Protocol I6T-MC-AMBY (b)

A Bioequivalence Study of Subcutaneous Injections of Mirikizumab Reference Solution Using Investigational 1-mL and 2-mL Prefilled Syringes and Mirikizumab Test Solution Formulation Using Investigational 1-mL and 2-mL Prefilled Syringes in Healthy Participants

NCT05644353

Approval Date: 01-FEB-2023

Title Page

Protocol Title: A Bioequivalence Study of Subcutaneous Injections of Mirikizumab Solution using Investigational 1-mL and 2-mL Prefilled Syringes and Mirikizumab Citrate-free Solution Formulation using Investigational 1-mL and 2-mL Prefilled Syringes in Healthy Participants

Protocol Number: I6T-MC-AMBY

Amendment Number: b

Compound: Mirikizumab (LY3074828)

Brief Title: A bioequivalence study of subcutaneous injections of mirikizumab solution and mirikizumab citrate-free solution using investigational 1-mL and 2-mL prefilled syringes in healthy participants.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number: IND: 130052

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-077573

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	*11-October-2022*
Original Protocol	*21-September-2022*

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

Protocol I6T-MC-AMBY(a) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to the protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design Section 9.5 Sample Size Determination	Number of participants to be enrolled changed from 'approximately 410' to 'approximately 440'. As such 'approximately 220' participants will be randomized to each arm instead of 'approximately 205' participants, and 'approximately 73 participants per injection site' instead of 'approximately 68 participants'.	At 1 investigative site, an incorrect injection technique was used for 31 participants, as the injection was given at a 90-degree angle rather than a 45-degree angle. These participants will be included in the safety analysis set but excluded from the PK analysis set, as per the PK analysis set exclusion criteria in Section 9.2. Approximately 30 further participants will therefore be enrolled in order to achieve the PK and immunogenicity objectives of the study.
Section 9.2 Analyses Sets	Clarification of PK analysis set exclusion criterion 'administration of an incorrect or incomplete dose' to 'administration of an incorrect dose, incomplete dose, or incorrect use of procedure instructions'	The original criterion was expanded to clarify that the use of an incorrect technique or procedure of study drug administration warrants exclusion from the PK analysis set.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Bioequivalence Study of Subcutaneous Injections of Mirikizumab Solution using Investigational 1-mL and 2-mL Prefilled Syringes and Mirikizumab Citrate-free Solution Formulation using Investigational 1-mL and 2-mL Prefilled Syringes in Healthy Participants

Brief Title: A bioequivalence study of subcutaneous injections of mirikizumab solution and mirikizumab citrate-free solution using investigational 1-mL and 2-mL prefilled syringes in healthy participants.

Regulatory Agency Identifier Number: IND: 130052

Rationale: Study I6T-MC-AMBY (AMBY) will assess the pharmacokinetics (PK), safety, and tolerability of a 300-mg dose of mirikizumab (LY3074828) in:

- solution formulation administered as 1 × 100-mg subcutaneous (SC) injection using an investigational 1-mL prefilled syringe (PFS) and 1 × 200-mg SC injection using an investigational 2-mL PFS, or

- citrate-free solution formulation administered as 1 × 100-mg SC injection using an investigational 1-mL PFS and 1 × 200-mg SC injection using an investigational 2-mL PFS.

The study will provide bioequivalence data on the mirikizumab citrate-free solution formulation planned to be used in the investigational PFS devices for use in 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 single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety and tolerability of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• TEAEs and SAEs

Abbreviations: 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; PFS = prefilled syringe; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Overall Design:

Study AMBY is a Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study 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 clinical research unit (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, and

- more than 85.0 kg.

Participants will also be randomized 1:1 to either mirikizumab solution (reference) or citrate-free solution (test) with a computer-generated allocation code using an interactive web-response system (IWRS). Injection-site location (arm, thigh, or abdomen) will be assigned in an approximately equal distribution within each study arm using an IWRS.

Approximately 440 participants will be enrolled to ensure 368 completers for primary analysis. Approximately 220 participants will be randomized to the test arm and approximately 220 participants will be randomized to the reference arm, with approximately 73 participants for each injection site in each study arm.

A minimum of approximately 70 participants in each weight category should complete the study.

On Day 1, participants will receive 1 × 1-mL and 1 × 2-mL SC dose of 100 mg/mL mirikizumab (total dose: 300 mg mirikizumab).

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 and immunogenicity sampling and safety assessments at predefined times up to approximately 12 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed through clinical laboratory tests, vital signs measurements, recording of adverse events and product complaints, physical examination, and immunogenicity.

Brief Summary:

The purpose of this study is to evaluate the bioequivalence of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation (test) using investigational 1-mL and 2-mL PFSs compared to mirikizumab solution formulation (reference) using investigational 1-mL and 2-mL PFSs in healthy participants.

Study Population:

Participants will be healthy males or females between 18 and 65 years of age, inclusive, and with a body mass index within the range of 18.0 and 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 440 (approximately 220 participants in the mirikizumab solution [reference] group and approximately 220 participants in the mirikizumab citrate-free solution [test] group) participants may be enrolled.

Intervention Groups and Duration:

All participants will be screened within 35 days prior to Day 1. A single SC dose of mirikizumab in either the mirikizumab solution formulation (reference) or mirikizumab citrate-free solution

formulation (test) will be administered as 1 × 1-mL and 1 × 2-mL injections by PFS into the arm, thigh, or abdomen on Day 1 and participants will be followed through Day 85, ±3 days.

Ethical Considerations of Benefit/Risk:
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 (TB) and hepatitis B, although such infections have not been reported in healthy volunteer clinical trials administering mirikizumab to date. Therefore, participants testing positive for hepatitis B, hepatitis C, human immunodeficiency virus, 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 (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 participants exposed to mirikizumab up to the highest doses given (single 2400-mg intravenous and SC doses). Of note, the 2400-mg SC dose of mirikizumab was administered in conjunction with human recombinant hyaluronidase as an integral component of the formulation.

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

As this study will use PFSs, 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 investigative site staff on proper injection techniques. Systemic effects may include sweating, feeling faint, or fever, as a sign of infection.

Data Monitoring Committee: No.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

	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	85 ±3d or ED	
Informed consent	X																	
Participant admission to CRU		X																
Participant discharge from CRU			X															Participants may be discharged after completing the 4-hour safety assessments on Day 1, or later at the investigator's discretion.
Outpatient visit	X			X	X	X	X	X	X	X		X		X		X	X	
Safety assessment (telephone call)											X		X		X			To check on the presence of any AEs and concomitant medications.
Medical history and demographics	X																	
Review and confirm inclusion and exclusion criteria	X	X																See Section 5 for details.
Randomization using an IWRS		X	P															On Day -1 or Day 1, participants will be randomized 1:1 to 1 of 2 formulations and assigned 1 of 3 injection sites per weight category.
Height, weight, and BMI	X	X															X	Only weight will be measured on Day -1, Day 85, or ED.

	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	85 ±3d or ED	
Physical examination	X	X															X	Complete physical examination at either screening or Day -1. Symptom-directed examinations and assessments at Day 85 or ED, and as deemed necessary by the investigator.
Vital signs (pulse rate and blood pressure) (sitting)	X	X	P, 2 to 4 hours					X				X					X	Day 1: 2- to 4-hour assessment to be conducted at least 2 hours after second injection and prior to discharge at approximately 4 hours postdose. Time points may be added if warranted and agreed on between the sponsor and the investigator.
Body temperature	X	X	P	X	X	X	X	X	X	X		X		X		X	X	
Clinical laboratory tests	X	X	P	X				X		X							X	See Appendix 2 (Section 10.2) for details. Performed locally at screening and Day -1 and centrally at Day 1 P and all postdose time points unless otherwise stated.
Serology	X																	See Appendix 2 (Section 10.2) for details.
QuantiFERON®-TB Gold test	X																	
Ethanol test and drug screen	X	X																Tests may be repeated at additional time points at the discretion of the investigator.

	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	85 ±3d or ED	
FSH	X																	Females only, as applicable, to confirm WNOCBP. See Appendix 4 (Section 10.4) for details.
Pregnancy test (females only)	X	X															X	Serum pregnancy testing will be performed at screening and Day -1. Urine pregnancy testing will be performed at Day 85 or ED.
Single 12-lead ECG (supine)	X	X															X	May be obtained at additional times, when deemed clinically necessary.
Mirikizumab administration (2 injections per dose)			X															
Mirikizumab PK sample			P	X	X	X	X	X	X	X		X		X		X	X	
Immunogenicity sample			P					X		X							X	
Pharmacogenetic sample			P															
AE, PC, and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If an AE of ISR is reported, the investigator or designee will complete a supplemental ISR AE form.

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; d = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; ISR = injection-site reaction; IWRS = interactive web-response system; P = predose; PC = product complaint; PK = pharmacokinetic; TB = tuberculosis; WNOCBP = women not of childbearing potential.

2. Introduction

2.1. Study Rationale

Study I6T-MC-AMBY (AMBY) will assess the PK, safety, and tolerability of a 300-mg dose of mirikizumab (LY3074828) in:

- solution formulation administered as 1 × 100-mg SC injection using an investigational 1-mL PFS and 1 × 200-mg SC injection using an investigational 2-mL PFS, or
- citrate-free solution formulation administered as 1 × 100-mg SC injection using an investigational 1-mL PFS and 1 × 200-mg SC injection using an investigational 2-mL PFS.

The study will provide bioequivalence data on the mirikizumab citrate-free solution formulation planned to be used in the investigational PFS devices for use in 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 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, including psoriasis, CD, and UC, in which the IL-23 pathway is thought to have a pathogenic role.

Clinical pharmacology studies have demonstrated an acceptable safety profile in healthy participants following single dose IV administration up to 2400 mg and single dose SC infusion up to 2400 mg (see Section 2.2.1).

Citrate has been associated with injection site pain in other injectable products (Humira Prescribing Information 2021; Kaiser et al. 2012; Nash et al. 2016). Evidence suggests that citrate chelation of endogenous divalent metal ions may lead to injection or infusion site pain (Krasner et al. 2012). To potentially lessen ISRs, including pain, Lilly developed a citrate-free solution formulation of mirikizumab that uses a different combination of buffer and tonicity agents to that of the mirikizumab solution formulation.

The PFS has been used in all clinical studies, including Phase 3 studies.

The recommended induction dosage regimen of mirikizumab for UC is 300 mg via IV infusion every 4 weeks for 3 doses, before a maintenance dose of 200 mg via SC injection (2 × 1-mL) every 4 weeks. The proposed dosage regimen of mirikizumab for moderately to severely active CD is 900 mg via IV infusion every 4 weeks for 3 doses, followed by a maintenance dose of 300 mg via SC injection (1 × 1-mL and 1 × 2-mL) every 4 weeks. Multiple 300-mg SC doses have been investigated in Phase 2 (Study I6T-MC-AMAF and Study I6T-MC-AMAG) and

Phase 3 (Study I6T-MC-AMAM and Study I6T-MC-AMAX) clinical trials in adult participants with moderate to severe plaque psoriasis or CD.

Ongoing Phase 3 studies investigating mirikizumab for the treatment of CD are utilizing a PFS and citrate-containing solution formulation.

Administration of an SC 300-mg dose of mirikizumab as the citrate-free solution would potentially decrease the incidence of injection-site pain in patients with CD, thus there is a need to demonstrate bioequivalence of this formulation compared with the mirikizumab citrate solution formulation.

2.2.1. Safety

As of 06 December 2021, there have been approximately 4649 participants included in Phase 1, 2, and 3 studies of mirikizumab. These studies include 851 healthy adult participants, 2170 patients with psoriasis, 1442 patients with UC, and 186 patients with CD. Phase 3 studies have been completed for UC and plaque psoriasis and are ongoing for CD.

In clinical pharmacology studies, single IV doses of up to 2400 mg have been administered to healthy Caucasian, Chinese, and Japanese participants (Study I6T-MC-AMAD and I6T-MC-AMBD). No dose-related safety or tolerability issues were observed in these studies or other ongoing clinical pharmacology studies with single SC doses ranging from 120 to 2400 mg (as an SC infusion in Study I9O-MC-AABA) and at multiple doses up to a maximum of 300 mg.

Study I6T-MC-AMBV compared the safety and tolerability of mirikizumab solution formulation and mirikizumab citrate-free solution formulation following SC administration using PFS in healthy participants. 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 (mean VAS pain score = 12.6) had a statistically significant lower mean VAS pain score at the 1-minute time point when compared to the mirikizumab solution formulation (mean VAS pain score = 26.1).

A mirikizumab PFS has been used in 7 completed clinical studies in healthy participants (all containing the mirikizumab solution formulation) and has shown acceptable safety and performance.

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 clinical pharmacology studies. One participant in Phase 1 Study AABC was discontinued due to 1 SAE of Malignant brain neoplasm; the event was not considered to be related to study treatment by the investigator. In unblinded Phase 2 and 3 studies with participants having psoriasis, UC, or CD, up to 06 December 2021, 17 deaths were reported as a result of:

- 1 disseminated intravascular coagulation,
- 1 sudden cardiac death,
- 2 myocardial infarctions,

- 3 COVID-19 deaths,
- 3 COVID-19 pneumonia,
- 1 respiratory failure due to COVID-19 infection,
- 1 lung cancer,
- 1 colon cancer metastatic,
- 1 lymphoma,
- 1 haemorrhage intracranial,
- 1 sepsis, and
- 1 unrecorded cause.

Three of the deaths, one each of myocardial infarction, colon cancer metastatic, and lymphoma, were considered to be related to study drug by the investigator.

SAEs, ADRs, and discontinuations due to AEs are summarized in the IB.

2.2.3. Other Treatment-Emergent Adverse Events

In Phase 1 studies that were integrated for safety analyses, the most frequently reported (≥5.0%) TEAEs in the 851 healthy participants and participants with psoriasis treated with mirikizumab in clinical pharmacology studies were ISRs (including Injection-site pain; 22.2%), Nasopharyngitis (7.3%), and Headache (7.2%). All TEAEs were mild to moderate in severity. AEs reported as Injection site reaction included instances of erythema, induration, pain, pruritus, and edema reported postdose. Most were mild or moderate in severity.

Administration of mirikizumab using PFSs has previously shown to be well accepted in healthy participants, based on TEAEs and injection-site pain, for the 1-mL PFS in Studies I6T-MC-AMAE, I6T-MC-AMAQ, I6T-MC-AMAR, AMBD, I6T-MC-AMBE, AMBV, and I6T-MC-AMBW, and the 2-mL PFS in Study AMAQ and the ongoing Study I6T-MC-AMBX.

TEAEs in Phase 2 and 3 studies with participants having psoriasis, UC, or CD are summarized in the IB.

2.2.4. Pharmacokinetics

Studies in healthy participants and participants with psoriasis, UC, or CD found that systemic exposure of mirikizumab increases in proportion to dose, and that mirikizumab has a half-life of approximately 10 days and SC bioavailability of 44% across participant populations.

Body weight and BMI were identified as covariates on the clearance and bioavailability of mirikizumab, respectively, 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.

<u>Pharmacokinetics of Mirikizumab Solution Formulation and Mirikizumab Citrate-free Solution Formulation via PFS</u>

Study AMBV investigated the relative bioavailability, safety, and tolerability of a 200-mg SC dose of the mirikizumab solution formulation and mirikizumab citrate-free solution formulation

administered via PFS. Doses were administered as 2 × 1-mL SC injections into the arms, thighs, or abdomen.

Sixty healthy participants were dosed and completed the study. No statistically significant differences in C_{max}, AUC(0-∞), and AUC(0-t_{last}) were observed following administration of the mirikizumab solution formulation and mirikizumab citrate-free solution formulation overall or 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.

2.2.5. Immunogenicity

TE-ADAs have been observed in participants in all clinical trials involving mirikizumab administration. In the majority of TE-ADA+ participants, titers were low and had no clear impact on drug exposure and, if measured, efficacy. With a few participants, titers were sufficiently high to impact drug exposure. There was no clear association between the development of immunogenicity to mirikizumab and participants reporting ISRs or hypersensitivity events.

2.3. Benefit/Risk Assessment

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 volunteer clinical trials administering mirikizumab to date. Therefore, participants testing positive for hepatitis B, hepatitis 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 (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 participants exposed to mirikizumab up to the highest doses given (single 2400-mg IV and SC doses). Of note, the 2400-mg SC dose of mirikizumab was administered in conjunction with human recombinant hyaluronidase as an integral component of the formulation.

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

As this study will use PFSs, 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 the use of proper injection techniques by investigative staff. Systemic effects may include sweating, feeling faint, or fever, as a sign of infection.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety and tolerability of a single 300-mg SC dose of mirikizumab in a citrate-free solution formulation using a 1-mL and 2-mL PFS (test) compared to the mirikizumab solution formulation using a 1-mL and 2-mL PFS (reference)	• TEAEs and SAEs
Exploratory	
• To evaluate the effect of mirikizumab citrate-free solution formulation using a 1-mL and 2-mL PFS and of mirikizumab solution formulation using a 1-mL and 2-mL PFS on immunogenicity	• TE-ADA
• To evaluate the impact of injection-site location (arm, thigh, or abdomen) on PK	• C_{max}, AUC(0-∞), and AUC(0-t_{last})

Abbreviations: 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; PFS = prefilled syringe; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TE-ADA = treatment-emergent antidrug antibody; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study AMBY is a Phase 1, participant-blind, randomized, 2-arm, 2-formulation, parallel-design, single-dose, multi-center study 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, and
- more than 85.0 kg.

Participants will also be randomized (Table AMBY.1) 1:1 to either mirikizumab solution (reference) or citrate-free solution (test) with a computer-generated allocation code (Section 6.3) using an IWRS. Injection site location (arm, thigh, or abdomen) will be assigned in an approximately equal distribution within each study arm using an IWRS.

Approximately 440 participants will be enrolled to ensure 368 completers for primary analysis. Approximately 220 participants will be randomized to the test arm and approximately 220 participants will be randomized to the reference arm, with approximately 73 participants for each injection site in each study arm.

A minimum of approximately 70 participants in each weight category should complete the study.

On Day 1, participants will receive 1 × 1-mL and 1 × 2-mL SC dose of 100 mg/mL mirikizumab (total dose: 300 mg mirikizumab).

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 and immunogenicity sampling and safety assessments at predefined times up to approximately 12 weeks postdose. Participants will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed through clinical laboratory tests, vital signs measurements, recording of AEs and PCs, physical examination, and immunogenicity.

Table AMBY.1. Study AMBY Weight Stratification, Formulation Randomization, and Injection Site Assignment

Weight Category (Participants)	Mirikizumab Formulation[a]	Subcutaneous Injection Site[a,b]
Low <75.0 kg	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Arm
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Abdomen
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Thigh
Medium 75.0 – 85.0 kg	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Arm
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Abdomen
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Thigh
High >85.0 kg	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Arm
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Abdomen
	1 × 1-mL and 1 × 2-mL Solution PFS (Reference) 1 × 1-mL and 1 × 2-mL Citrate-free Solution PFS (Test)	Thigh

Abbreviations: PFS = prefilled syringe.

a Using an interactive web-response system, participants will be stratified by weight, assigned an injection site, and randomized 1:1 to mirikizumab solution formulation or citrate-free formulation.

b A dose of study intervention will consist of 2 subcutaneous injections of mirikizumab into the arm, thigh, or abdomen.

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 with UC, CD, and psoriasis. A population of healthy participants is frequently used in the assessment of the PK of both small and large molecules.

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

The mirikizumab solution formulation has been used and is currently being used in pivotal Phase 3 mirikizumab clinical trials. The mirikizumab citrate-free solution formulation is being investigated as a potential replacement for the mirikizumab solution formulation and has been used in a single Phase 1 clinical trial where a 200-mg dose (2 × 1-mL) was administered by PFS (Study AMBV) and is currently planned to be used in a Phase 1 clinical trial where a 200-mg dose (2 × 1-mL) will be administered by autoinjector (Study I6T-MC-AMBT).

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.

Participants will be assigned to receive injections in the arm, thigh, or abdomen, as injection location has been observed to have an impact on bioavailability in some studies with mirikizumab.

Weight will be stratified into 3 categories, formulation will be randomized, and injection site will be assigned. The number of participants randomized to each formulation and the number of participants assigned to each site of injection are 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 mirikizumab reference and test solution formulation.

A parallel-group design is chosen because a crossover design is impractical for mirikizumab, which has a half-life of approximately 10 days across participant populations. Additionally, a crossover study could confound PK data if participants develop neutralizing ADAs.

4.3. Justification for Dose

The 300-mg dose of mirikizumab chosen for this study is based on:

- 300 mg being found safe and tolerable in Phase 2 and Phase 3 studies,
- 300 mg being evaluated in the Phase 3 CD development program, and
- the volume of solution that can be delivered through a 1-mL and a 2-mL PFS and the concentration of mirikizumab drug product (100 mg/mL).

The 300-mg dose administered as 1 × 1-mL and 1 × 2-mL injections is the maintenance dosing regimen being used in Phase 3 studies in CD patients and is anticipated for use once marketed.

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 of the study including the last visit shown in the SoA (Section 1.3).

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening or Day -1 only unless otherwise specified, and not continuously throughout the study.

Screening may occur up to 35 days prior to Day -1. 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 (females 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 informed consent and of an acceptable age to provide informed consent according to local law.

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 within the normal reference range for the population or 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 and Contraceptive/Barrier Requirements

5. are males or nonpregnant WOCBP or WNOCBP.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 4 (Section 10.4).

Informed Consent

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

Other Inclusions

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 mirikizumab, related compounds, or any components of the formulation, or a 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.
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 immunoglobulin IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
15. have a diagnosis or history of malignant disease within 5 years prior to screening, with the following exceptions:
    a. basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, and
    b. cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to screening.
16. have had breast cancer within the past 10 years.

Prior or Concomitant Therapy

17. 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.

18. 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.
19. 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.
20. have received live vaccine(s), including attenuated live vaccines and those administered intranasally, within 8 weeks of screening, or intend to during the study (non-live or inactivated vaccinations are not allowed 2 weeks prior to, or 2 weeks after mirikizumab dosing, and then they must be given at an injection-site remote from mirikizumab administration).
21. have been treated with oral steroids within 1 month of screening, or intend to during the study (mild topical steroid creams or ointments are permitted, with the exception of ±24 hours from last injection of the study intervention as specified in Section 6.8).

Prior or Concurrent Clinical Study Experience

22. 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.
23. 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.
24. have previously completed or withdrawn from this study or any other study investigating mirikizumab, and have previously received mirikizumab).

Diagnostic Assessments

25. have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.
26. have abnormal blood pressure, pulse rate, or temperature as determined by the investigator.
27. show evidence of HIV infection, or positive HIV antibodies, or both.
28. show evidence of hepatitis C virus infection or positive hepatitis C virus antibodies.
29. have a current infection with hepatitis B virus (that is, positive for hepatitis B surface antigen and/or polymerase chain reaction positive for hepatitis B virus DNA.

30. infections:
    a. have had a serious infection (such as pneumonia, cellulitis, or sepsis), have been hospitalized, or have received IV antibiotics for an infection within 12 weeks prior to Day 1; have had a serious bone or joint infection within 24 weeks prior to Day 1 or have ever had an infection of an artificial joint, or are immunocompromised to an extent that participation in the study would pose an unacceptable risk to the participant as determined by the investigator.
    b. have or have had an infection typical of an immunocompromised host or that occurs with increased incidence in an immunocompromised host (including, but not limited to, *Pneumocystis jirovecii* pneumonia, histoplasmosis, or coccidioidomycosis) or have a known immunodeficiency.
    c. have or have had a herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks of Day 1.
    d. have had any other active or recent infection within 4 weeks of Day 1 that, in the opinion of the investigator, would pose an unacceptable risk to the participant if participating in the study; these participants may be rescreened (once) at least 4 weeks after documented resolution of symptoms.
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 given. 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 (Section 8.2.7).

Other Exclusions

32. are lactating or pregnant.
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 study screening.
35. have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), have a positive test for ethanol, or are unwilling to abide by the alcohol restrictions described in Section 5.3.2 of 3 units per day (males) or 2 units per day (females) (number of units = [total volume of drink (mL) × alcohol by volume (%)]/1000).
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 and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
39. are employees of Lilly, Labcorp, or associated Contract Research 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 males or 2 units per day for females.

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 prior to any visit in which laboratory safety tests will occur. 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 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 Interventions and Concomitant Therapy

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This study involves a comparison of mirikizumab solution formulation versus citrate-free solution formulation using 1 × 1-mL (100 mg) and 1 × 2-mL (200 mg) SC injections of 100 mg/mL mirikizumab using PFS into the arm, thigh, or abdomen for a total administered dose of 300 mg.

Participants assigned to a group with the arm or thigh as the injection area will have:

1. the first injection administered to the left limb using the 2-mL PFS, and
2. the second injection administered to the corresponding (contra-lateral) right limb using the 1-mL PFS.

Participants assigned to the group with the abdomen as the injection area will have:

1. the first injection administered to the lower left quadrant using the 2-mL PFS, and
2. the second injection administered to the lower right quadrant of the abdomen using the 1-mL PFS.

Whenever possible, study drug administration should be carried out by the same trained personnel with the use of proper injection techniques. Table AMBY.2 lists the interventions used in this clinical study.

Table AMBY.2. Study Interventions Administered

Intervention Name	Mirikizumab solution in a 1-mL PFS and a 2-mL PFS	Mirikizumab citrate-free solution in a 1-mL PFS and a 2-mL PFS
Unit Dose Strengths/ Dosage Levels	1 × 100 mg and 1 × 200 mg 100 mg/mL	1 × 100 mg and 1 × 200 mg 100 mg/mL
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	1 × 1-mL and 1 × 2-mL injections at site according to the IWRS	1 × 1-mL and 1 × 2-mL injections at site according to the IWRS

Abbreviations: IWRS = interactive web-response system; PFS = prefilled syringe.

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.

6.1.1. Devices

The Lilly-manufactured devices provided for use in this study are mirikizumab 1-mL and 2-mL PFSs. Pharmacy Preparation Instructions for the PFSs are part of the Study Materials provided to sites. All PCs (including malfunction, use error, and inadequate labeling) will be reported to the sponsor per instructions provided (see Section 8.3). 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 interventions received and that 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 interventions 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 separately. In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a participant-blind, randomized study. Potential bias will be reduced by central weight stratification, randomization, and blinding. The site will contact the IWRS prior to the start of study intervention administration for each participant.

All participants will be centrally randomized to mirikizumab solution formulation with weight 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.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

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 injection 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 300 mg is considered an overdose.

In the event of an overdose, the investigator should:

- contact the medical monitor immediately, and
- closely monitor the participant for any AE or SAE and laboratory abnormalities until mirikizumab no longer has a clinical effect or can no longer be detected systemically (at least 84 days postdose [Day 85]).

6.8. 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, hormone-replacement therapy, and thyroid replacement. In addition, occasional acetaminophen is acceptable at the discretion of the investigator. However, acetaminophen should not be administered on the dosing day within 4 hours prior to and 4 hours after dosing. If acetaminophen (or paracetamol) treatment is needed for pain management, the maximal allowed dose will be 3 g per 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.

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.

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:

- 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 Lilly CP, CRP, or designee should be contacted if there are any questions regarding concomitant or prior therapy.

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 CP, CRP, or designee.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or the study as a whole is handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

This section is not applicable for this single-dose study.

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,
- at the request of the participant's designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- 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, or
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit, as shown in the SoA (Section 1.3).

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 he or she repeatedly fails to return for scheduled visits and is 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 are otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

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

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

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.The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based on emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (such as equipment technical problems, venous access difficulty, or participant defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.

Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.

Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

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 (Section 1.3).

8.2.1. Physical Examinations

Physical examinations and routine medical assessments will be conducted as specified in the SoA (Section 1.3) and as clinically indicated.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological systems, and dermal and ear, nose, and throat examination. Height, weight, and BMI will also be measured and recorded at screening. Weight will be measured and recorded on Day -1, and Day 85 or ED.

A symptom-directed physical examination will be performed at Day 85 or ED, as specified in the SoA and as deemed necessary by the investigator.

8.2.2. Vital Signs

For each participant, vital signs and body temperature measurements should be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured after at least 5 minutes sitting.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals, according to the SoA (Section 1.3).

ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

ECGs will be interpreted by an investigator or qualified designee as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visits and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his or her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

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

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 or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor or designee notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), 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, AE or dose modification), then the information will be reported as an AE.

8.2.5. Pregnancy Testing

Pregnancy testing will be performed for all female participants at the time points detailed in the SoA (Section 1.3). Serum pregnancy testing will be performed at screening and Day -1. Urine pregnancy testing will be performed at Day 85 or ED if necessary. See Section 8.3.2 for more detail.

8.2.6. Safety Monitoring

The Lilly CP or CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review:

- trends in safety data,
- laboratory analytes, and
- AEs and PCs.

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6; Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing if one or more of these conditions occur:

If a participant with baseline results of...	**develops the following elevations:**
ALT or AST <1.5× ULN	ALT or AST ≥3× ULN
ALP <1.5× ULN	ALP ≥2× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and 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 a physical examination and a thorough medical history, including symptoms, recent illnesses (for example,

heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥3× ULN with hepatic signs/symptoms[a], or ALT or AST ≥5× ULN
ALP <1.5× ULN	ALP ≥3× ULN
TBL <1.5× ULN	TBL ≥2× ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5× ULN	ALT or AST ≥2× baseline with hepatic signs/symptoms[a], or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥2× baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Hepatic signs or symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, or eosinophilia greater than 5%.

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized 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,
- magnetic resonance cholangiopancreatography,
- endoscopic retrograde cholangiopancreatography,
- cardiac echocardiogram, or
- a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in the hepatic safety CRF should be performed in study participants who meet 1 or more of the following 4 conditions:

1. Elevation of serum ALT to greater than or equal to 5× ULN on 2 or more consecutive blood tests (if baseline ALT is less than 1.5× ULN)
    - In participants with baseline ALT greater than or equal to 1.5× ULN, the threshold is ALT greater than or equal to 3× baseline on 2 or more consecutive tests
2. Elevated TBL to greater than or equal to 2× ULN (if baseline TBL is less than 1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL greater than or equal to 1.5x ULN, the threshold should be TBL greater than or equal to 2× baseline
3. Elevation of serum ALP to greater than or equal to 2× ULN on 2 or more consecutive blood tests (if baseline ALP is less than 1.5× ULN)
    - In participants with baseline ALP greater than or equal to 1.5× ULN, the threshold is ALP greater than or equal to 2× baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE.

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

8.2.6.2. 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 Appendix 2 (Section 10.2.2). Laboratory results are provided to the sponsor via the central laboratory.

8.2.7. Tuberculosis Testing and Monitoring

Participants will be tested as indicated in the SoA (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.

8.2.8. Other Tests

8.2.8.1. Injection-Site Reactions

Although there will be no prospective collection of ISR information, spontaneously reported ISRs by the participant will be recorded as AEs. 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.

The ISR CRF is used to collect supplemental data on the following specific findings:

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

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.

8.2.8.2. Bleeding and Bruising Assessment

There will be no prospective collection of ISR information; the presence of visible bleeding or bruising at the injection site will be recorded on the CRF 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 the following events can be found in Appendix 3 (Section 10.3):

- AEs,
- SAEs, and
- PCs.

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 mirikizumab study (see Section 7).

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

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 AESIs (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 and or causality, or both. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3.4).

8.3.1. Timing and Mechanism for Collecting Events

Table AMBY.3 describes the timing, deadlines, and mechanism for collecting events.

Table AMBY.3. Timing 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 informed consent form	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 informed consent form	start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	SAE paper form
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
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Day 85 (±3 days) or upon ED	Within 24 hours of awareness (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
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	

Abbreviations: AE = adverse event; CRF = case report form; ED = early discontinuation; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive mirikizumab.

After learning of a pregnancy in the female partner of a study participant, the investigator will attempt to:

- obtain consent to release information from the pregnant female 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 female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following 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.

Female participants who become pregnant

The investigator will collect pregnancy information on any female 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 less than 20 weeks gestational age) or stillbirth (occurring at equal to or more than 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, he or she may learn of an SAE through spontaneous reporting.

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

8.3.3. Adverse Events of Special Interest

AESIs for this program include:

- hepatic safety,
- infections, including opportunistic and serious infections,
- hypersensitivity reactions,
- ISRs,
- cerebro-cardiovascular events,
- malignancies, and
- suicidal ideation or behavior and depression.

If any of these AESIs are reported, sites will be prompted to collect additional details and data. A PK, immunogenicity, and hypersensitivity cytokine panel (Appendix 2; Section 10.2.2) will be collected when possible for any participant who experiences an AE of hypersensitivity reaction during the study.

8.4. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 3 mL each will be collected to determine the serum concentrations of mirikizumab. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed on between both the investigator and sponsor. 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 sampling will be recorded.

8.4.1. Bioanalysis

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 enzyme-linked immunosorbent assay method.

Bioanalytical samples collected to measure mirikizumab concentrations will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, bioanalytical method cross-validation, or all.

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 Appendix 5 (Section 10.5) for information regarding genetic research.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples of approximately 10 mL each will be collected to determine antibody production against mirikizumab. To interpret the results of immunogenicity, venous blood samples will be collected at the same time points to determine the serum concentrations of mirikizumab. 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 sampling will be recorded.

TE-ADAs are defined in Section 9.3.4.1.

Immunogenicity will be assessed using a validated assay designed to detect ADAs in the presence of mirikizumab at a laboratory approved by the sponsor. Antibodies may be evaluated for their ability to neutralize the activity of mirikizumab.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and IRBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to mirikizumab. Any samples remaining after 15 years will be destroyed.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The SAP 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.

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate bioequivalence of the mirikizumab citrate-free solution formulation compared to the mirikizumab solution formulation, administered using a 1-mL and 2-mL PFS.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

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.

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

- a device malfunction,
- administration of only 1 of the 2 PFS doses, or
- administration of an incorrect dose, incomplete dose, or incorrect use of procedure instructions.

9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

9.2.2. Study Participant Characteristics

The participants' age, sex, weight, height, BMI, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

9.3. Statistical Analyses

9.3.1. General Considerations

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

PK analyses will be conducted for the PK analysis set according to the actual mirikizumab formulation. Safety analyses will be conducted for the safety analysis set.

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

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

9.3.2. Primary Endpoint Analysis

PK 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 $t_{1/2}$, CL/F, and Vz/F, may be reported.

9.3.2.1. 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 solution formulation, injection location, and weight category stratification as fixed effects. The solution formulation 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 solution formulations and then between the 3 injection locations.

The 2 solution formulations will be considered bioequivalent if the 90% CIs of the ratio of geometric least squares means fall within 0.8 to 1.25.

In addition, the t_{max} of mirikizumab between the solution formulations will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference, 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, will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.3.4. Exploratory Analysis

9.3.4.1. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADAs and with TE-ADA may be tabulated. TE-ADAs are defined as those with a titer 2-fold (1 dilution) or greater than the minimum required dilution if no ADAs are detected at baseline (treatment-induced ADA) or those with a 4-fold or greater (2 dilutions) increase in titer compared to baseline if ADAs are detected at baseline (treatment-boosted ADA). For the TE-ADA+ participants, the distribution of maximum titers may be described. The frequency of neutralizing antibodies may also be tabulated in TE-ADA+ participants.

The relationship between the presence of antibodies to mirikizumab and the PK parameters and pharmacodynamic response including safety and efficacy may be assessed.

9.3.4.2. 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 SAP.

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 440 (approximately 220 participants in the mirikizumab solution [reference] group and approximately 220 participants in the mirikizumab citrate-free solution [test] group) participants may be enrolled. This is to ensure that approximately 368 participants (184 participants in the mirikizumab solution [reference] group and 184 participants in the mirikizumab citrate-free solution [test] group) complete the study for the primary analysis.

Within each weight category, participants will be assigned to an SC injection site of either the arm, thigh, or abdomen (approximately 73 participants per injection site for the reference and test arms).

A sample size of 184 participants per treatment group will provide approximately 90% power that the 90% CI of the geometric mean ratio of C_{max} and AUC between groups will fall within the equivalence range of 0.8 to 1.25. This sample size calculation was based on the assumptions that the PK parameters have log-normal distribution, the %CV of C_{max} and AUC are approximately 44% (based on the PFS arm of Study AMBX), the expected ratio of geometric means is 0.91 (based on the results of Study I6T-MC-AMBV), and the %CV is the same for participants from each treatment group.

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,
- ISO 14155,
- applicable ICH GCP guidelines, and
- applicable laws and regulations.

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

Any amendments to the protocol will require IRB 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB,
- notifying the IRB of SAEs or other significant safety findings as required by IRB 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, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- 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 participant or the participant's legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives 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 or study center.

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant 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.

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

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

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 study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone 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 data set 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.

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.

Source data may include laboratory tests, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct 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, regulatory agencies, or all, 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 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 system(s) 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 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 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 Section 10.1.6.

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the 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, follow-up, or both.

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.

10.2. Appendix 2: Clinical Laboratory Tests

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

Pregnancy testing will be conducted as detailed in the SoA (Section 1.3).

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests[a]

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Cell morphology
- Absolute counts and/or % of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Clinical Chemistry
- 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
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Leukocytes
- Blood
- Nitrite
- Microscopy (if dipstick abnormal; blood, protein, nitrites, or leukocyte esterase is positive)

Other Tests
- Ethanol testing[c]
- Urine drug screen[c]
- Pregnancy test (females only)[d]
- FSH (females only, as applicable)[b]
- QuantiFERON®-TB Gold[b]

Serology
- Hepatitis B surface antigen[b]
- Hepatitis B DNA[b]
- Hepatitis C antibody[b]
- HIV[b]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

Note: Results of these assays will be validated by the local or central laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Performed locally at screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated.

[b] Performed at screening only.

[c] Urine drug screen and ethanol tests may be repeated locally at additional time points at the discretion of the investigator.

[d] Serum pregnancy test to be performed at screening and Day -1. Urine pregnancy test to be performed locally at Day 85 or early discontinuation.

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.

Protocol I6T-MC-AMBY Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Local clinical laboratory tests and pregnancy tests[a]	12	1	12
Central clinical laboratory tests[a]	4.5	5	22.5
Pharmacokinetics	3	15[b]	45
Immunogenicity	10	4	40
Pharmacogenetics	10	1	10
Total			174.5
Total for clinical purposes			180

[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 test 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) ADA mirikizumab (LY3074828) concentration

Abbreviations: ADA = antidrug antibodies; IL = interleukin.

[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 ISO 14155.

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.3.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, are 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, intensity of the condition, or both. • 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 Adverse Event 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. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social, convenience admission to a hospital, or both). • 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 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been 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.
d. Results in persistent disability or 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.
e. Is a congenital anomaly or birth defect • Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. 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.
g. 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:
  o Deficiencies in labeling information, and
  o Use errors for device or drug-device combination products due to ergonomic design elements of the product.
• PCs 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.
• Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
• An event may meet the definition of both a PC and an AE or SAE. In such cases, it should be reported as both a PC and as an AE or SAE.

10.3.4. Recording and Follow-Up of Adverse Event, Serious Adverse Events, and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE, SAE, or 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, or PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE or 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 or SAE. In such cases, it should be reported as both a PC and as an AE or 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 or 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 or 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, 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 or SAE. The investigator will use clinical judgment to determine the relationship. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and 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, Product Information, or both for marketed products, in their assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he or she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature, causality, or both 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 post-mortem findings including histopathology.

10.3.5. Reporting of Serious Adverse Events

Serious Adverse Event Reporting via SAE Report
• Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE Report.

10.3.6. Regulatory Reporting Requirements

Serious Adverse Event Regulatory Reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, 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, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Women of childbearing potential

Adult females are considered WOCBP unless they are WNOCBP.

Women not of childbearing potential

Females are considered WNOCBP if they:

- have a congenital anomaly such as Müllerian agenesis,
- are infertile due to surgical sterilization, or
- are postmenopausal.

Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, bilateral tubal ligation, bilateral tubal occlusion, or bilateral oophorectomy. Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal state

The postmenopausal state is defined as a woman:

- at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, medical history, or physical examination; or
- aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone greater than 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 hormone replacement therapy.

*Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Male Participants

No male contraception is required except in compliance with specific local government study requirements.

Female Participants

Women not of childbearing potential

WNOCBP are not required to use contraception.

Women of childbearing potential

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	**Must not…**

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	**Condition**
Contraception	Agree to use 1 highly effective method of contraception or a combination of 2 effective methods of contraception. These forms of contraception must be used for the duration of the study.

All females will receive pregnancy testing and must have a negative serum test result at screening followed by a negative serum result within 24 hours prior to treatment exposure. See the protocol SoA (Section 1.3) for subsequent pregnancy testing requirements.

Examples of different forms of contraception:

Methods	**Examples**
Highly effective contraception (less than 1% failure rate)	• combination oral contraceptive pill, • progestin-only contraceptive pill (mini-pill), • implanted contraceptives, • injectable contraceptives, • contraceptive patch (only women less than 198 pounds or 90 kg), • total abstinence, • vasectomy (if only sexual partner), • fallopian tube implants (if confirmed by hysterosalpingogram), • combined contraceptive vaginal ring, or • intrauterine devices.
Effective contraception	• male or female condoms with spermicide, or • diaphragms with spermicide or cervical sponges

	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective. Use of male and female condoms as a double barrier method is not considered effective.
Ineffective forms 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 or 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 molecular subtype of the disease being treated. Therefore, where local regulations and IRB 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 or assays including diagnostic tests related to mirikizumab, interventions of this drug class and IL-23-mediated autoimmune disease, or all. Genetic research may consist of the analysis of 1 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 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 or study interventions of this class or indication continues but no longer than 15 years or amother 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 must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: Ig = immunoglobulin; INR = international normalization ratio.

a Not required if anti-actin antibody is tested.

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

c Not required if anti-smooth muscle antibody is tested.

d Assayed ONLY by investigator-designated local laboratory; no central testing available.

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

Refer to Appendix 3 (Section 10.3) for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
%CV	percent coefficients of variation
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
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
blinding	A single-blind study is one in which the investigator, the investigator's staff, or both are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator, investigator's staff, or both and the participant are not.
CD	Crohn's disease
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra-vascular administration
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.
COVID-19	coronavirus disease-19
CP	clinical pharmacologist

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.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
device deficiencies	Equivalent to product complaint
ECG	electrocardiogram
ED	early discontinuation
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
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
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.
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.
IRB	institutional review board
ISO	International Organization for Standardization
ISR	injection-site reaction
IV	intravenous
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 5 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
SAP	statistical analysis plan
SC	subcutaneous
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
$t_{1/2}$	half-life associated with the terminal rate constant
TB	tuberculosis
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibodies
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 to maximum observed drug concentration
UC	ulcerative colitis
ULN	upper limit of normal
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
VAS	visual analog scale
Vz/F	apparent volume of distribution during the terminal phase after extra-vascular administration

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.

Amendment (a): 11 October 2022

Overall Rationale for the Amendment:

Amendment (a) corrects an error in the IND number shown on the cover page and in the Synopsis (Section 1).

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	*11-October-2022*
Original Protocol	*21-September-2022*

11. References

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