Protocol I6T-MC-AMBV (a)

Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

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Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

Confidential Information

Mirikizumab (LY3074828)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on 13 December 2019
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1. Protocol Synopsis

Title of Study:
Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

Rationale:
Changes in buffer composition are being investigated as a potential way to address injection-site reactions, including pain, for mirikizumab. Study I6T-MC-AMBV (AMBV) is being conducted to evaluate the relative bioavailability and tolerability of mirikizumab administered using a new formulation compared to the reference formulation that has been administered in completed and ongoing clinical studies.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the relative bioavailability of a single 200-mg SC dose (2 × 1-mL PFS injections) of Mirikizumab Test Formulation compared to the Reference Formulation	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To evaluate the safety and tolerability of a single 200-mg SC dose (2 × 1-mL PFS injections) of Mirikizumab Test Formulation compared to the Reference Formulation	• TEAEs and SAEs

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

Summary of Study Design:

Study AMBV is a Phase 1, subject-blind, investigator-blind, 2-arm, randomized, single-dose, parallel-design study in healthy subjects.

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1 to 1 of 2 possible treatments and, within treatments, 1:1:1 to 3 possible injection locations (arms, thighs, or abdomen) using a computer-generated allocation code. Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and will return for pharmacokinetic and immunogenicity sampling and safety assessments at predefined outpatient visits up to 12 weeks postdose. Subjects will also be monitored for safety by way of telephone assessment on 3 occasions when outpatient visits are separated by 2 weeks.

Safety and tolerability will be assessed from clinical laboratory tests, vital sign measurements, recording of adverse events, physical examination, and immunogenicity.

Treatment Arms and Planned Duration for an Individual Subject:
All subjects will be screened within 28 days prior to enrollment.

On Day 1, subjects will receive a single dose consisting of 2 subcutaneous injections of 1 of the following treatment formulations according to the randomization schedule:

- 200-mg Mirikizumab Reference Formulation (100 mg/mL), 2 × 1-mL pre-filled syringe (PFS) (administered in completed and ongoing clinical studies)
- 200-mg Mirikizumab Test Formulation (100 mg/mL), 2 × 1-mL PFS

Subjects will participate in the study for up to 12 weeks postdose.

Number of Subjects:
Up to 60 subjects may be enrolled to ensure the following number of subjects complete the study:

- 48 subjects randomized to 2 treatment formulations with approximately
    - 24 subjects per Reference and Test Formulations, respectively, and
    - 8 subjects per arms, thighs, and abdomen injection locations, respectively, for each treatment formulation.

Statistical Analysis:

Pharmacokinetic parameters will be evaluated to estimate relative bioavailability of Test Formulation compared with the Reference Formulation. Log-transformed maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) parameters will be evaluated in a linear mixed-effects model with fixed effects for formulation and injection-site location and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

The time of C_{max} (t_{max}) will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

Safety parameters will be listed and summarized using standard descriptive statistics, where possible.

The frequency and percentage of subjects with preexisting antidrug antibodies (ADAs) and with treatment-emergent ADAs that are positive (TE-ADA+) to mirikizumab will be tabulated. For the TE-ADA+ subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE-ADA+ subjects.

Additional analysis will be performed if warranted upon review of the data.

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMBV

	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																
Subject admission to CRU		X																
Subject discharge from CRU			X															Subjects discharged after completing the 4-hour safety assessments on Day 1, at the investigator's discretion.
Outpatient visit				X	X	X	X	X	X	X		X		X		X	X	
Safety assessment (telephone call)											X		X		X			
Randomization			X															Subjects will be randomized 1:1 to 1 of 2 treatment formulations and 1:1:1 to 1 of 3 injection locations per treatment formulation.
Height, weight, and BMI	X																X	Only weight will be measured on Day 85 or ED.
Body temperature	X	X		X	X	X	X	X	X	X		X		X		X	X	
Physical examination	X	X															X	Full physical examination at screening or Day -1 (not both). 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, blood pressure, and temperature) (sitting) (hours)	X	X	P, 2 to 4					X				X					X	Day 1: 2- to 4-hour assessment (excluding temperature) 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						X		X							X	See Appendix 2, Clinical Laboratory Tests, for details.
Serology	X																	See Appendix 2, Clinical Laboratory Tests, for details.
QuantiFERON®-TB Gold test	X																	
Ethanol test and drug screen	X	X																May be repeated at the discretion of the investigator.
FSH test	X																	Females only, if applicable. See Section 6.1.
Pregnancy test (females only, as applicable)	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 Section 6.1 Inclusion [1b].
Single 12-lead ECG (supine)	X																X	Single screening ECG but may be obtained at additional times, when deemed clinically necessary.

	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 administration (2 injections per dose)			X															See Section 7.1. Subjects will fast (only water is allowed) from 1 hour before until 1 hour after dosing. Injections at Times 0 and 20 ± 2 min.
CCI			1															Assess within the first minute and then, if there is bleeding, at 1-min intervals following the injection until the bleeding stops. See Section 9.4.5.2.
CCI			1, 5, 15, 30, 60, 120, 240															Assess all injections as described in Section 9.4.5.3. Time points on Day 1 after each injection are • within 1 min, • 5 min (±1.5 min) • 15 and 30 min (each ±2 min), and • 60, 120, and 240 min (each ±5 min). • For VAS, see Section 9.4.5.3.1.
Mirikizumab PK sample			P	X	X	X	X	X	X	X		X		X		X	X	

	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	
CCI [redacted]			P					X		X							X	
CCI [redacted]		X																
AE and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	ISRs will be reported on supplemental ISR form, and not as AEs

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; min = minutes; P = pre-dose; PK = pharmacokinetic(s); SC = subcutaneous; TB = tuberculosis; VAS = visual analog scale.

[a] Administration of the pain VAS is mandatory at 1, 5, and 15 min regardless of whether pain is reported as "yes" or "no" during the injection-site assessment. At other time points, the VAS is administered only if pain is reported as "yes" during an injection-site assessment.

3. Introduction

3.1. Study Rationale

Mirikizumab (LY3074828) as a solution formulation is currently being studied in Phase 3 trials for the treatment of psoriasis, ulcerative colitis (UC), and Crohn's disease. In Phase 3 UC trials, a 200-mg dose of mirikizumab (2 × 1-mL injections) is being administered. In a Phase 3 Crohn's disease trial, a 300-mg dose (1 × 2-mL and 1 × 1-mL injections) is being administered. Injection-site reactions (ISRs), including pain, have been reported in these studies, which use the mirikizumab "reference" formulation. Several solution-associated factors may contribute to pain perception associated with injectable therapeutics, including active pharmaceutical ingredient, pH, buffer composition, and tonicity (Laursen et al. 2006).

To potentially lessen ISRs, including pain, Lilly developed an alternate (test) formulation of mirikizumab that uses a different combination of buffer and tonicity agents to that of the reference formulation. The CCI [redacted] which are commonly used excipients in formulations of monoclonal antibodies. The active ingredient concentration and the injection volume remain the same as the reference formulation. The reference formulation contains the inactive ingredients anhydrous citric acid, polysorbate 80, sodium chloride, and sodium citrate dihydrate.

Study I6T-MC-AMBV (AMBV) will evaluate the relative bioavailability and tolerability of this test formulation compared to the reference formulation when administered subcutaneously (SC) using a pre-filled syringe (PFS). This is the first human administration of the test formulation.

3.2. 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 UC, in which the IL-23 pathway is thought to have a significant pathogenic role. Neutralization of IL-23 with an anti-mouse IL-23 surrogate antibody (directed against the p19 subunit) significantly reduced the development of arthritis and inhibited ileal inflammation in a mouse model of spondyloarthropathy with bowel inflammation (Ruutu et al. 2012). Additionally, neutralization of IL-23 significantly reduced the disease score in the relapsing-remitting experimental autoimmune encephalomyelitis (multiple sclerosis-like) model in mice. Anti-IL-23 antibody also demonstrated some efficacy in preclinical arthritis models, depending on the timing of intervention (Cornelissen et al. 2013).

Ulcerative colitis is a chronic disease of unknown etiology characterized by inflammation of the rectum and colon. Symptoms include diarrhea, rectal bleeding, urgency, and tenesmus (a feeling of incomplete evacuation of the rectum after defecation). Ulcerative colitis has a relapsing–remitting course, meaning that many patients have intermittent disease flares that are interspersed with periods of remission. Treatment goals in UC include induction of remission (typically within a 6- to 12-week time frame) and maintenance of remission in the longer term (assessed over 52 weeks of continuous treatment in clinical trials). Control of intestinal

inflammation in UC is also associated with a reduction in the risk of hospitalization, colectomy, and in the longer term, UC-associated dysplasia and colorectal cancer.

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 patients with psoriasis, 230 patients with UC, 186 patients with Crohn's disease, and 409 healthy subjects 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.

Single IV doses of up to 600 mg mirikizumab were evaluated in Study I6T-MC-AMAA (AMAA; healthy subjects and patients with psoriasis) and up to 2400 mg in Study I6T-JE-AMAD (healthy Caucasian and Japanese subjects). No dose-related safety or tolerability issues were observed in these studies or in other ongoing clinical pharmacology studies. Subcutaneous bioavailability was approximately 40% relative to IV administration in Study AMAA.

In addition, 3 completed studies (I6T-MC-AMAL [AMAL], I6T-MC-AMAE [AMAE], and I6T-MC-AMAQ) and 1 ongoing study (I6T-MC-AMAR) compared the bioavailability, safety, and tolerability of various formulations of mirikizumab. These studies showed that mirikizumab was well tolerated; however, asymptomatic reductions in neutrophil counts were seen in a minority of subjects. The incidence of ISRs was highly variable across studies and treatments, but ISRs were mostly mild to moderate pain and very slight to well-defined erythema.

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

In Phase 1 studies with healthy subjects or patients with psoriasis, no deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported. In Phase 2 and 3 studies with patients having psoriasis, UC, or Crohn's disease:

- 2 deaths occurred from myocardial infarction and lung cancer, respectively, but neither was considered related to study drug, and
- serious adverse events and discontinuations due to an AEs are summarized in the IB.

3.2.2. Other Treatment-Emergent Adverse Events

In Phase 1 studies, the most frequently reported (≥5.0%) treatment-emergent adverse events (TEAEs) in the 442 healthy subjects and patients with psoriasis treated with mirikizumab in clinical pharmacology studies were ISRs (including injection-site pain), nasopharyngitis, and headache. Three of the clinical pharmacology studies (AABA, AMAL, and AMAE) actively observed injection sites to allow recording of, eg, erythema, swelling, and induration. Treatment-emergent adverse events in Phase 2 and 3 studies with patients having psoriasis, UC, or Crohn's disease are summarized in the IB.

3.2.3. Pharmacokinetics

Phase 1 studies in healthy subjects and patients with psoriasis 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%.

CCI [redacted]

3.3. 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. Therefore, subjects 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 patients or healthy subjects exposed to mirikizumab at 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 subjects are not expected to derive any benefit from participating in studies in which mirikizumab is administered.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of mirikizumab is to be found in the IB.

4. Objectives and Endpoints

Table AMBV.1 shows the objectives and endpoints of the study.

Table AMBV.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the relative bioavailability of a single 200-mg SC dose (2 × 1-mL PFS injections) of Mirikizumab Test Formulation compared to the Reference Formulation	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To evaluate the safety and tolerability of a single 200-mg SC dose (2 × 1-mL PFS injections) of Mirikizumab Test Formulation compared to the Reference Formulation	• TEAEs and SAEs
CCI	

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

5. Study Design

5.1. Overall Design

Study AMBV is a Phase 1, subject-blind, investigator-blind, 2-arm, randomized, single-dose, parallel-design study in healthy subjects.

All subjects will be screened within 28 days prior to enrollment. Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized

- 1:1 to 2 treatment formulations and
- within each treatment formulation, 1:1:1 to 3 injection sites (arm, thigh, or abdomen)

using a computer-generated allocation code (Section 7.2). On Day 1, subjects will receive a 2 × 1-mL (200 mg mirikizumab) SC dose of 1 of the following treatments according to the randomization schedule:

- 200 mg Mirikizumab Reference Formulation (100 mg/mL), 2 × 1-mL PFS (administered in completed and ongoing clinical studies [see Section 3.2])
- 200 mg Mirikizumab Test Formulation (100 mg/mL), 2 × 1-mL PFS

The maximum total dose of mirikizumab a subject will receive is 200 mg.

Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and will return for pharmacokinetic (PK) and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose. Subjects will be monitored for safety between outpatient visits by way of telephone assessment. Subjects will participate in the study for up to 12 weeks after last dose.

Safety and tolerability will be assessed through clinical laboratory tests, vital sign measurements, recording of AEs, physical examination, and immunogenicity. At prospectively defined time points, injection-related assessments will be made including a pain visual analog scale (VAS).

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 60 subjects may be enrolled so that 48 subjects (24 subjects per formulation with approximately 8 subjects per treatment formulation and injection site) complete the study. For the purposes of this study, a subject completes the study when all procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients. A population of healthy subjects is frequently used in the assessment of the relative bioavailability 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.

Subjects will be randomized to receive injections in the arms, thighs, or abdomen, as injection location has been observed to have an impact on bioavailability in some studies with mirikizumab.

A parallel-group design was 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 subjects develop neutralizing antidrug antibodies (ADAs).

5.5. 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 (1 mL per PFS) and the solubility of mirikizumab (100 mg/mL).

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG) at screening.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented. Laboratory tests at screening and Day -1 may be repeated once at the discretion of the investigator for any results that are outside the reference range.

Screening may occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening:

[1] are overtly healthy male or female subjects, as determined through medical history and physical examination

[1a] male subjects:

- no male contraception required, except in compliance with specific local government study requirements

[1b] female subjects:

- All female subjects must test negative for pregnancy prior to initiation of treatment, as indicated by negative serum pregnancy test at the screening visit and on Day -1 prior to initial 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 informed consent form (ICF) to 12 weeks following dosing with the investigational product [IP])

- 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 subject 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 and include those who are
  - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, tubal ligation, or bilateral salpingectomy) or congenital anomaly such as Müllerian agenesis; or
  - postmenopausal, defined as 1 of the following:
    - A woman at least 50 years of age with an intact uterus, not on hormone replacement therapy, who has had either:
      - cessation of menses for at least 1 year; or
      - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone level >40 mIU/mL at screening; or
    - A woman at least 55 years of age, not on hormone replacement therapy, who has had at least 6 months of spontaneous amenorrhea; or
    - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are between 18 and 75 years of age at the time of screening

[3] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive

[4] have clinical laboratory test results within normal reference ranges for the study site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[5] have venous access sufficient to allow for blood sampling as per the protocol

[6] agree not to donate blood or plasma until after the end of their participation in the study

[7] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[8] are able and willing to give signed informed consent

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or Day -1:

[9] are site staff directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[10] are Lilly employees or are employees of a third-party organization involved in the study

[11] are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study

[12] have participated in a clinical trial involving an IP 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

[13] have previously completed or withdrawn from this study or any other study investigating mirikizumab, and have previously received the IP

[14] 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

[15] have known allergies to mirikizumab, related compounds, or any components of the formulation, or history of significant atopy

[16] have self-perceived dullness or loss of sensation in either arm or thigh or on either side of the abdomen

[17] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[18] have an abnormal blood pressure, pulse rate, or temperature as determined to be clinically significant by the investigator

[19] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

[20] Infections:

[20a] have had a serious infection (eg, pneumonia, cellulitis, sepsis); have been hospitalized or have received IV antibiotics for an infection within 12 weeks prior to Day 1; have had a serious bone or joint infection within 24 weeks prior to Day 1 or have ever had an infection of an artificial joint; or are immunocompromised to an extent that participation in the study would pose an unacceptable risk to the subject as determined by the investigator

[20b] 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

[20c] have or have had a herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks of Day 1

[20d] 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 subject if participating in the study; these subjects may be re-screened (once) ≥4 weeks after documented resolution of symptoms

[21] have known or ongoing psychiatric disorders deemed clinically significant by the investigator

[22] regularly use known drugs of abuse and/or show positive findings on drug screening

[23] show positive HIV antibodies

[24] show positive hepatitis C antibody

[25] show positive hepatitis B surface antigen or hepatitis B core antibody

[26] are women who are lactating

[27] intend or are likely to use over-the-counter or prescription medication for pain or inflammation within 7 days prior to dose administration. Subjects on stable doses of other medications (eg, statins and antihypertensives) may be eligible for enrolment following discussion with the sponsor (Section 7.7)

[28] have donated blood or plasma of more than 500 mL within 1 month prior to screening

[29] 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 6.3.2 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)

[30] 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 6.3.2

[31] show evidence of active or latent TB, as documented through medical history, examination, and TB testing (positive [not indeterminate] QuantiFERON®-TB Gold test; if a repeat test is also indeterminate, the subject will not be eligible); or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been given. Subjects with any history of active TB are excluded from the study, regardless of previous or current TB treatments

[32] 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)

[33] 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 7.7)

[34] have significant allergies to humanized monoclonal antibodies

[35] 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)

[36] 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

[37] have had breast cancer within the past 10 years

[38] have any condition that could affect pain perception from an injection

[39] have excessive tattoos over either arm, 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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criteria [9] and [10] prevent conflict of interest in study subjects. Exclusion criteria [11] through [39] exclude items including, but not limited to medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study. Female subjects will also be required to adhere to contraceptive requirements, as outlined in the inclusion criteria (Section 6.1).

6.3.1. Meals and Dietary Restrictions

Subjects will receive a light breakfast on the morning of Day 1 but are required to fast (water is permitted) from 1 hour prior to dosing until 1-hour postdose. Standard meals will be provided at all other times while subjects are resident at the CRU, per the CRU's policy.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will not be allowed to consume caffeinated products during study visits and while resident at the CRU, but otherwise subjects will be allowed to maintain their regular caffeine consumption.

Alcohol consumption is not permitted while subjects 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. In addition, subjects must abide by the CRU smoking restrictions during study visits and while resident at the CRU.

6.3.3. Activity

Subjects 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 15, Day 29, and Day 85). While certain study procedures are in progress at the site, subjects may be required to remain recumbent or sitting.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened, except as described in exclusion criterion Section 6.2 [20d].

7. Treatment

7.1. Treatment Administered

One 200-mg dose of IP will consist of 2 × 1-mL SC injections using 2 PFS of 100 mg mirikizumab into the arms, thighs, or abdomen, according to the randomization schedule.

Subjects 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.

Subjects 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.

The second injection should be administered 20 (±2) minutes after the first injection.

This study will compare single doses of 2 formulations:

- 200 mg of Mirikizumab Reference Formulation (100 mg/mL), 2 × 1-mL PFS (administered in completed and ongoing clinical studies [see Section 3.2])
- 200 mg of Mirikizumab Test Formulation (100 mg/mL), 2 × 1-mL PFS

Trained site staff will administer all doses. Prior to the PFS injections, the investigator or designee will clean the subject's skin. The injections will be administered according to the instructions provided by the sponsor.

The investigator or designee is responsible for

- explaining the correct use of the IP to the site staff
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection, and
- returning all unused medications to Lilly or its designee at the end of the study

Note: In some cases, site may destroy the material if, during the investigational-site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

Mirikizumab will be supplied by the sponsor or its designee in accordance with current good manufacturing practice, labeled according to the country's regulatory requirements, and supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Each 1-mL syringe of mirikizumab (100 mg/mL) is designed to deliver 100 mg of mirikizumab. The following products will be supplied by Lilly, with study-specific labels, for use in the study:

- Mirikizumab Reference Formulation (solution for injection) in 1-mL single-dose, pre-filled, disposable manual syringes
- Mirikizumab Test Formulation (solution for injection) in 1-mL single-dose, pre-filled, disposable manual syringes

7.1.2. Medical Device

The investigator or designee will ensure that the instructions have been followed properly, maintaining accurate records of study devices, dispensing, and collection. The used or unused PFS may be destroyed by a qualified vendor. However, a used PFS that is associated with a product complaint will need to be returned to Lilly.

7.2. Method of Treatment Assignment

Subjects will be randomly assigned to 1 of 2 possible treatments and 1 of 3 possible injection sites (arms, thighs, or abdomen) using a computer-generated allocation code (Section 5.1).

7.2.1. Selection and Timing of Doses

Each subject will be administered 2 injections approximately 20 minutes apart to complete the single dose. The actual time of all injections will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Blinding will be in place for subjects and for site staff conducting any injection-site assessments.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

Dose modification is not permitted in this study.

7.4.1. Special Treatment Considerations

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to, rash, pruritus (itching), urticaria (hives), angioedema (swelling of the lips and/or tongue), and anaphylactic reaction. Sometimes these reactions can be life-threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all subjects should be

- closely monitored for signs or symptoms that could result from such reactions
- educated on the signs or symptoms of these types of reactions, and

- instructed to contact the study site immediately if they experience any of these symptoms after discharge from the CRU.

If a subject experiences an acute allergic/hypersensitivity reaction after an injection of IP, he or she should be managed appropriately and receive relevant supportive care. The event should be recorded as an AE and a hypersensitivity cytokine panel (Appendix 6) should be collected.

7.5. Preparation/Handling/Storage/Accountability

Investigational products will be stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Investigational products should not be frozen or shaken.

Site will be required to monitor the temperature of on-site IP storage conditions. The investigator or designee must confirm that appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all IPs received and must confirm that any discrepancies are reported and resolved before use of the IPs.

Unblinded site staff will be responsible for handling and administering IP. Unblinded site staff are also responsible for ensuring that subjects remain blinded to treatment (ie, subjects must not see the syringe before, during, or after IP administration). Blinded assessors of any injection-site assessments and bleeding will not have access to the IP.

Only subjects enrolled in the study may receive IPs or study materials, and only authorized site staff may supply or administer IPs. All IPs should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for IP accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The IPs will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Subjects 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 the first injection and until at least 4 hours after the second injection. No more than 3 g of acetaminophen will be permitted in any 24-hour period. Inclusion of subjects on any other concomitant medication (eg, statins and anti-hypertensives) is contingent upon approval following consultation with the sponsor.

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

If the need for any additional concomitant medication arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP). Any medication used during the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason should complete AE and other Day 85/early discontinuation procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Not applicable in this single-dose study.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study. If the subject received IP, he or she will continue to be monitored for safety and tolerability for the planned duration of the study.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study prior to receiving IP in this study. If the subject received IP, he or she will continue to be monitored for safety and tolerability for the planned duration of the study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Investigator decision
    - the investigator decides that the subject should be discontinued from the study
- Subject decision
    - the subject, or legal representative, requests to be withdrawn from the study

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 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.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects 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 subject.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the subject to discontinue the IP before completing the study. The subject should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

The investigator will record all relevant AE and SAE information in the eCRF. After the informed consent form is signed, site staff will record, via eCRF, the occurrence and nature of each subject's preexisting conditions. Additionally, site staff will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP, study device and/or study procedure, and the AE.

Planned surgeries should not be reported as AEs, unless the underlying medical condition has worsened during the course of the study.

Prospective collection of ISRs at predefined time points is included as part of this protocol. As such, any identified ISRs will not be collected as AEs but will instead be recorded using the predefined ISR collection tools.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above

Site staff must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, site staff must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Adverse Device Effects

Any AE believed to have a reasonable possibility of being related to or associated with an issue with the PFS, such as a malfunction or a deficiency, is considered an adverse device event.

These events must be clearly indicated as such in the eCRF and reported to the sponsor. A product complaint should also be reported.

For the purposes of this protocol, "unanticipated" serious adverse device effect means any SAE alleged to have a reasonable possibility of being associated with or related to the device, which was not previously defined as anticipated in study documents, such as the device IB or Instructions for Use. The SAE relatedness must be clearly indicated as such in the eCRF, and reported to the sponsor within 24 hours of site knowledge of the event. A product complaint should also be reported.

9.2.1.2. Adverse Events of Special Interest

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

Adverse events of special interest for mirikizumab are

- 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 6) will be collected when possible for any subject who experiences an AE of systemic allergic/hypersensitivity reaction during the study.

9.2.1.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems used in clinical trials to ensure the safety of study subjects, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if they have a complaint or problem with the IP or drug delivery system so that the situation can be assessed.

The investigator or designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed Product Complaint Form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he or she will return a copy of the product complaint form with the product.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of mirikizumab is considered any dose higher than the 200-mg dose assigned through randomization. Syringes used in this study can deliver a 1-mL volume of mirikizumab and each dose will require 2 syringes.

There is no specific antidote for mirikizumab. In the event of an overdose, the subject should receive appropriate supportive care and any AEs should be documented.

Refer to the mirikizumab IB for further details.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

9.4.2. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2). Additional vital signs may be measured during the study, if warranted.

Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes.

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

9.4.3. Electrocardiograms

For each subject, a single 12-lead ECG should be collected according to the Schedule of Activities (Section 2).

Electrocardiograms must be recorded before collecting any blood samples. Subjects 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 study 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 subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

9.4.4. Temperature

Body temperature will be assessed at the times indicated in the Schedule of Activities (Section 2).

9.4.5. Other Tests

9.4.5.1. Tuberculosis Testing

Subjects will be tested as indicated in the Schedule of Activities (Section 2) for evidence of active or latent TB using the QuantiFERON-TB Gold test. If the test is indeterminate, 1 re-test is allowed. If the re-test is indeterminate, the subject will be excluded from the study.

Subjects who have had household contact with a person with active TB within 1 year of screening must be excluded, unless appropriate and documented prophylaxis treatment for TB has been completed

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

9.4.5.2. Injection-Site Bleeding

The investigator or designee will assess both injection sites per dose and record on the eCRF the presence of visible bleeding

- within 1 minute after each injection, and
- if bleeding is observed, continue at 1-minute intervals until bleeding has stopped.

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

CCI [redacted]

CCI [redacted]

9.4.6. Safety Monitoring

The Lilly-assigned CP or CRP/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 therapeutic area physician or clinical research scientist.

9.4.6.1. Hepatic Safety

If a study subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the serum concentrations of mirikizumab. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

CCI

[redacted]

CCI [redacted]

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 60 subjects may be enrolled to ensure that 48 subjects (24 subjects per treatment formulation with approximately 8 subjects per treatment formulation and injection site [arm, thigh, or abdomen]) complete the study.

Based on previous trials, it is expected that the coefficient of variation for area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) to be approximately 40%. A sample size of 48 completed subjects (24 subjects per treatment formulation) will provide >90% probability that the limits of the 90% confidence interval (CI) for the ratio of geometric means will be within 24% of the estimate.

Subjects who are randomized but not administered treatment may be replaced to ensure that 48 subjects (24 per treatment formulation) complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee.

Pharmacokinetic analyses will be conducted on data from all subjects who receive mirikizumab and have evaluable PK data.

Safety analyses will be conducted for all enrolled subjects, regardless of whether they complete all protocol requirements.

CCI [redacted]. 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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs 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 IP 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 using the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of IP-related SAEs will be reported.

CCI

[redacted]

10.3.1.2.2. Statistical Evaluation of Other Safety Parameters

As detailed in the Statistical Analysis Plan, other safety data will be listed and summarized using standard descriptive statistics, where possible.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

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

The primary parameters for PK analysis of mirikizumab will be 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}]). Other noncompartmental parameters, such as time of C_{max} (t_{max}), half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), apparent clearance, and apparent volume of distribution may be reported. Pharmacokinetic parameters may also be normalized by body weight in the event that there are differences in body weight between the treatment groups.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate the relative bioavailability of the Test Formulation compared with the Reference Formulation. Log-transformed C_{max} and AUC parameters will be evaluated in a linear fixed-effects model with fixed effects for formulation and injection-site location. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon rank sum test will be calculated.

CCI [redacted]

10.3.4. Data Review during the Study

Review of the PK and safety data may be conducted during the conduct of this study to inform internal Chemistry, Manufacturing, and Control processes with regard to the test mirikizumab formulation development.

10.3.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP/CRP/investigator or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine 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 last the time point with a measurable concentration
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignments. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or site staff are aware of the treatment, but the subject is not, or vice versa; or when the sponsor is aware of the treatment, but the investigator, site staff, and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
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 the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist

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
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
ISR	injection-site reaction
IV	intravenous
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

PFS	pre-filled syringe
PK	pharmacokinetic(s)
randomize	The process of assigning subjects to an experimental group on a random basis
SAE	serious adverse event
SC	subcutaneous; subcutaneously
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.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
TB	tuberculosis
TBL	total bilirubin
TE-ADA	treatment-emergent antidrug antibody
TE-ADA+	treatment-emergent antidrug antibody positive
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed drug concentration
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)

- Cell morphology
  - Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
  - Platelets

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopy (if dipstick abnormal)

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

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[b,c]
- Urine drug screen[b,c]
- Pregnancy test (females only, if applicable)
- FSH[a]
- QuantiFERON®-TB Gold[a]

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 at screening only.

[b] Performed at screening and Day -1 only.

[c] Urine drug screen and ethanol level may be repeated at other times indicated in the Schedule of Activities (Section 2).

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that subjects understand the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment materials should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the study site(s). Lilly or its representatives must approve the ICF before it is used at the study site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and Summary of Product Characteristics and updates during the course of the study
- ICF, and
- relevant curricula vitae.

Regulatory Considerations

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

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study site, as appropriate.
- Provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the site staff through email, telephone, or fax.
- Review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Site

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly or its designated CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth Muscle Antibody**
CPK	**(or Anti-actin Antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and testing availability.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, clinical laboratory, PK, immunogenicity, and bioanalytical assays) during the study.

Protocol I6T-MC-AMBV Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	4	48
Pharmacokinetics	3	15[b]	45
Immunogenicity	10	4	40
Pharmacogenetics	10	1	10
Total			188
Total for clinical purposes			190

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

[b] Includes additional 3 samples, if required.

Appendix 6. Allergic/Hypersensitivity Reaction Kit

Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

Hypersensitivity Tests[a]

Anti-mirikizumab antibodies (immunogenicity)	Tryptase
Mirikizumab concentration (PK)	N-methylhistamine
	Drug-specific IgE[b]
	Basophil activation test[b]
	Complements
	Cytokine panel

Abbreviations: Ig = immunoglobulin; PK = pharmacokinetics.

[a] Assayed by Lilly-designated laboratory.

[b] Basophil activation test will be performed if a drug-specific IgE assay is unavailable.

Appendix 7. Protocol Amendment I6T-MC-AMBV (a) Summary Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Healthy Subjects

Overview

Protocol I6T-MC-AMBV, "Relative Bioavailability of a Mirikizumab Test Formulation Compared to the Reference Formulation in Heathy Subjects", has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Expanded exclusion criterion [10] to exclude employees of any third-party organization to be involved in the study
- The language in exclusion criteria [23], [24], and [25] is modified to clarify subjects with positive HIV antibodies, hepatitis C antibodies, hepatitis B surface antigen or hepatitis B core antibodies will be excluded
- Included timeframe for subjects who have had household contact with a person with active TB to be excluded from study
- Throughout the protocol changes have been made to reflect the fact that the study will be conducted at a single study site. These changes are not presented in the revised section below.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

6.2 Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or Day -1:

[9] are site staff directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[10] are Lilly ~~or Covance~~ employees or are employees of a third-party organization involved in the study

[23] show ~~evidence of HIV infection and/or~~ positive HIV antibodies

[24] show ~~evidence of hepatitis C and/or~~ positive hepatitis C antibody

[25] show ~~evidence of hepatitis B and/or~~ positive hepatitis B surface antigen or hepatitis B core antibody

9.4.5.1 Tuberculosis Testing

Subjects who have had household contact with a person with active TB within 1 year of screening must be excluded

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