Title Page

Protocol Title: A Bioequivalence Study of Injections of Mirikizumab Solution Using an Investigational 1-mL Pre-Filled Syringe and an Investigational 1-mL Autoinjector in Healthy Participants

Protocol Number: I6T-MC-AMBW
Amendment Number: This is the initial protocol

Compound: Mirikizumab (LY3074828)

Study Phase: 1

Short Title: A bioequivalence study of injections of mirikizumab solution using an investigational 1-mL pre-filled syringe and an investigational 1-mL autoinjector in healthy participants

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 125444

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Bioequivalence Study of Injections of Mirikizumab Solution Using an Investigational 1-mL Pre-Filled Syringe and an Investigational 1-mL Autoinjector in Healthy Participants

Short Title: A bioequivalence study of injections of mirikizumab solution using an investigational 1-mL pre-filled syringe and an investigational 1-mL autoinjector in healthy participants.

Rationale:

Study I6T-MC-AMBW (AMBW) will assess the pharmacokinetics (PK), safety, and tolerability of a 200-mg subcutaneous (SC) dose of mirikizumab (LY3074828) solution formulation administered using an investigational manual 1-mL pre-filled syringe (PFS) or an investigational 1-mL autoinjector (AI). Both devices will be evaluated at 3 different injection sites (arm, thigh, and abdomen) in order to expand the options for administration in patient use. The study will provide data to bridge PFS administration of mirikizumab, with the investigational AI device planned for use in subsequent studies and patient use.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PK of mirikizumab after SC administration of 200-mg doses of solution formulation using a 2× 1 mL PFS and a 2× 1 mL AI in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety and tolerability of mirikizumab in healthy participants	• TEAEs and SAEs

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

Overall Design

Study AMBW is a Phase 1, open-label, 2-arm, randomized, parallel-design, single-dose, multi-site study in healthy participants.

Screening

All participants will be screened within 28 days prior to enrollment. At screening, participants will be stratified into 1 of 3 weight categories (less than 70 kg, 70 to 80 kg, and more than 80 kg).

Treatment and Assessment Period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1.

Within the 3 weight categories, participants will be randomized using a computer-generated allocation code:

- 1:1 to delivery device (either PFS [reference] or AI [test])
- within each delivery-device group 1:1:1 to injection site (arm, thigh, or abdomen)

On Day 1, participants will receive a 2× 1mL (total 200 mg mirikizumab) SC dose delivered via the device and in the location assigned by the randomization.

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 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 sign measurements, recording of adverse events (AEs), physical examination, and immunogenicity.

Disclosure Statement: This is an open-label, parallel group bioequivalence study with 2 arms.

Number of Participants:

Up to approximately 240 participants may be enrolled so that approximately 216 participants (108 in the PFS group and 108 in the AI group) complete the study.

Intervention Groups and Duration:

All participants will be screened within 28 days prior to enrollment. A single dose of mirikizumab will be administered SC by either PFS or AI into the arm, thigh, or abdomen on Day 1 and participants will be followed through Day 85.

Data Monitoring: No

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

Study Schedule Protocol I6T-MC-AMBW

	Screening	**Study Day**															**Comments**
Procedure	-28 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 ±2d	71 ±3d	85 ±3d or ED	
Informed consent	X																	
Medical history and demographics	X																	
Review and confirm inclusion and exclusion criteria	X	X																
Admission to CRU		X																
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.
Randomization			X															Participants will be randomized 1:1 to 1 of 2 delivery devices and 1:1:1 to 1 of 3 injection locations per delivery device.
Height, weight, and BMI	X																X	Only weight will be measured on Day 85 or ED.
Body temperature	X	X	P	X	X	X	X	X	X	X		X		X		X	X	
Physical examination		X															X	Full physical examination at Day -1. Symptom-directed examinations and assessments at other times, and as deemed necessary by the investigator.

	Screening	Study Day																Comments
Procedure	-28 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 ±2d	71 ±3d	85 ±3d or ED	
Vital signs (pulse rate and blood pressure) (sitting) (hours)	X	X	P, 2 to 4					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 upon between Lilly and the investigator.
Clinical laboratory tests	X	X	P	X				X		X							X	See Appendix 10.2, Clinical Laboratory Tests, for details.
Serology	X																	See Appendix 10.2, Clinical Laboratory Tests, 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.
FSH	X																	Females only. See Appendix 10.4.
Pregnancy test (females only)	X	X															X	Serum pregnancy test will be performed at screening and Day -1. Urine pregnancy test will be performed at Day 85 or ED. See Appendix 10.4.
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															See Section 6.1.

	Screening	**Study Day**															**Comments**
Procedure	-28 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 ±2d	71 ±3d	85 ±3d or ED	
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 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; P = pre-dose; PK = pharmacokinetic; TB = tuberculosis.

2. Introduction

2.1. Study Rationale

Study I6T-MC-AMBW (AMBW) will assess the pharmacokinetics (PK), safety, and tolerability of a 200-mg subcutaneous (SC) dose of mirikizumab (LY3074828) solution formulation administered using an investigational manual 1-mL pre-filled syringe (PFS) or an investigational 1-mL autoinjector (AI). Both devices will be evaluated at 3 different injection sites (arm, thigh, and abdomen) in order to expand the options for administration in patient use. The study will provide data to bridge PFS administration of mirikizumab, with the investigational AI device planned for use in subsequent studies and patient use.

2.2. Background

Mirikizumab is a humanized immunoglobulin G4–variant monoclonal antibody that is directed against the p19 subunit of interleukin (IL)-23 and does not bind IL-12. Mirikizumab is being developed for the treatment of autoimmune diseases, including psoriasis, Crohn's disease (CD), and ulcerative colitis (UC), in which the IL-23 pathway is thought to have a significant pathogenic role.

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

Bioavailability of mirikizumab when administered SC by either PFS or AI at different injection sites was evaluated in study I6T-MC-AMBE (AMBE). No statistically significant difference in exposure following administration with the PFS compared to the AI was noted. Comparison of AUC by injection location showed the highest AUC ratio was 1.5 for the PFS (thigh versus abdomen) and 1.4 for the AI (abdomen versus arm) (see Section 2.2.4).

Administration of a 200-mg dose via AI would improve ease of administration in patients with UC, thus there is a need to investigate the bioavailability of this dose administered by AI at various injection sites.

2.2.1. Safety

As of the Investigator's Brochure (IB) cutoff date (06 February 2019), there have been approximately 1061 participants in studies on mirikizumab. These include 236 participants with psoriasis, 230 participants with UC, 186 participants with CD, and 409 healthy participants who were exposed to either placebo or mirikizumab at single doses ranging from 5 to 2400 mg. Across Phase 2 studies, multiple doses of mirikizumab have been studied at a maximum of 1000 mg intravenous (IV) and 300 mg SC. Two ongoing Phase 3 studies are being conducted in participants with UC, receiving an induction dose of 300 mg IV on Weeks 0, 4, and 8 (Study I6T-MC-AMAN) followed by maintenance dosing in those achieving clinical response of 200 mg SC Q4W (Study I6T-MC-AMBG).

In clinical pharmacology studies, single IV doses of up to 2400 mg have been administered to healthy Caucasian and Japanese participants (Study I6T-MC-AMAD). No dose-related safety or tolerability issues were observed in this study or in other ongoing clinical pharmacology studies

with single SC doses ranging from 120 to 2400 mg and at multiple doses up to a maximum of 300 mg.

Six completed studies (I6T-MC-AMAL [AMAL], I6T-MC-AMAE [AMAE], I6T-MC-AMAQ [AMAQ], I6T-MC-AMAR [AMAR], I9O-MC-AABC [AABC], and AMBE) compared the bioavailability, safety, and tolerability of various formulations of mirikizumab delivered by either PFS, AI, or SC infusion. Mirikizumab was well tolerated; however, asymptomatic reductions in neutrophil counts were seen in a minority of participants. The incidence of injection-site reactions (ISRs) was highly variable across studies due to their differing designs and treatments; however, ISRs comprised mostly mild to moderate pain and very slight to well-defined erythema.

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

In Phase 1 studies with healthy participants or participants with psoriasis that were integrated for safety analyses, no deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported. Of the studies that have completed since the IB cutoff date, there was 1 SAE of malignant brain neoplasm that led to discontinuation of a healthy participant in Study AABC; the event was not considered to be related to study treatment by the investigator. In Phase 2 and 3 studies with participants having psoriasis, UC, or CD, up to the IB cutoff date, 1 death occurred from myocardial infarction and 1 death occurred from lung cancer, neither of which was considered related to study drug by the investigator,

Serious adverse events 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 in the IB, the most frequently reported (≥5.0%) treatment-emergent adverse events (TEAEs) in the 442 healthy participants and participants with psoriasis treated with mirikizumab were ISRs (including injection-site pain), nasopharyngitis, and headache. Three of the integrated clinical pharmacology studies (AABA, AMAL, AMAE) and 3 subsequently completed studies (AMAR, AMBE, and AABC) actively observed injection sites to allow recording of events such as erythema, swelling, and induration.

Studies AMBE and AMAQ showed that administration of mirikizumab using the 1-mL AI is safe and well-tolerated in healthy participants based on TEAEs and injection-site pain.

Treatment-emergent adverse events 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 40%.

Study AMBE investigated the PK, safety and tolerability of and pain associated with a 125-mg SC dose of mirikizumab solution formulation administered using the investigational manual PFS, or the investigational AI. Doses were administered as 1× 1-mL SC injections into the arm, thigh, or abdomen. When all injection sites were considered together, the study showed no statistically

significant difference in exposure following administration with the PFS compared to the AI; however, the upper bounds of the 90% CI for AUC(0-t_{last}), AUC(0-∞), and C_{max} were greater than the 1.25 bioequivalence boundary. Comparison of exposure by injection location demonstrated statistically significant differences (that is the 90% CI for the ratio of geometric least squares means excluded unity) when comparing the 2 administration methods:

- PFS and AI administration into the abdomen
    - exposure increased by up to 62% following administration using the AI compared to PFS

And for each administration method the following statistically significant differences were noted between injection sites:

- AI administration into the arm compared to the abdomen,
    - exposure decreased by up to 36% following administration into the arm compared to the abdomen
- PFS administration into the thigh compared to the abdomen.
    - exposure increased by up to 73% following administration into the thigh compared to the abdomen.

2.2.5. Immunogenicity

Treatment-emergent antidrug antibodies (TE-ADA) 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 with the development of immunogenicity to mirkizumab and patients reporting injection site reactions/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 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/C, human immunodeficiency virus (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.

Healthy participants are not expected to derive any benefit from participating in studies in which mirikizumab is administered.

As this study will use PFS and AIs, device-based risks will be evaluated. Possible device-based risks include local effects such as pain at the injection sites from either the needle or the solution entry into the SC tissue, swelling, erythema, bleeding, and bruising. These risks are mitigated by training of investigative site staff on proper injection techniques. Systemic effects may include sweating, feeling faint, or fever, as a sign of infection.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mirikizumab may be found in the IB and risks as well as reasonably anticipated adverse device effects of the AI are found in the device IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PK of mirikizumab after SC administration of 200-mg doses of solution formulation using a 2× 1-mL PFS and a 2× 1-mL AI in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To describe the safety and tolerability of mirikizumab in healthy participants	• TEAEs and SAEs
Tertiary/Exploratory	
• To evaluate the effect of mirikizumab delivery device on immunogenicity • To evaluate the impact of injection-site location on PK	• TE-ADA • C_{max}, AUC(0-∞), and AUC(0-t_{last})

Abbreviations: AI = autoinjector; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; PFS = pre-filled 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 AMBW is a Phase 1, open-label, 2-arm, randomized, parallel-design, single-dose, multi-site study in healthy participants.

Screening

All participants will be screened within 28 days prior to enrollment. At screening, participants will be stratified into 1 of 3 weight categories (less than 70 kg, 70 to 80 kg, and more than 80 kg).

Treatment and Assessment Period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1.

Within the 3 weight categories, participants will be randomized (Table AMBW.1) using a computer-generated allocation code (Section 6.3):

- 1:1 to delivery device (either PFS [reference] or AI [test])
- within each delivery-device group 1:1:1 to injection site (arm, thigh, or abdomen)

On Day 1, participants will receive a 2× 1mL (total 200 mg mirikizumab) SC dose delivered via the device and in the location assigned by the randomization.

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 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 sign measurements, recording of AEs, physical examination, and immunogenicity.

Table AMBW.1. Study AMBW Stratification and Randomization Plan

Weight Category (Participants)	Injection Device	Subcutaneous Injection Location[a]	Desired Number of Participants
Low <70 kg (72 participants)	2 x 1-mL PFS (Reference)	Arm	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Abdomen	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Thigh	12
	2 x 1-mL AI (Test)		12
Medium 70 – 80 kg (72 participants)	2 x 1-mL PFS (Reference)	Arm	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Abdomen	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Thigh	12
	2 x 1-mL AI (Test)		12
High >80 kg (72 participants)	2 x 1-mL PFS (Reference)	Arm	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Abdomen	12
	2 x 1-mL AI (Test)		12
	2 x 1-mL PFS (Reference)	Thigh	12
	2 x 1-mL AI (Test)		12

Abbreviations: AI = autoinjector; PFS = prefilled syringe.

a. A dose of study intervention will consist of 2 subcutaneous injections of mirikizumab into the arm, thigh, or abdomen. All doses will be administered by trained site staff.

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. 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.

Participants will be randomized 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.

Previous population PK analyses have shown that patients with a lower body weight tended to have a lower clearance and/or central volume of distribution. 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, approximately equal numbers of participants in each weight category are proposed to avoid a large difference in mean weight between the test and the reference delivery-device groups. A participant population of 72 per weight group is an approximate target with the recommended weight categories selected based on the distribution of weights in prior studies. The number of participants assigned to each delivery device and the number of participants assigned to each site of injection is desired to be balanced.

A parallel-group design is chosen because a crossover design is impractical for mirikizumab, which has a half-life of approximately 10.5 days. Additionally, a crossover study could confound PK data if participants develop neutralizing antidrug antibodies (ADAs).

4.3. Justification for Dose

The 200-mg dose of mirikizumab chosen for this study is based on

- 200 mg being found safe and tolerable in Phase 2 studies,
- 200 mg being evaluated in the Phase 3 UC development program, and
- the volume of solution that can be delivered through 2 PFS/AI (1 mL per PFS/AI) and the solubility of mirikizumab (100 mg/mL).

The 200-mg dose administered as 2× 1-mL injections is the maintenance dosing regimen being used in Phase 3 studies and anticipated for use once marketed.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit shown in the Schedule of Activities (SoA; Section 1.3).

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

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 electrocardiogram (ECG). The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat the following screening tests and procedures: weight, 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 and Sex

1. are between 18 and 65 years of age
2. are males or non-pregnant females of childbearing or non-childbearing potential.
    - Reproductive definitions and contraceptive requirements are provided in Appendix 4 (Section 10.4)

Weight

3. have body mass index (BMI) within the range 18.0 to 32.0 kg/m^2 (inclusive)

Type of Participant and Disease Characteristics

4. participants who are overtly healthy, as determined by medical evaluation including:
    - medical history
    - physical examination
    - clinical laboratory tests,
    - ECG and
    - vital signs.
5. have clinical laboratory test results within 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
6. have venous access sufficient to allow for blood sampling as per the protocol
7. agree not to donate blood or plasma until after the end of their participation in the study
8. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

10. have known allergies to mirikizumab, related compounds, or any components of the formulation, or history of significant atopy
11. have self-perceived dullness or loss of sensation in either arm or thigh or on either side of the abdomen
12. have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study
13. have an abnormal blood pressure, pulse rate, or temperature determined to be clinically significant by the investigator
14. have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, neurological, or dermatological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study intervention; or of interfering with the interpretation of data
15. Infections:
    a. have had a serious infection (such as, pneumonia, cellulitis, sepsis); have been hospitalized or have received intravenous 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 and/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.
16. have known or ongoing psychiatric disorders deemed clinically significant by the investigator

17. regularly use known drugs of abuse and/or show positive findings on drug screening
18. show evidence of HIV infection and/or positive HIV antibodies
19. show evidence of hepatitis C and/or positive hepatitis C antibody
20. show evidence of hepatitis B and/or positive hepatitis B surface antigen or hepatitis B core antibody
21. are females who are pregnant or lactating
22. 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
23. have significant allergies to humanized monoclonal antibodies
24. have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
25. have had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
26. have had breast cancer within the past 10 years

Prior/Concomitant Therapy

27. intend or are likely to use over-the-counter or prescription medication within 7 days prior to dose administration. Participants on stable doses of some medications (such as, statins and antihypertensives) may be eligible for enrolment following discussion with the sponsor (Section 6.5)
28. have ever received anti-IL-12p40 antibodies (eg, ustekinumab [Stelara®]) or anti-IL-23p19 antibodies (eg, risankizumab [BI-655066], brazikumab [MEDI2070], guselkumab [CNTO 1959], or tildrakizumab [MK-3222]) for any indication, including investigational use
29. 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)
30. have been treated with oral steroids within 1 month of screening, or intend to during the study (mild topical steroid creams/ointments are permitted, with the exception of the injection day as specified in Section 6.5)

Prior/Concurrent Clinical Study Experience

31. 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
32. have participated in a clinical trial involving an investigational product within 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 Day 1
33. have previously completed or withdrawn from this study or any other study investigating mirikizumab, and have previously received mirikizumab

Other Exclusions

34. 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
35. are Lilly or Covance employees
36. have donated blood or plasma of more than 500 mL within 1 month prior to screening
37. 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) (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)
38. have a tobacco consumption of more than 10 cigarettes per day (or equivalent), or who are unwilling to abide by the CRU smoking guidelines described in Section 5.3.2
39. have excessive tattoos, scars, moles, skin hyperpigmentation, birth marks, or stretch marks over either arm, either thigh, or either side of the abdomen that would interfere with injection site assessments
40. in the opinion of the investigator, 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. Caffeine, Alcohol, and Tobacco

Caffeine

Participants will not be allowed to consume caffeinated products during study visits and 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/exercise; however, they should not undertake vigorous or prolonged exercise within 48 hours prior to any visit in which laboratory safety tests will occur (Day -1, Day 1, Day 3, Day 15, Day 29, and Day 85). While certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet all inclusion/exclusion criteria, are not alternates, and subsequently are not enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, unless stated in Section 5. Repeating of laboratory tests during the screening period or repeating screening assessments to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

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

6.1. Study Intervention Administered

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

Table AMBW.2. Study Interventions Administered

Study Intervention	Mirikizumab PFS	Mirikizumab AI
Dosage Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s)	100 mg/mL in a 1-mL PFS	100 mg/mL in a 1-mL AI
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	2× 1-mL injections at site according to the randomization	2× 1-mL injections at site according to the randomization

Abbreviations: AI = autoinjector; PFS = prefilled syringe.

6.1.1. Administration Details

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

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

Participants randomized to the group with the abdomen as the injection area will have

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

6.1.2. Medical Devices

1. The Lilly-manufactured medical devices (or devices manufactured for Lilly by a third party) provided for use in this study are
    a. The fully assembled mirikizumab 1-mL PFS
    b. The fully assembled mirikizumab 1-mL AI.
2. Instructions for medical device use will be provided as part of the Study Materials provided to investigators and sites.

3. All device deficiencies (including malfunction, use error, and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.7) and appropriately managed by the sponsor.
4. Each device will be labelled according to the country's regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided separately.

Note: 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 an open-label randomized study. Potential bias will be reduced by central randomization.

On Day 1, participants will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment, within their weight stratification category, to one of the 2 possible delivery devices (PFS or AI) and 3 possible injection sites (arm, thigh, or abdomen), according to the randomization schedule generated prior to the study by the Statistics Department at Covance. Each participant will be dispensed study intervention labeled with his/her unique randomization number.

6.4. Study Intervention Compliance

Participants are dosed at the site; they will receive study intervention directly from the investigator or designee, under medical supervision. The date, time, and location of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. 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. No more than 3 g of acetaminophen will be permitted in any 24-hour period. Inclusion of participants on any other concomitant medication (eg, statins and anti-hypertensives) is contingent upon approval following consultation with the sponsor.

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
- dosage information including dose and frequency for concomitant therapy of special interest.

The Lilly clinical pharmacologist (CP) or clinical research physician (CRP) 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 or CRP.

6.6. Dose Modification

Not applicable for this single-dose study.

6.7. Intervention after the End of the Study

Not applicable for this study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Not applicable for this single-dose study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrolled in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study at that time.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued unless there are extenuating circumstances that make it medically necessary for the participant to continue in the study.

If the investigator and the sponsor CP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CP to allow the inadvertently enrolled participant to continue in the study. The documented approval must contain the benefit/risk assessment and a robust clinical justification that continuing in the study will not jeopardize the participant's safety. All inadvertently enrolled participants will complete safety follow-up as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

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 are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

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

Protocol waivers or exemptions are not allowed.

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 upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF. 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

A complete physical examination will be conducted on Day -1 and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded at screening.

A symptom-directed physical examination will be performed at other visits, as specified in the SoA and as deemed necessary by the investigator.

8.2.2. Vital Signs

For each participant, vital signs 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.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during the study, if warranted.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes.

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

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA (Section 1.3). Electrocardiograms 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. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified investigator (the physician or qualified designee) at the site 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 visit(s) and for immediate participant management, should any clinically relevant findings be identified.

Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Assessments

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 report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

The laboratory reports must be filed with the source documents.

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

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

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

If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered

clinically significant by the investigator (for example, SAE or AE), then the results must be recorded in the eCRF.

If a central vendor is used for the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

8.2.4.1. Tuberculosis Testing

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.

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

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

8.2.5. Other Tests

8.2.5.1. Injection-Site Reactions

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

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

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

If injection-site pain is reported at any time during the study, the intensity of pain will be quantified using the 100-mm validated pain visual analog scale (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.

8.2.5.2. Bleeding/Bruising Assessment

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

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

8.2.6. Safety Monitoring

The Lilly CP or clinical research physician/scientist 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.

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

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL), and direct bilirubin, should be repeated within 48 to 72 hours if possible with additional testing for gamma-glutamyltransferase and creatine kinase, to confirm the abnormality and to determine if it is increasing or decreasing, if 1 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 ≥2× baseline (except for participants with Gilbert's syndrome)

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 CP. At a minimum, this evaluation should include 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 lab 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 1 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*, 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*, or ALT or AST ≥3× baseline
ALP ≥1.5× ULN	ALP ≥2× baseline
TBL ≥1.5× ULN	TBL ≥1.5× baseline (except for participants with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time - international normalized ratio (PT-INR); tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computerized tomography [CT] scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated CP, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

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

Additional hepatic safety data collection in the hepatic safety eCRF should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

8.3. Adverse Events and Serious Adverse Events

The definitions of device-related safety events, (adverse device effects [ADEs], unanticipated adverse device effects [UADEs], and serious adverse device effects [SADEs]), can be found in Appendix 8 (Section 10.8). Product complaints are covered in Section 8.3.7.

Adverse 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 the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the 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.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time of signing of the ICF until participation in study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received mirikizumab. However, if an SAE occurs after signing the ICF, but prior to receiving mirikizumab, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs reported after a participant has received mirikizumab will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6) 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). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

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

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

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

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 10.4 (Section 10.4) to collect data on the outcome for both mother and fetus.

8.3.6. Adverse Events of Special Interest

The following AEs of special interest will be used to determine the safety and tolerability of mirikizumab administered through PFS or AI in this clinical study:

- infection
- systemic allergic/hypersensitivity reactions.

If infections or allergic/hypersensitivity reactions are reported, site staff will provide details on these events as instructed on the eCRF. A PK, immunogenicity, and hypersensitivity cytokine panel (Appendix 7, Section 10.7) will be collected when possible for any participant who experiences an AE of systemic allergic/hypersensitivity reaction during the study.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

The sponsor collects product complaints on study interventions and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

Note: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor. The method of documenting Medical Device Deficiency is provided in Appendix 8 (Section 10.8).

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

Device deficiencies will be reported to the sponsor within 72 hours after the investigator determines that the event meets the definition of a medical device deficiency.

The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method provided in the form should be utilized.

8.3.7.3. Follow-up of Product Complaints

Follow-up applies to all participants.

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

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

8.3.7.4. Regulatory Reporting Requirements for Product Complaints

The investigator will promptly report all device related product complaints to the sponsor to facilitate timely regulatory reporting.

As required by local regulations, the investigator will report to their IRB/IEC any unanticipated adverse device effect or UADE (unanticipated problem that resulted in an SAE), or any product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

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

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the CP immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.

8.5. Pharmacokinetics

Blood samples of approximately 3 mL will be collected for measurement of serum concentrations of mirikizumab as specified in the SoA (Section 1.3.).

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

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5.1. 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 (ELISA) 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, and/or bioanalytical method cross-validation.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

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

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. 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.

Treatment-emergent ADAs are defined in Section 9.4.4.

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 will 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.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate PK following administration using PFS and AI.

9.2. Sample Size Determination

Up to approximately 240 participants may be enrolled so that approximately 216 participants (108 in the PFS [reference] group and 108 in the AI [test] group) complete the study.

A sample size of 108 participants per treatment group will provide approximately 90% power that the 90% confidence interval (CI) of the geometric mean ratio of maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) between groups will fall within 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 percent coefficients of variation (%CV) of C_{max} and AUC are approximately 40% (based on previous trials), the expected ratio of geometric means is 1.07, and the %CV are the same for participants from each treatment group.

Participants who are randomized but not administered treatment and participants who do not complete PK sampling through Day 85 may be replaced to ensure that approximately 216 participants (108 in each group) complete the study.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants randomly assigned to study intervention.
Safety	All participants randomly assigned to study intervention and who receive study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All enrolled participants who receive a full dose of study intervention and have evaluable PK data.

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant characteristics

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

9.4. Statistical Analyses

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

Any change to the data analysis methods described in the protocol will require an amendment, only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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

9.4.1. General Considerations

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

No adjustments for multiple comparisons will be made.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameter Estimation

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

The primary parameters for analysis will be the C_{max}, AUC from time zero to infinity (AUC[0-∞]), and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]) of mirikizumab. The secondary parameter for analysis will be the time to maximum observed drug concentration (t_{max}) of mirikizumab. Other noncompartmental parameters, such as half-life associated with the terminal rate constant ($t_{1/2}$), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration (Vz/F), may be reported.

9.4.2.2. Pharmacokinetic Statistical Inference

The C_{max}, AUC(0-∞), and AUC(0-t_{last}), will be log-transformed and analyzed using a linear fixed-effects model. The model will include delivery device, injection location, and weight stratification as fixed effects. The dosing regimen differences between AI and PFS administrations 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 delivery devices and then between the 3 injection locations.

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

The t_{max} of mirikizumab between AI and PFS administrations 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.

9.4.3. Safety Analyses

9.4.3.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with study intervention as perceived by the investigator. Symptoms reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of study intervention- and device-related SAEs and any related product complaints will be reported.

9.4.3.2. 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 analyses will be performed if warranted upon review of the data.

9.4.4. Evaluation of Immunogenicity

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

The relationship between the presence of antibodies and PK and safety parameters of mirikizumab may be assessed.

9.5. Interim Analyses

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.

9.6. Data Monitoring Committee (DMC)

No data monitoring committee is required for this study.

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 (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs and/or UADEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

Participants must be re-consented 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.

10.1.3. 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant 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 his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure 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.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

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

Reports

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

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.

10.1.5. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or electronic CRF 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. Source data may include laboratory tests, medical records, and clinical notes.

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

Data management and monitoring

The Monitoring Plan includes

- 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
- requirements
- handling of noncompliance issues
- monitoring techniques.

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).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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 retention and audits

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 CTA 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.

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 sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC 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 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 sponsor will be encoded and stored in the global product complaint management system.

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

The definition of what constitutes source data can be found in 10.1.6.

10.1.7. Study and Site Start and Closure

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

Site Closure

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

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

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

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

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

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

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 each laboratory safety report.

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 % of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

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

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

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorous
- Glucose (random)
- BUN
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Direct bilirubin
- ALP
- AST
- ALT
- Creatinine

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

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

a. Performed locally at Screening and Day -1 and centrally at Day 1 predose and all postdose timepoints 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-AMBW Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Local clinical laboratory 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.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to 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 sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via SAE Report

- Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames.

- Contacts for SAE reporting can be found in the SAE report.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are considered not of childbearing potential:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion, or bilateral tubal ligation), congenital anomaly such as mullerian agenesis; or
B. post-menopausal – defined as either
   i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
   ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
   iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy.

Contraception Guidance:

Females

All female participants must test negative for pregnancy prior to initiation of treatment, as indicated by negative serum pregnancy test at the screening visit and Day -1 prior to exposure to mirikizumab

- Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
- Otherwise, women of childbearing potential participating in this study must agree to use 1 highly effective method (<1% failure rate) of contraception or a combination of 2 effective methods of contraception from the time of signing the ICF to 12 weeks following dosing with the study intervention)
    - Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, an intrauterine device, or vaginal ring) or a combination of 2 effective methods of contraception

(such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The participant may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not reliable or acceptable methods. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined

- Women not of childbearing potential may participate.

Males

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

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 obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and 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, including 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 still birth (occurring at greater 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 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

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

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

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

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

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

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

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, International Normalized Ratio (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)
Hepatis 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 [d]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.
[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Recommended Laboratory Testing for Hypersensitivity Events

Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected.

- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample after approximately 4 weeks.

Clinical Lab Tests for Hypersensitivity Events

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
LY3819253 anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
LY3819253 concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. Urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Collect a follow-up urine sample after approximately 4 weeks. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, collect a urine sample for N-methylhistamine testing.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **NOTE:** The basophil activation test is an in vitro cell based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE.
Complement (C3, C3a and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: IgE = immunoglobulin E; PK = pharmacokinetic.

10.8. Appendix 8: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (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.

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational 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. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE and UADE

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

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term ‘life-threatening' in the definition of serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. 2. A permanent impairment of a body structure or a body function.

3. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

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

d. Any device deficiency that might have led to serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

SADE definition

- A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

UADE definition

- A UADE is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see section 2.3).

10.8.3. Definition of Device Deficiency

Device Deficiency definition

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

10.8.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate CRF or the Product Complaint Form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE/SAE/device deficiency CRF or the Product Complaint Form.
- There may be instances when copies of medical records for certain cases are requested by 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 sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with 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 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE/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 sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

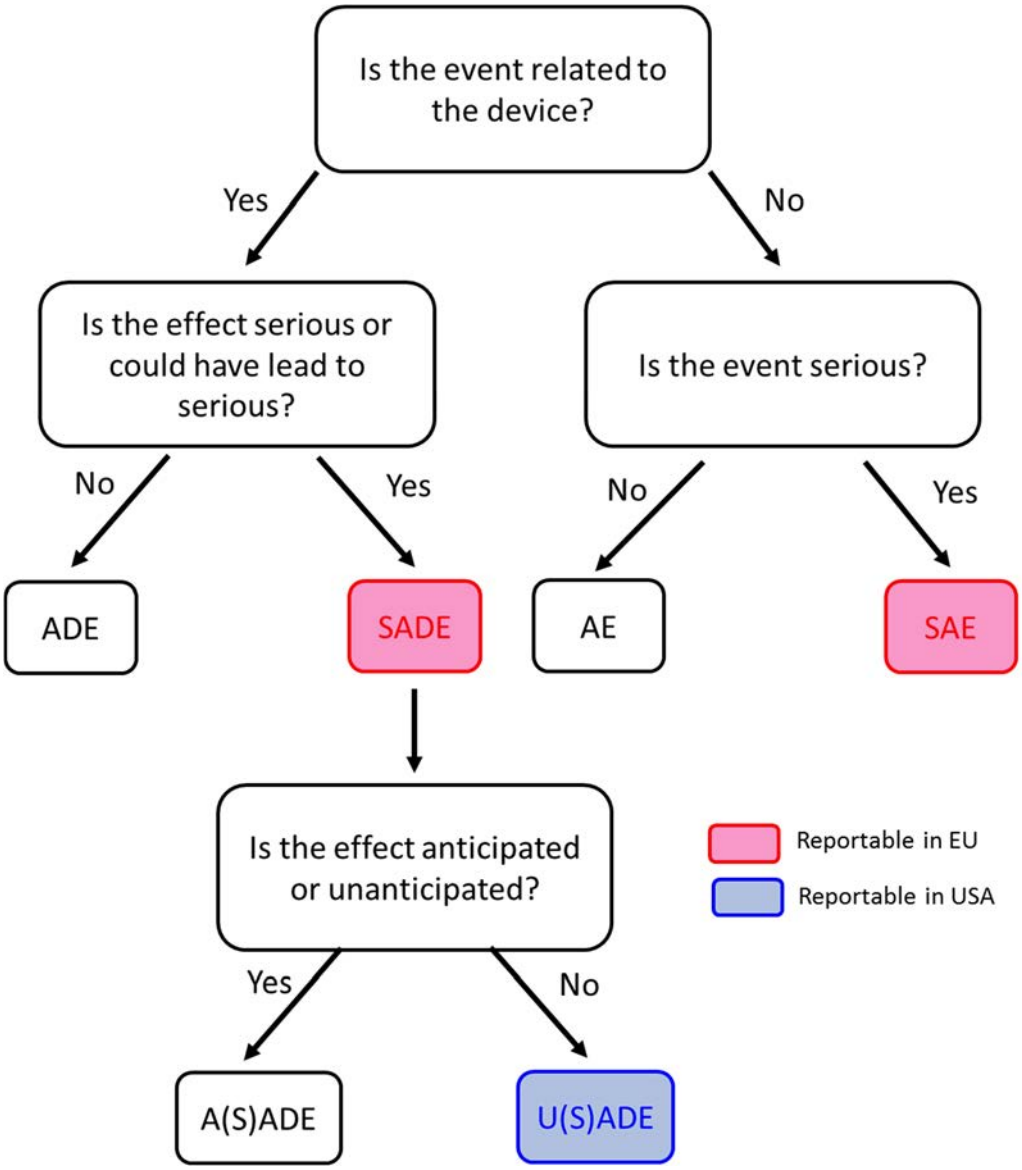
SAE Reporting via SAE Report
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated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

10.8.6. Reporting of SADEs

SADE Reporting
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in the SAE report.

10.8.7. AE, ADE, SAE, SADE Determination Flow Chart

Note: Adverse event reporting for countries other than the USA and EU must follow the regulatory and ethical requirements for that country.



10.9. Appendix 9: Abbreviations

Term	Definition
ADA	antidrug antibody
ADE	adverse device effect
AE	adverse event
AI	autoinjector
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
CD	Crohn's disease
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form
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
CTA	clinical trial agreement

CV	coefficient of variation
device deficiencies	Equivalent to product complaint.
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
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
IEC	Independent Ethics Committees
IL	interleukin
Informed consent	A process by which a participant voluntarily confirms his or her 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
ISR	injection-site reaction
IV	intravenous
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
PFS	pre-filled syringe
PK	pharmacokinetics

SADE	serious adverse device effect
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
TB	tuberculosis
TBL	total bilirubin level
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
UADE	unanticipated adverse device effect
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale

11. References

Cornelissen F, Asmawidjaja PS, Mus AM, Corneth O, Kikly K, Lubberts E. IL-23 dependent and independent stages of experimental arthritis: no clinical effect of therapeutic IL-23p19 inhibition in collagen-induced arthritis. *PLoS One*. 2013;8(2):e57553.

Ruutu M, Thomas G, Steck R, Degli-Esposti MA, Zinkernagel MS, Alexander K, Velasco J, Strutton G, Tran A, Benham H, Rehaume L, Wilson RJ, Kikly K, Davies J, Pettit AR, Brown MA, McGuckin MA, Thomas R. β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. *Arthritis Rheum*. 2012;64(7):2211-2222.

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

Leo Document ID = 036c4557-9cc7-4d79-8cea-e5efaa82487d

Approver: PPD

Approval Date & Time: 14-Aug-2020 04:13:42 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 14-Aug-2020 13:21:23 GMT

Signature meaning: Approved