screening.
35. have alcohol intake that exceeds recommended average weekly alcohol consumption limits per local regulation, or an amount deemed significant by the investigator.
36. smoke more than 10 cigarettes per day, or equivalent, or are unable to abide by investigative site smoking restrictions described in Section 5.3.2.
37. have 2 or more of the injection sites (arm, thigh, or abdomen) obscured by tattoos, scars, moles, skin hyperpigmentation, birth marks, or stretch marks that would interfere with injection site assessments.
38. are investigative site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
39. are Lilly employees or are employees of third party organizations involved in the study conduct.
40. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will receive a light breakfast on the morning of Day 1 prior to dosing. Standard meals will be provided at all other times while participants are resident at the CRU, per the CRU's policy.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Caffeine

Participants will follow clinic caffeine restrictions while resident at the CRU, but otherwise participants will be allowed to maintain their regular caffeine consumption.

Alcohol

Alcohol consumption is not permitted while participants are resident at the CRU and for 24 hours prior to each study visit. Alcohol intake during outpatient periods should not exceed 3 units per day for participants who are assigned male at birth or 2 units per day for participants who are assigned female at birth.

Tobacco

Participants must abide by the CRU smoking restrictions during study visits and while resident at the CRU.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity and exercise but will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study, for example, watching television, or reading. While certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Repeating of laboratory tests during the screening period or repeating screening assessments to comply with the protocol-designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Whenever possible, study intervention administration should be carried out by the same trained personnel.

This table lists the interventions used in this clinical study.

Intervention Name	Mirikizumab citrate-free solution in a 1-mL AI (reference)	Mirikizumab citrate-free solution in a 2-mL AI (test)
Dosage Level(s)	2 × 100 mg 100 mg/mL	1 × 200 mg 100 mg/mL
Route of Administration	Subcutaneous injection into the arm, abdomen, or thigh	Subcutaneous injection into the arm, abdomen, or thigh
Dosing Instructions	2 × 1-mL injections at site according to the IWRS	1 × 2-mL injection at site according to the IWRS
Packaging and labeling	Study interventions will be supplied by the sponsor in accordance with current good manufacturing practice. Study interventions will be labeled as appropriate for country requirements.	

Participants randomized to the 1 × 2-mL SC injections into the abdomen will be administered in the lower quadrants of the abdomen.

Participants randomized to the 2 × 1-mL SC injections will be administered as shown.

	First injection	**Second injection**
Arm or thigh	left limb	corresponding (contra-lateral) right limb
Abdomen	lower left quadrant	lower right quadrant

6.1.1. Medical Devices, Investigational Devices, or Device Constituents

The sponsor-manufactured medical devices provided for use in this study are 1-mL and 2-mL AIs containing 100 mg/mL citrate-free mirikizumab.

Instructions for medical device use are provided as part of the study materials provided to investigators and sites.

All PCs, including malfunction, use error, and inadequate labelling, shall be documented and reported by the investigator throughout the clinical investigation as described in Section 8.3 and

appropriately managed by the sponsor. Each device will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention 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 study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

Samples of the specific batches of mirikizumab used in the study will be retained; details will be provided separately.

6.3. Assignment to Study Intervention

This is an open-label study. Potential bias will be reduced by central weight category stratification and randomization. The site will contact the IWRS prior to the start of study intervention administration for each participant.

All participants will be assigned a unique participant identifier and randomized to citrate-free mirikizumab administration methods with weight category as a stratification factor and injection site assignment using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. The site will record the intervention assignment on the applicable CRF, if required.

6.4. Study Intervention Compliance

Participants are dosed at the site. Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing by a member of the study site staff other than the person administering the study intervention. The date, time, and injection location of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.5. Dose Modification

Not applicable for this single-dose study.

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.7. Treatment of Overdose

For this study, any dose of mirikizumab greater than 200 mg will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately, and
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, until mirikizumab no longer has a clinical effect or can no longer be detected systemically (at least 71 days postdose).

6.8. Prior and Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Permitted Concomitant Therapy

Participants on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Permitted concomitant medications, at the discretion of the investigator, include

- hormonal contraceptives
- thyroid-replacement therapy
- hormone-replacement therapy, and
- occasional acetaminophen (or paracetamol). Acetaminophen should not be administered on the dosing day within 4 hours prior to and 4 hours after dosing. If acetaminophen treatment is needed for pain management, the maximal allowed dose will be 3 g/day from all acetaminophen-containing medicinal products.

Inclusion of participants on any other concomitant medication (for example, statins and anti-hypertensives) is contingent upon approval following consultation with the sponsor or designee.

If the need for any additional concomitant medication arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist, clinical research physician, or designee.

6.8.2. Prohibited Concomitant Therapy

Participants must abstain from taking the medications described in Section 5.2 until completion of the last follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants will be restricted from applying any creams or lotions on the arm, thigh, or abdominal skin within 24 hours prior to or after the injections and participants should not receive any additional SC injections at the site of mirikizumab administration for the duration of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit as shown in the SoA in Section 1.3. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

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

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

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

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

Further details are provided in the sections shown.

Section 10.2	List of laboratory tests that will be performed
Section 10.2.1	Summary of the maximum number and volume of invasive samples
Section 10.1.11	Details about sample retention and custody

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examinations, height, weight, and BMI will be conducted according to the SoA in Section 1.3.

A complete physical examination will include, at a minimum, assessments of the dermatological, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Symptom-directed physical examinations will also be performed.

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA in Section 1.3. If warranted, additional vital signs may be measured.

Blood pressure and pulse rate should be measured after at least 5 minutes sitting. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and measurement obtained between 2 to 3 minutes after standing.

If the participant feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of *Dizziness* or posture-induced symptoms. Additional vital signs may be measured throughout the study per investigator discretion.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA in Section 1.3. All single ECGs recorded should be stored at the investigational site. ECGs may be obtained at additional times when deemed clinically necessary, for example, to assess participants' safety.

During the study, ECGs should be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake during ECG collection.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported to the sponsor, or its designee, as an AE via the eCRF.

ECGs will be interpreted by the investigator (a physician or qualified designee) at the site as soon after the time of ECG collection as practical, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a source document agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are

considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Pregnancy Testing

Pregnancy testing will be performed as detailed in the SoA in Section 1.3.

8.2.6. Safety Monitoring

8.2.6.1. Hepatic Safety Monitoring and Evaluation

This table summarizes actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)

If this laboratory value is observed…	Then…	
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation
ALT or AST ≥3 × ULN	X	
ALP ≥2 × ULN	X	
TBL ≥2 × ULN[b]	X	
ALT or AST ≥5 × ULN	X	X
ALP ≥2.5 × ULN	X	X
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a]	X	X
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR ≥ 1.5	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

8.2.6.1.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

ALT or AST ≥3 × ULN **or**
ALP ≥2 × ULN **or**
TBL ≥2 × ULN[b]

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests detailed in Section 10.6, including ALT, AST, alkaline phosphatase, TBL, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to laboratory tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.6.1.2. Comprehensive Hepatic Monitoring

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

ALT or AST ≥5 × ULN **or**
ALP ≥2.5 × ULN **or**
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a] **or**
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR≥ 1.5

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.7. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.2. Laboratory results are provided to the sponsor via the central laboratory.

8.2.8. Tuberculosis Testing and Monitoring

Participants will be tested as indicated in the SoA, in Section 1.3, for evidence of active or latent TB using the QuantiFERON-TB Gold test. If the test is indeterminate, 1 retest is allowed. If the retest is indeterminate, the participant will be excluded from the study.

Participants who have had household contact with a person with active TB must be excluded, unless appropriate and documented prophylaxis treatment for TB has been completed at least 3 months prior to treatment.

Participants with any history of active TB are excluded from the study, regardless of previous or current TB treatments.

8.2.9. Injection-Site Reactions

Although there will be no prospective collection of ISR information, spontaneously reported ISRs by the participant will be recorded as AEs, with the ISR CRF used to collect supplemental data on the following specific findings:

- induration
- pain
- edema
- pruritus, and
- erythema.

The findings of ISR for a specific injection will be captured as a single AE of *Injection-site reaction*, if 1 or more than 1 of the findings is positive, and the severity that is recorded on the ISR AE form will be the highest severity across the findings at each applicable visit.

If injection-site pain is reported at any time during the study, the intensity of pain will be quantified using the 100-mm validated pain VAS. The VAS is a well validated tool (Williamson and Hoggart 2005) to assess injection-site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually “no pain” and “worst imaginable pain.” The participant will be asked to rate any pain at the injection site on a scale of 0 to 100 on the line as soon as is practical following reporting of the event.

Injection-site assessments should be conducted at the next planned visit following the reporting of an injection-related AE.

8.2.9.1. Bleeding and Bruising Assessment

The presence of visible bleeding or bruising at the injection site will be recorded on the eCRF as applicable and will be recorded as an AE if judged to be more severe than expected with a typical SC administration.

A bandage may be placed on the injection site after assessment.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of AEs, SAEs, and PCs can be found in Section 10.3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study as described in Section 7.

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest as defined in Section 8.3.3 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	**Collection Start**	**Collection Stop**	**Timing for Reporting to Sponsor or Designee**	**Mechanism for Reporting**	**Back-up Method of Reporting**
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	N/A
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	N/A
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in participants and partners of participants	After the start of study intervention	Day 71 (±3 days) or upon early discontinuation	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	N/A
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	-

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Collection of Pregnancy Information

8.3.2.1. Participants Who Become Pregnant

The investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, 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 for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study may be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.2.2. Participants With Partners Who Become Pregnant

When to collect pregnancy information

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

After learning about a pregnancy in the partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status, presence or absence of anomalies, or indication for the procedure.

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant in these circumstances:

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm or ova that resulted in the pregnancy.

8.3.3. Adverse Events of Special Interest

AEs of special interest for this program include:

- infection and
- systemic allergic/hypersensitivity reactions.

If infections or allergic/hypersensitivity reactions are reported, site staff will provide details on these events as instructed on the eCRF. A PK and hypersensitivity cytokine panel will be collected, as detailed in Section 10.2.2, when possible, for any participant who experiences an AE of systemic allergic/hypersensitivity reaction during the study.

8.4. Pharmacokinetics

At the visits and times specified in the SoA in Section 1.3, venous blood samples will be collected from all participants to determine the serum concentrations of mirikizumab. Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of mirikizumab will be assayed using a validated bioanalytical assay.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

The actual date and time (24-hour clock time) of each sample must be recorded.

Further details on sample retention are described in Section 10.1.11.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Section 10.5 for information regarding genetic research and Section 10.1.11 for details about sample retention and custody.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9. Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.1. Statistical Hypothesis

The primary objective of this study is to evaluate the bioequivalence of a single 2-mL SC dose of citrate-free mirikizumab solution in AI compared to 2 × 1-mL SC doses of citrate-free mirikizumab solution in AI.

9.2. Analyses Sets

Participant Analysis Set	Description
Enrolled	All participants randomly assigned to study intervention.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All enrolled participants who receive a dose of study intervention and have evaluable PK data according to the study intervention actually received.

Participants may be excluded from the PK analysis set in the event of

- a device malfunction
- administration of only 1 of the 2 × 1-mL AI doses, or
- administration of an incorrect or incomplete dose.

9.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or designee.

Safety analyses will be conducted for all enrolled participants who were administered study intervention, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as appropriate. Study results may be pooled with the results of other studies for safety and population PK analysis purposes, for totality of evidence.

9.3.1. General Considerations

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the statistical analysis plan, where appropriate. Adjustments to the planned analyses will be described in the final clinical study report.

9.3.2. Primary Endpoint Analysis

9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for mirikizumab will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be the C_{max}, AUC(0-∞), and AUC(0-t_{last}) of mirikizumab. The secondary parameter for analysis will be the t_{max} of mirikizumab. Other noncompartmental parameters, such as half-life associated with the terminal rate constant, apparent clearance, and apparent volume of distribution, may be reported.

9.3.2.2. Pharmacokinetic Statistical Inference

The C_{max}, AUC(0-∞), and AUC(0-t_{last}) will be log-transformed and analyzed using a linear fixed-effects model. The model will include mirikizumab administration method (2 × 1-mL SC injections of 100 mg/mL citrate-free mirikizumab as reference, and 1 × 2-mL SC injections of 100 mg/mL citrate-free mirikizumab as test), injection location, and weight category stratification as fixed effects. The administration method differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI. Comparisons will be made between the 2 administration methods.

The 2 administration methods will be considered bioequivalent if the 90% CIs of the ratio of geometric least squares means fall within 0.80 to 1.25.

In addition, the t_{max} of mirikizumab between the administration methods will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, approximately 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

9.3.3. Secondary Endpoint Analysis

9.3.3.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs and PCs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. The incidence of TEAEs for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. AEs reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of SAEs will be reported.

9.3.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical laboratory parameters and vital signs. The parameters and changes from baseline (predose), where appropriate, may be listed and

summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.4. Exploratory Endpoint Analysis

9.3.4.1. Pharmacokinetic Parameter Estimation – Injection-site Location

See Section 9.3.2.1. Additional exploratory analyses may be conducted, and the details will be included in the statistical analysis plan.

9.3.5. Other Safety Analyses

9.3.5.1. Injection-site Assessments

If available, any incidence of erythema, induration, pain, pruritus, edema, bleeding, and bruising will be listed.

9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.5. Sample Size Determination

Approximately 484 participants, approximately 242 participants in each treatment arm, may be enrolled so that approximately 400 participants, 200 in each test and reference group, complete the study.

Within each weight category, participants will be assigned to an SC injection site of either the arm, thigh, or abdomen, approximately 80 participants per injection site for the reference and test arms.

A sample size of 200 participants per treatment group will provide approximately 90% probability that the 90% CI of the geometric mean ratio of C_{max} and AUC between groups will fall within the equivalence boundary of 0.80 to 1.25. This sample size calculation was based on the assumptions that the coefficient of variation of PK parameters is up to 41.8% for each treatment group and the expected ratio of geometric means is between 0.9 and 1.1.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- International Organization for Standardization 14155
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents, for example, advertisements, must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and IRB/IEC consenting guidance.

A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

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

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the EU General Data Protection Regulation.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.6. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

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

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

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

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF 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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor’s database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global PC management system.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.8. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

The sponsor or sponsor's 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

- for study termination due to discontinuation of further study intervention development
- for site termination due to
    - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - inadequate recruitment, evaluated after a reasonable amount of time of participants by the investigator, or
    - total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.10. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.11. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of mirikizumab or after mirikizumab becomes commercially available.

Sample Type	**Custodian**	**Retention Period After Last Participant Visit**
Pharmacokinetics	Sponsor or designee	1 year
Pharmacogenetic	Sponsor or designee	15 years
Clinical laboratory tests (not otherwise specified)	Sponsor or designee	After completion of testing or 60 days

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central or local laboratory as specified below.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

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

Investigators must document their review of the laboratory safety results.

Clinical Laboratory Tests		**Comments**
Hematology		Performed locally at screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated. *reported as required.
Hematocrit Hemoglobin Erythrocyte count Mean cell volume Mean cell hemoglobin Mean cell hemoglobin concentration Leukocytes Cell morphology* Platelets	Absolute counts and/or % of: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry		Performed locally at screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated.
Sodium Potassium Calcium Phosphorous Glucose (random) Blood urea nitrogen Uric acid	Total cholesterol Total protein Albumin Total bilirubin Direct bilirubin Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Creatinine	
Urinalysis		Performed locally at screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated.
Specific gravity pH Protein Glucose Ketones Leukocyte esterase	Bilirubin Urobilinogen Blood Nitrite Microscopy (if dipstick abnormal; blood, protein, nitrites, or leukocyte esterase is positive)	

Clinical Laboratory Tests		Comments
Hormones (participants assigned female at birth)		Performed by a local laboratory.
Serum and urine pregnancy test	Follicle-stimulating hormone test	
Other		Performed by a local laboratory.
Breath or urine ethanol test	Urine drug screen	
TB, HIV, and hepatitis serology		Performed by a local laboratory. [a] If hepatitis B core antibody is positive, further testing for hepatitis B DNA will be performed. [b] If hepatitis C antibody is positive, further testing for hepatitis C virus RNA will be performed.
Hepatitis B surface antigen Hepatitis B core antibody[a] Hepatitis C antibody[b]	HIV QuantiFERON® TB Gold	
Pharmacokinetic samples		Performed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Mirikizumab concentration		
Pharmacogenetic sample		Performed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Local hematology, clinical chemistry, and pregnancy tests[a]	12	1	12
Central hematology and chemistry[a]	4.5	5	22.5
Pharmacokinetics	3	14[b]	42
Pharmacogenetics	10	1	10
Total			131.5
Total for clinical purposes			140

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

10.2.2. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up samples at the next regularly scheduled laboratory sample collection to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 minutes to 4 hours after the start of the event. • Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
	complements (C3, C3a, and C5a)
	cytokine panel (IL-6, IL-1β, IL-10, or any cytokine panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. • Note: If collecting, collect up to 12 hours after the start of the event.	mirikizumab (LY3074828) concentration

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 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 devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. 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 a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.
- An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational device.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, 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 condition detected or diagnosed after study intervention 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.
- Medication error, misuse, or abuse of investigational medicinal product, including signs, symptoms, or clinical sequelae.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- 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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) 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.
- 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, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.

- Other situations:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include 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.
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

If the participant identifies a PC or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. 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 the sponsor or designee.

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 one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an 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 one 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/SAE. The investigator will use clinical judgment to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

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

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. 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 the sponsor or designee.

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

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

Follow-up of 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 the sponsor or designee 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.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor and designee.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of suspected unexpected serious adverse reactions according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and

then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions and Guidance

Word/Phrase	Definition
Individuals assigned female at birth	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals assigned male at birth are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP) [a]	Adult individuals assigned female at birth are considered IOCBP unless they are INOCBP. Note: Adolescent or adult individuals assigned female at birth who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP) [b]	Individuals assigned female at birth are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or • are menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state [c]	The menopausal state is defined as an individual: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥40 mIU/mL; or

	• 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting HRT.

a IOCBP is inclusive of the concept of women of childbearing potential, a term often used in literature and regulatory guidance documents.

b INOCBP is inclusive of the concept of women not of childbearing potential.

c The individual **should not** be taking medications during amenorrhea such as oral contraceptives, HRT, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

10.4.2. Contraception Guidance

Individuals Assigned Male at Birth

For individuals assigned male at birth, no contraception is required except in compliance with specific local government study requirements.

Individuals Assigned Female at Birth

IOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are assigned female at birth as their preferred and usual lifestyle must follow the rules in this table.

Must…	**Must not…**

agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are assigned female at birth, and not plan a pregnancy during the study	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are assigned female at birth as their preferred and usual lifestyle, must follow the rules in this table.

Must…
Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These methods of contraception must be used for the duration of the study.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the INOCBP definition above • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injected contraceptives • contraceptive patch (only individuals <198 pounds or 90 kg) • total abstinence • sexual relationships exclusively between individuals who are assigned the same sex at birth • vasectomy – for individuals assigned male at birth in clinical trials and for the partner of an individual assigned female at birth (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • vaginal ring containing combination hormone medication, or • intrauterine devices
Effective contraception	• penile condom with spermicide • vaginal condom with spermicide • diaphragm with spermicide • cervical sponge with spermicide, or • cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to mirikizumab or IL-23-mediated autoimmune disease, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to mirikizumab and/or interventions of this drug class and IL-23-mediated autoimmune disease. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to mirikizumab or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on mirikizumab continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Section 8.2.6.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed in addition to central testing when necessary for immediate participant management. The local laboratory must be qualified in accordance with applicable local regulations. If testing is not available in certain regions based on local requirements, consult with Lilly-designated medical monitor.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody [a]
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA [b]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV total antibody [a]
Platelets	HCV RNA [b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV total antibody [a]
Total bilirubin	HDV IgM antibody
Direct bilirubin	HDV RNA [b]
Alkaline phosphatase (ALP)	**Hepatitis E virus (HEV) testing:**
Alanine aminotransferase (ALT)	HEV IgG antibody
Aspartate aminotransferase (AST)	HEV IgM antibody
Gamma-glutamyl transferase (GGT)	HEV RNA [b]
Creatine kinase (CK)	**Anti-nuclear antibody (ANA)**
Hepatic Coagulation Panel	**Anti-smooth muscle antibody (ASMA) or anti-actin antibody**
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts [c]	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA [b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (ethanol, EtOH)	HSV (Type 1 and 2) DNA [b]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA [b]	

[a] If lab does not offer total antibody testing, IgG and/or IgM are acceptable substitutes

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Availability of acetaminophen protein adducts testing is limited, so testing may be performed at central labs, if needed.

10.7. Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AI	autoinjector
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BMI	body mass index
CD	Crohn's disease
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRU	clinical research unit
device deficiencies	Equivalent to product complaint
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HIV	human immunodeficiency virus

HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL	interleukin
INR	international normalized ratio
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INOCBP	individuals not of childbearing potential
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IOCBP	individuals of childbearing potential
IRB	institutional review board
ISR	injection-site reaction
IV	intravenous(ly)
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.

misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PFS	prefilled syringe
PK	pharmacokinetics
SAE	serious adverse event
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
TB	tuberculosis
TBL	total bilirubin
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale

10.9. Appendix 9: Protocol Amendment History

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

11. References

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14:(7)798-804

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