J2T-MC-KGBG Protocol (b)

A Phase 1, Open-Label, Single-Dose Bioequivalence Study of Injections of Lebrikizumab Using a 2-mL Pre-Filled Syringe with Needle Safety Device and an Investigational 2-mL Autoinjector in Healthy Participants

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Title Page

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Protocol Number: J2T-MC-KGBG

Amendment Number: b

Compound: Lebrikizumab (LY3650150)

Study Phase: 1

Short Title: A Bioequivalence Study of Lebrikizumab Using a Pre-Filled Syringe with Needle Safety Device and an Investigational Autoinjector in Healthy Participants

Sponsor Name: Eli Lilly and Company

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Regulatory Agency Identifier Number(s): IND: 119866

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol *J2T-MC-KGBG*	*04 March 2021*
Amendment (a)	*19 May 2021*

Amendment (b)

Overall Rationale for the Amendment:

This protocol has been amended in response to comment from study site to provide clarification regarding procedures in section on Preparation/Handling/Storage/ accountability. Minor editorial changes have been done which is not reflected in the below table. The following table describes the change made in amendment (b).

Section # and Name	Description of Change	Brief Rationale
6.2. Preparation/ Handling/ Storage/accountability	The following statement is removed. The investigator or designee will return all used and unused AI devices to Lilly or its designee at the end of the study.	The device group no longer requests sites to return used and unused devices to Lilly.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Single-Dose Bioequivalence Study of Injections of Lebrikizumab Using a 2-mL Pre-Filled Syringe with Needle Safety Device and an Investigational 2-mL Autoinjector in Healthy Participants

Short Title: A Bioequivalence Study of Lebrikizumab Using a Pre-Filled Syringe with Needle Safety Device and an Investigational Autoinjector in Healthy Participants

Rationale: Study J2T-MC-KGBG (KGBG) will assess the PK, safety, and tolerability of a 250-mg SC dose of lebrikizumab (LY3650150) solution formulation administered using a 2-mL PFS-NSD or an investigational 2-mL AI. Both devices will be evaluated at 3 different injection sites (arm, thigh, and abdomen) to expand the options for administration in patient use. Both the PFS-NSD and the AI are planned for use to administer lebrikizumab in subsequent studies and patient use.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the PK of lebrikizumab after SC administration of 250-mg dose using a 2-mL PFS-NSD and a 2-mL AI in healthy participants	• C_{max} • AUC(0-∞) • AUC(0-t_{last})
Secondary	
To describe the safety and tolerability of lebrikizumab 250-mg dose through SC in healthy participants	Number and incidence of • SAEs • TEAEs

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-NSD = pre-filled syringe with needle safety device; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Overall Design

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

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

Number of Participants:

Approximately 240 participants may be enrolled so that approximately 216 participants (108 in the PFS-NSD 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 lebrikizumab will be administered SC through either PFS-NSD or AI into the arm, thigh, or abdomen on Day 1 and participants will be followed through Day 99.

Data Monitoring Committee: No

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

Study Schedule Protocol J2T-MC-KGBG

	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 ±2d	64 ±2d	71 ±3d	85 ±3d	99 ±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 scheduled activities on Day 1, or later at the investigator's discretion.
Outpatient visit	X			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 randomly assigned 1:1 to 1 of 2 delivery devices and 1:1:1 to 1 of 3 injection locations per delivery device.

	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 ±2d	64 ±2d	71 ±3d	85 ±3d	99 ±3d or ED	
Height, weight, and BMI	X	X																X	Participant weight at Day -1 will be used for weight category stratification at randomization. Weight, but not height, will be measured on Day -1, and Day 99 or ED.
Physical examination	X	X																X	Full physical examination at screening or at Day -1. Symptom-directed examinations at other times, and as deemed necessary by the investigator.
Vital signs (pulse rate and blood pressure) (sitting), and body temperature	X	X	P, 3hr					X				X						X	Predose Day 1 conducted within 2 hours predose. Postdose assessment 3 ± 1 hour. Time points may be added if warranted at the discretion of the investigator.
Clinical laboratory tests	X	X	P	X				X		X								X	Day 1 conducted within 2 hours predose. See Section 10.2 Appendix 2, Clinical Laboratory Tests, for details.
Serology	X																		See Section 10.2 Appendix 2, Clinical Laboratory Tests, for details.

	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 ±2d	64 ±2d	71 ±3d	85 ±3d	99 ±3d or ED	
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 (females only)	X																		See Section 10.4, Appendix 4.
Pregnancy test (females of childbearing potential only)	X	X																X	Serum pregnancy test will be performed at screening and Day -1. Urine pregnancy test will be performed at Day 99 or ED. See Section 10.4, Appendix 4.
Single 12-lead ECG (supine)	X	X																X	May be obtained at additional times, when deemed clinically necessary.
Lebrikizumab administration (1 injection per dose)			X																See Section 6.1.
Lebrikizumab PK sample			P	X	X	X	X	X	X	X		X		X		X	X	X	Day 1: collected within 2 hours predose.
Immunogenicity sample			P					X		X								X	Day 1: collected within 2 hours predose.
Pharmacogenetic sample			P																Day 1: collected within 2 hours predose.

	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 ±2d	64 ±2d	71 ±3d	85 ±3d	99 ±3d or ED	
AE, product complaints, and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If an AE of ISR is reported, see Section 8.2.5.2.

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 = pharmacokinetics; TB = tuberculosis.

2. Introduction

2.1. Study Rationale

Study J2T-MC-KGBG (KGBG) will assess the PK, safety, and tolerability of a 250-mg SC dose of lebrikizumab (LY3650150) solution formulation administered using a 2-mL PFS-NSD or an investigational 2-mL AI. Both devices will be evaluated at 3 different injection sites (arm, thigh, and abdomen) to expand the options for administration in patient use. Both the PFS-NSD and the AI are planned for use to administer lebrikizumab in subsequent studies and patient use.

2.2. Background

Lebrikizumab (LY3650150) is a humanized monoclonal antibody based on the human immunoglobulin G4 antibody stabilized by a mutated Fc region. Lebrikizumab binds specifically to soluble IL-13 and blocks IL-13 signaling through the IL-4 receptor alpha/IL-13 receptor alpha 1 pathway, thereby preventing the downstream effects of human IL-13 with high potency. Lebrikizumab has been investigated for the treatment of AD, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and refractory Hodgkin lymphoma. Currently, lebrikizumab is being actively developed for the treatment of AD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of lebrikizumab is provided in the Investigator's Brochure.

Safety summary

As of the Investigator's Brochure cutoff date of 22 September 2020, 311 healthy participants and an estimated 4484 patients have been exposed to at least 1 dose of lebrikizumab. Safety information provided in the Investigator's Brochure is summarized here.

Healthy participants

Lebrikizumab has been evaluated in 5 healthy participant studies. Single IV doses included 0.1, 0.3, 1.0, 3.0, and 5.0 mg/kg. Doses administered SC included a dose at 1 mg/kg, and single doses including 37.5, 125, 250, and 375 mg.

Five treatment-emergent SAEs were reported in lebrikizumab-treated participants. All events were assessed by the investigator as not related to study drug. No SAE PT was reported in more than 1 participant. No deaths were reported in healthy participant studies. Administration of a single dose of lebrikizumab in healthy participant studies was well tolerated.

Patients

Lebrikizumab has been evaluated in 686 patients with AD, 3321 patients with asthma, and 477 patients with other indications.

Studies in patients with AD

In Phase 2 studies, the doses administered were 125, 250, and 500 mg. In Phase 3 studies, the dose was 250 mg administered every 2 or 4 weeks. One death from myocardial infarction has been reported in the ongoing Phase 3 study and was assessed as not related by the investigator. This death was reported after the Investigator's Brochure cutoff date of 22 September 2020.

In the 3 completed Phase 2 studies

- A low frequency of SAEs were reported in the lebrikizumab-treated groups and placebo or topical corticosteroid groups.
- No PT was reported in more than 1 patient.
- A majority of SAEs were assessed by the investigator as not related.
- A similar proportion of patients in each treatment group reported AEs leading to study discontinuation.

Studies in patients with asthma

In Phase 2 studies, doses included 37.5, 125, or 250 mg every 4 weeks, and in some studies patients were dosed at 0.3 mg/kg to 5 mg/kg. In Phase 3, doses studied included 37.5 or 125 administered once every 4 weeks. Six deaths were reported in these studies.

In the 3 completed Phase 3 studies of adult patients

- A similar proportion of patients in all treatment groups had at least 1 SAE.
- In both treatment groups, the most commonly reported SAE was the PT asthma.
- A similar proportion of patients in each treatment group reported AEs leading to study discontinuation.

Studies in patients with chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, or Hodgkin lymphoma

In one Phase 2 study of patients with chronic obstructive pulmonary disease, the dose was 125 mg administered once every 4 weeks. Three deaths were reported in this study, all assessed as not related to study drug. In one Phase 2 study of patients with idiopathic pulmonary fibrosis, the dose was 250 mg administered once every 4 weeks. Forty-eight deaths were reported in this study, the majority of which were due to progression of disease. In one Phase 1/2 study of patients with Hodgkin lymphoma, doses from 0.1 to 10.0 mg/kg were administered intravenously every 2 weeks for a maximum of 24 weeks. Nine deaths were reported in this study, all of which were due to disease progression.

Overall, the safety findings in the lebrikizumab groups were similar to the placebo or comparator groups across these clinical studies. There were no significant trends observed in the treatment-emergent adverse events reported between the treatment groups in all 3 indications.

Anti-lebrikizumab antibodies

In the completed studies of patients with AD, 12.3% to 24.5% of patients developed ADAs. In general, the presence of anti-lebrikizumab antibodies had no apparent impact on PK results, and overall there was no relationship between anti-lebrikizumab antibody status and efficacy or safety events.

2.3. Benefit/Risk Assessment

Risk from immunomodulatory therapy

As an immunomodulatory therapy, lebrikizumab may increase the risk of developing an infection or may exacerbate an existing infection. In patients with moderate-to-severe AD in the lebrikizumab program, the most commonly reported infections include nasopharyngitis and

upper respiratory tract infection. Overall, the incidence of infections is balanced between patients in the lebrikizumab and placebo groups. No serious or parasitic infections have been reported in lebrikizumab-treated patients with moderate-to-severe AD. No opportunistic infections or TB infections have been reported in the Phase 2 AD program. No serious infections were reported in 5 completed healthy participant studies. Immunomodulatory therapies may increase the risk of malignancies; however, due to the single dose of lebrikizumab being administered in this study, it is not considered necessary to monitor for such effects.

Hypersensitivity reactions

There were no reported hypersensitivity events in the Phase 2 AD program. In a pooled analysis of Phase 3 asthma studies, there was 1 patient with an anaphylactic event in the lebrikizumab group.

Device-based risks

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

Known and expected benefits and risks

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lebrikizumab may be found in the Investigator's Brochure as well as reasonably anticipated ADEs found in the AI Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the PK of lebrikizumab after SC administration of 250-mg dose using a 2-mL PFS-NSD and a 2-mL AI in healthy participants	• C_{max} • AUC(0-∞) • AUC(0-t_{last})
Secondary	
To describe the safety and tolerability of lebrikizumab 250-mg dose through SC in healthy participants	Number and incidence of • SAEs • TEAEs
Tertiary/Exploratory	
• To evaluate the potential development of anti-lebrikizumab antibodies • To evaluate the impact of injection-site location on PK	• TE-ADA • C_{max} • AUC(0-∞) • 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-NSD = pre-filled syringe with needle safety device; 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 KGBG is a Phase 1, multi-site, randomized, parallel-design, open-label, 2-arm, single-dose study in healthy participants.

Infection risk

Participants should follow local guidance and CRU precautions to minimize risk for COVID-19 infection.

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 70.0 kg,
- 70.0 to 80.0 kg, and
- more than 80.0 kg.

Study participants

Approximately 240 participants will be randomly assigned according to Table KGBG.1, so that approximately 216 participants complete the study. If a participant needs to be replaced, a participant of the same weight category will be selected as their replacement.

Treatment and assessment period

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

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

- 1:1 to delivery device (either PFS-NSD [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-mL (total 250 mg lebrikizumab) SC dose, administered by the investigator or designee, and delivered via the device and in the location assigned by the randomization.

Participants may be allowed to leave the CRU after completing the 3(±1)-hour safety assessments on Day 1, or later at the investigator's discretion. Participants will return for PK and immunogenicity sampling and safety assessments at predefined times up to 99 days 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 KGBG.1. Study KGBG Stratification and Randomization Plan

Weight Category (Desired Number of Participants)	Injection Device	Subcutaneous Injection Location	Desired Number of Participants
Low <70.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12
Medium 70.0 – 80.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12
High >80.0 kg (72 participants)	2-mL PFS-NSD (Reference)	Arm	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Abdomen	12
	2-mL AI (Test)		12
	2-mL PFS-NSD (Reference)	Thigh	12
	2-mL AI (Test)		12

Abbreviations: AI = autoinjector; PFS-NSD = pre-filled syringe with needle safety device.

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 AD. A population of healthy participants is frequently used in the assessment of the PK of both small and large molecules.

A single dose of lebrikizumab and the PK sampling time points have been selected to generate PK profiles sufficient to fulfill the study objectives.

Participants will be randomly assigned to receive injections in the arm, thigh, or abdomen to evaluate the impact injection site has on bioavailability of lebrikizumab.

Previous population PK analyses have shown that patients with a lower body weight tended to have a lower clearance and volume of distribution (Zhu et al. 2017). 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 lebrikizumab, which has a half-life of approximately 25 days. Additionally, a crossover study could confound PK data if participants develop neutralizing ADAs.

4.3. Justification for Dose

A 250-mg dose of lebrikizumab has been selected for this study for the following reasons:

- the 250-mg dose was well tolerated in 3 completed Phase 2 studies in patients with AD, and
- the 250-mg dose is being investigated in ongoing Phase 3 studies in patients with AD.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. Participants may be replaced to ensure that approximately 216 participants (108 in each group) complete the study (see Section 9.2).

5. Study Population

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

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, and not continuously throughout the trial.

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 of childbearing potential only)

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

5.1. Inclusion Criteria

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

Age

1. Participant must be aged 18 to 65 years inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined through medical evaluation including:
   - medical history
   - physical examination (conducted at screening or Day -1)
   - laboratory tests, and
   - cardiac monitoring.
3. 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.
   Note: Screening and/or Day -1 laboratory testing may be repeated (once) at the discretion of the investigator for any out-of-range results.
4. have venous access sufficient to allow for blood sampling as per the protocol.
5. agree not to donate blood or plasma until after the end of their participation in the study.
6. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Weight

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

Sex

8. are males or nonpregnant females of childbearing or non-childbearing potential.
    - Reproductive definitions and contraceptive requirements are provided in Appendix 4 (Section 10.4)

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 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 lebrikizumab, related compounds, or any components of the formulation, or history of anaphylaxis as defined by the Sampson criteria (Sampson et al. 2006)
11. have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.
12. have an abnormal blood pressure and/or pulse rate as determined to be clinically significant by the investigator.
13. 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 investigational product; or of interfering with the interpretation of data.
14. have a history or presence of psychiatric disorders deemed clinically significant by the investigator.
15. regularly use known drugs of abuse or show positive findings on drug screening or Day -1.
16. show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
17. show evidence of hepatitis C and/or positive hepatitis C antibody.
18. show evidence of hepatitis B and/or positive hepatitis B surface antigen or hepatitis B core antibody.

19. Infections:
    a. have had a serious infection (such as, 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 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 simplex infection, 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.
20. 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.
21. medical history of allergic reaction to humanized monoclonal antibodies.
22. clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, history of anaphylaxis, and exfoliative dermatitis).
23. ALT or AST >1.5x ULN.
24. TBL >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if TBL is fractionated and direct bilirubin <35%).
25. absolute eosinophil count >ULN.
26. current or chronic history of liver disease. This includes but is not limited to hepatitis virus infections, drug- or alcohol-related liver disease, nonalcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the investigator.
27. known hepatic or biliary abnormalities (with the exception of Gilberts syndrome or asymptomatic gallstones).
28. have donated blood of more than 500 mL within the previous 4 weeks of study screening.

29. 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.
30. have had breast cancer within the past 10 years.
31. are females who are pregnant or lactating.

Prior/concomitant therapy

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 lebrikizumab.
34. intend to use over-the-counter or prescription medication including herbal medications within 7 days prior to dosing. Specific medications listed in Section 6.5, may be allowed.
35. live vaccine(s) within 12 weeks prior to screening or plans to receive such vaccines during the study.
36. it is suggested that participants do not receive nonlive or inactivated vaccinations from 2 weeks prior to, until 2 weeks after lebrikizumab dosing.
37. treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

Prior/concurrent clinical study experience

38. are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
39. are Lilly employees or are employees of Covance.
40. are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

Other exclusions

41. have an average weekly alcohol intake exceeding >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 (25 mL) measure of spirits.
42. are unwilling to stop alcohol consumption 24 hours prior to each study visit.
43. smoke more than 10 cigarettes per day or the equivalent including electronic cigarettes or are unable to abide by CRU smoking restrictions.
44. 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.

45. 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 99). 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 are not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, based upon investigator or designee discretion and discussion with Lilly clinical pharmacologist. Rescreened participants should be assigned a new participant number and must sign a new ICF.

Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period, as stated in Section 5, 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 Interventions Administered

This study involves a comparison of 2-mL (125 mg/mL) SC injections of lebrikizumab using PFS-NSD and AI into the arm, thigh, or abdomen for a total administered dose of 250 mg (Table KGBG.2).

Table KGBG.2. Study Interventions Administered

Study Intervention	Lebrikizumab PFS-NSD	Lebrikizumab AI
Dosage Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s)	125 mg/mL in a 2-mL PFS-NSD	125 mg/mL in a 2-mL AI
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	2-mL injections at site according to the randomization	2-mL injections at site according to the randomization

Abbreviations: AI = autoinjector; PFS-NSD = pre-filled syringe with needle safety device.

6.1.1. Medical Devices

- Lebrikizumab will be administered by the investigator or designee, using a PFS-NSD and an AI.
- Instructions on how to use the PFS-NSD and the AI will be provided.
- All product complaints (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.
- Each device will be labeled according to the country's regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only study personnel may supply, prepare, or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided separately.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. In order to minimize potential bias, assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. On Day 1 (referred to as Visit 1 in IWRS), the site will process Visit 1 in the IWRS prior to the start of study intervention administration and the participant will be assigned a unique subject number and randomized in a 1:1 ratio for delivery device (either PFS-NSD or AI) and within each delivery device group in a 1:1:1 ratio for injection site (arm, thigh, or abdomen) resulting in a 1:1:1:1:1:1 ratio between 6 possible assignment options. The randomization will be stratified by weight categories (less than 70.0 kg, 70.0 to 80.0 kg, and more than 80.0 kg).

6.4. Study Intervention Compliance

Participants are dosed at the site. The investigator or designee will administer study intervention through SC injection to participants. The study intervention (i.e. device and injection location) and study participant identification will be confirmed prior to the time of dosing. The date and time of the administration will be recorded in the source documents and in the CRF.

6.5. Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the last visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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

Acetaminophen, at doses of ≤3 g/day, is permitted for use during the study, other than on the dosing day within 4 hours prior to and 4 hours after dosing. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

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

- reason for use

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

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

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 lebrikizumab administration for the duration of the study.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Not applicable.

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, and
- if enrollment 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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. 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 both from the study interventions and 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 identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), 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 or designee are

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

8. Study Assessments and Procedures

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

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

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

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

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 CRF. Failure or being late (i.e. outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (for example, 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 the following subsections, 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 include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

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

8.2.2. Vital Signs

For each participant, vital sign 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. Measurement from supine is allowed if the participant feels unable to stand.

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.

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 each study period if warranted.

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).

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

ECGs will be interpreted by 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 to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

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

If laboratory values from nonprotocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

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 re-test is allowed. If the re-test 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. Safety Monitoring

The Lilly clinical pharmacologist 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 clinical pharmacologist or CRP will periodically review

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

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests Appendix 6 (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver test results should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over the counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

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

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients 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 normalization ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and

blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

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

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

1. Elevation of serum ALT level to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevation of TBL level to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x 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.

8.2.5.2. Injection-Site Reactions

Symptoms of a local ISR may include erythema, induration, pain, pruritus, and edema.

If an ISR is reported by a participant, investigator, or site staff as an AE of a local ISR, the ISR AE CRF will be used to capture additional information about this reaction (for example, injection-site pain, degree and area of erythema, induration, pruritus, and edema).

In addition, all positive responses of injection-site pain will require an additional assessment using the Pain Visual Analog Scale (Williamson and Hoggart 2005).

8.2.5.3. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the electronic CRF.

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

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 7 (Section 10.7). Laboratory results are provided to the sponsor via the central laboratory.

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

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.

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs
- ADEs
- UADEs
- SADEs, and
- product complaints

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

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

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

After the initial report, the investigator is required to proactively follow up each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE eCRF
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE eCRF
SAE – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	NA	Promptly	SAE paper form
Pregnancy in female participants and female partners of male participants	After the start of study intervention	125 days after dose	Within 24 hours of learning of the pregnancy	Pregnancy eCRF or SAE eCRF
Product complaint associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	product complaint form
Product complaint not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	product complaint form
Updated product complaint information	—	—	As soon as possible upon site awareness	Originally completed product complaint form with all changes signed and dated by the investigator
Product complaint (if investigator becomes aware)	Participation in study has ended	NA	Promptly	Product complaint form

8.3.2. Adverse Events of Special Interest

Adverse events of special interest for this study include

- conjunctivitis
- herpes infection or zoster, and
- parasitic infection or an infection related to an intracellular pathogen.

If these adverse events of special interest are reported, sites will be prompted to collect additional data.

8.4. Treatment of Overdose

For this study, any dose of lebrikizumab greater than 250 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 medical monitor 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 lebrikizumab as specified in the SoA.

A maximum of 5 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 (for example, to obtain data closer to the time of peak serum concentrations) 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.

Serum concentrations of lebrikizumab will be assayed CCI [redacted]. Analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study. CCI [redacted]

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

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

See Appendix 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, venous blood samples will be collected to determine antibody production against lebrikizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of lebrikizumab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of lebrikizumab. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of lebrikizumab at a laboratory approved by the sponsor. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor. Samples may also be used for development and control of an immunogenicity assay.

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 of lebrikizumab using a PFS-NSD and an AI.

9.2. Sample Size Determination

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

A sample size of 108 participants per device group will provide approximately 90% power that the 90% 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 less or equal to 30%, the expected ratio of geometric means is between 0.9 and 1.1, and the %CV are the same for participants from each device group. The 30% CV assumption is based on lebrikizumab PK data in several previous studies.

To properly evaluate AUC from time zero to infinity (AUC[0-∞]), lebrikizumab concentrations must be collected through at least Day 71. To ensure that approximately 216 participants (108 in each group) provide evaluable PK data, approximately 240 participants will be enrolled and receive study drug, assuming up to 10% of the participants may not complete through at least Day 71. Participants who do not complete at least through Day 22 (a period sufficient to determine C_{max}) may be replaced. The replacement participants should be in the same weight category as the original participants.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
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 received a full dose of study intervention and have evaluable PK sample.

9.4. Statistical Analyses

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

9.4.1. General Considerations

PK analyses will be conducted on data from all participants who receive the complete single dose of lebrikizumab and have sufficient evaluable PK data.

Safety analyses will be conducted for all enrolled participants who receive the single dose of lebrikizumab injection, whether or not they complete all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate, and 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.

9.4.2. Pharmacokinetic Analyses

PK parameter estimates for lebrikizumab will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), AUC(0-∞), and C_{max} of lebrikizumab. The time of C_{max} (t_{max}) will also be reported. Other noncompartmental parameters, such as slope of terminal elimination phase, half-life (t1/2), apparent oral clearance, and apparent volume of distribution during the terminal elimination phase may be reported as appropriate.

The primary PK parameter estimates for lebrikizumab will be compared between the reference PFS-NSD (R) and test AI (T). Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) estimates will be evaluated in a linear mixed-effects model with fixed effects for weight group, injection-site location, and device group, and a random effect for participant. The treatment differences will be back transformed to present the ratios of geometric means and the corresponding 90% CIs. Comparisons will be made between the 2 devices.

Bioequivalence between the PFS-NSD and the AI will be declared if the 90% CI for AUC(0-∞), AUC(0-t_{last}), and C_{max} are contained within the 0.80 to 1.25 range.

The t_{max} will be analyzed between the 2 device groups using a Wilcoxon signed rank test. A Hodges-Lehmann estimate of the median differences, 90% CIs, and p-values will be calculated for both treatments.

PK parameter estimates will be summarized by weight category (<70 kg, 70 to 80 kg, and >80 kg) as well as injection-site location (abdomen, arm, thigh) for each device group as appropriate. Additional analyses may be conducted if deemed appropriate.

9.4.3. Safety Analyses

All safety analyses will be made on the Safety Population. All AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of AEs for each device will be presented by severity and by association with lebrikizumab as perceived by the investigator. AEs reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from Medical Dictionary for Regulatory Activities. The number of SAEs will be reported.

9.4.4. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADAs and with TE-ADAs to lebrikizumab will be tabulated. TE-ADAs are defined as those with a titer 2-fold (1 dilution)

greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). 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. The relationship between the presence of antibodies and the safety and PK parameters to lebrikizumab may be assessed.

9.5. Interim Analyses

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

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 International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

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

The investigator will be responsible for the following:

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

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

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 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 that 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 his/her 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, through 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 are 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.

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records 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 clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, 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 system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into

the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). 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 the 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 electronic CRF 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.

Definition of what constitutes source data can be found in Section 10.1.5.

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

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

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

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

Pregnancy testing will be conducted as detailed in the SoA.

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

Clinical Laboratory Tests	Comments
Hematology	Performed locally at Screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated.
Hematocrit	
Hemoglobin	
Erythrocyte count (RBC)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBC)	
Platelets	
Cell morphology (RBC and WBC)	
Differential counts (% and absolute) of:	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Urinalysis	Performed locally at Screening and Day -1 and centrally at Day 1 predose unless otherwise stated.
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Microscopic examination of sediment	
Clinical Chemistry	Performed locally at Screening and Day -1 and centrally at Day 1 predose and all postdose time points unless otherwise stated.
Sodium	
Potassium	
Bicarbonate	
Chloride	
Calcium	
Phosphorus	
Glucose	
Blood urea nitrogen (BUN)	
Creatinine	
Uric acid	
Total cholesterol	

Safety Laboratory Tests

Clinical Laboratory Tests	Comments
Total protein	
Albumin	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	
Gamma-glutamyl transferase (GGT)	
Other tests	
Ethanol testing	Tests may be repeated locally at additional time points at the discretion of the investigator
Urine drug screen	Tests may be repeated locally at additional time points at the discretion of the investigator
Hepatitis B surface antigen	Performed at screening only
Hepatitis B core antibody	Performed at screening only
Hepatitis B surface antibody	Performed at screening only
Hepatitis C antibody	Performed at screening only
HIV	Performed at screening only
QuantiFERON®-TB Gold	Performed at screening only
Pregnancy test (females of childbearing potential only)	Performed at screening, Day -1, and Day 99 or early discontinuation.
FSH (females only)	Performed at screening only

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

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 J2T-MC-KGBG Sampling Summary

Purpose	Approximate 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	2	24
Central clinical laboratory tests[a]	4.5	5	22.5
Pharmacokinetics	3	13	39
Immunogenicity	10	4	40
Pharmacogenetics	10	1	10
Total			180.5
Total for clinical purposes			190

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

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

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.3.1. Definition of AEs and ADE

AE and ADE Definitions

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- An ADE is a nonserious AE that can be attributed to a device. 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 include only events related to investigational devices.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though they 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 NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/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 (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE, SADE, and UADE

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

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 preexisting 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 (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised 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 1 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.

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.

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

AE and SAE

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate electronic CRF page.

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

Assessment of Intensity

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 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.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure 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 the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change 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 the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.4. Reporting of SAEs

SAE Reporting via SAE Report

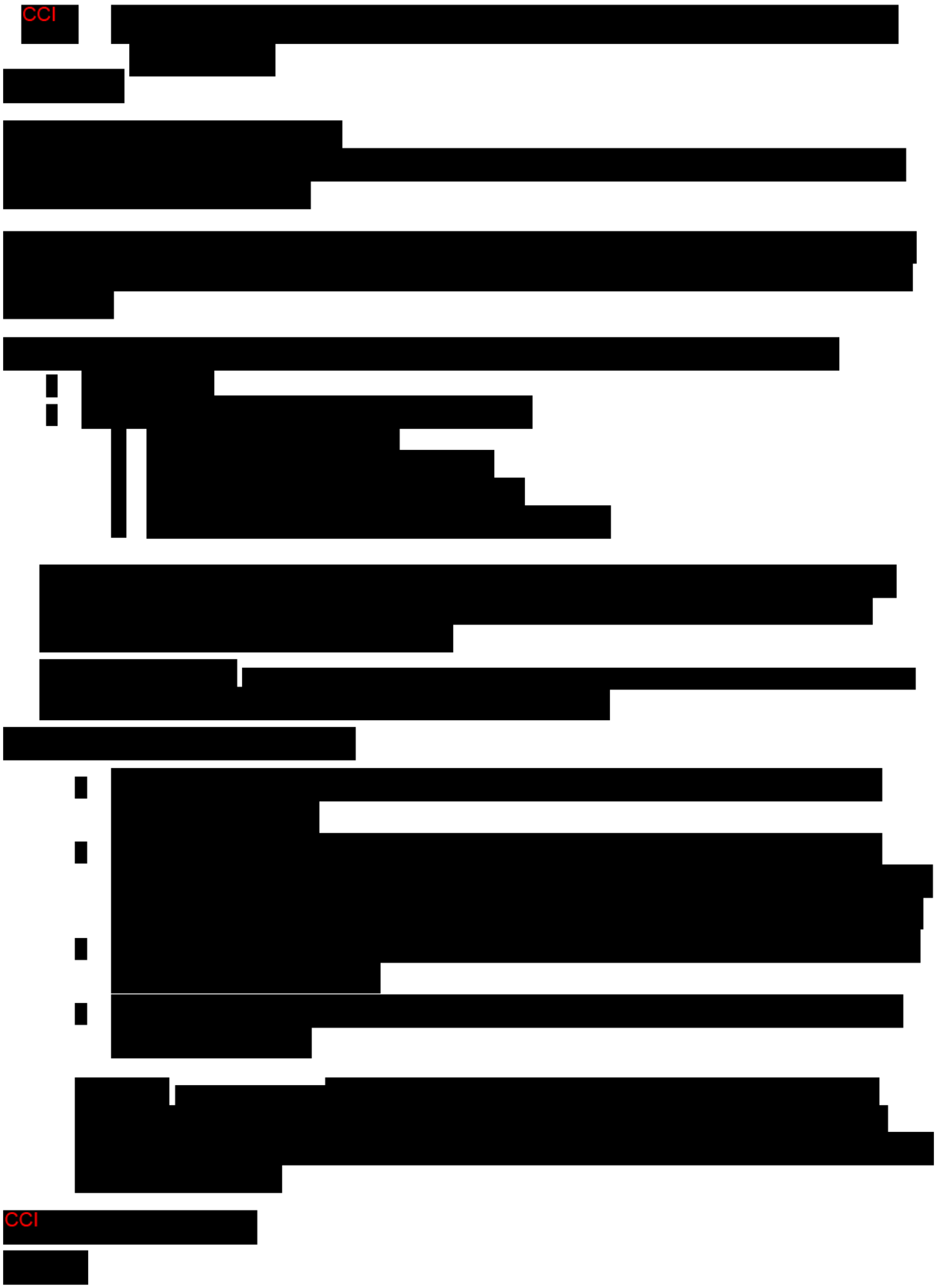
- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts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

10.3.5. Regulatory Reporting Requirements

SAE Regulatory Reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.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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

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

10.9. Appendix 9: Abbreviations

Term	Definition
AD	atopic dermatitis
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
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
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
CV	coefficient of variation
device deficiencies	equivalent to product complaint
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

GCP	good clinical practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IRB	Institutional Review Board
ISR	injection-site reaction
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.
IWRS	interactive web-response system
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as a recipient of an investigational medicinal product or as a control
PFS-NSD	pre-filled syringe with needle safety device
PK	pharmacokinetics
PT	preferred term
SADE	serious adverse device effect
SAE	serious adverse event
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
TE-ADA	treatment-emergent antidrug antibody
t_{max}	time of C_{max}

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.
UADE	unanticipated adverse device effect
ULN	upper limit of normal

10.10. Appendix 10: Protocol Amendment History

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

Amendment [a]: (19 May 2021)

Overall Rationale for the Amendment

This amendment incorporates changes to provide clarification on pregnancy testing, concomitant medications, and the definition of postmenopausal female.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Pregnancy test was revised to be required for females of childbearing potential only.	SoA revised to align with Section 10.2 Appendix 2.
5. Study Population	Pregnancy test was revised to be required for females of childbearing potential only.	Revised to align with Section 10.2 Appendix 2.
6.5. Concomitant Therapy	Clarified requirement to abstain from prescription or nonprescription drugs until the completion of the last visit.	Language was revised for clarity.
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Additional text was added to clarify the definition of postmenopausal female.	Definition of postmenopausal female clarified.
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Pregnancy test was revised to be required for females of childbearing potential only.	Section 10.4 Appendix 4 revised to align with Section 10.2 Appendix 2.

11. References

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