Protocol Addendum J2T-MC-KGBV (Initial)

A Phase 1, Participant- and Investigator-blinded, Randomized, Single-dose Study to Investigate the Safety and Pharmacokinetics of Lebrikizumab in Healthy Chinese Participants

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Approval Date: 01-Sep-2023

Title Page

Protocol Title:

A Phase 1, Participant- and Investigator-blinded, Randomized, Single-dose Study to Investigate the Safety and Pharmacokinetics of Lebrikizumab in Healthy Chinese Participants

Protocol Number: J2T-MC-KGBV

Amendment Number: This is the initial protocol.

Compound: Lebrikizumab (LY3650150)

Brief Title:

A study to investigate the safety and pharmacokinetics of a single subcutaneous dose of lebrikizumab compared with placebo in healthy Chinese participants

Study Phase: 1

Sponsor Name: Eli Lilly and Company

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

Regulatory Agency Identifier Number(s): Not applicable

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

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Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1, Participant- and Investigator-blinded, Randomized, Single-dose Study to Investigate the Safety and Pharmacokinetics of Lebrikizumab in Healthy Chinese Participants

Brief Title: A study to investigate the safety and pharmacokinetics of a single subcutaneous dose of lebrikizumab compared with placebo in healthy Chinese participants

Regulatory Agency Identifier Number: Not applicable

Rationale: Study J2T-MC-KGBV will assess the safety, tolerability, and pharmacokinetics (PK) of 250- and 500-mg subcutaneous (SC) single doses of lebrikizumab (LY3650150) in healthy Chinese participants. CCI

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To describe the safety of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	Incidence of TEAEs and SAEs
Secondary	
To evaluate the PK of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	C_{max}, AUC(0-∞), and AUC(0-t_{last}) of lebrikizumab

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

Overall Design:

This is a Phase 1, participant- and investigator-blinded, randomized, placebo-controlled, single-dose study to investigate the safety, tolerability, and PK of lebrikizumab in healthy Chinese participants.

Brief Summary:

Participants will be assigned sequentially into 1 of 2 cohorts, each with 12 participants. Within each cohort, participants will be randomized in a blinded manner to lebrikizumab or placebo. The planned doses are as follows:

Cohort 1: single 250 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)

Cohort 2: single 500 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)

Screening period

All participants will be screened within 28 days prior to enrollment.

Inpatient period

Eligible participants will be admitted to the clinical research unit (CRU) on Day -1. On Day 1, participants will be randomized, and will receive either lebrikizumab or placebo via SC injection.

Participants may be allowed to leave the CRU after completing assessments on Day 8, or later at ((Ł

Follow-up period

Participants will return for PK and immunogenicity sampling and safety assessments at predefined times up to approximately 120 days postdose.

Safety and tolerability will be assessed through safety laboratory assessments, 12-lead electrocardiograms, vital sign measurements, recording of adverse events, and physical examinations.

Study Population:

Overtly healthy male and female participants aged 18 to 65 years, inclusive, with a body mass index within the range of 18.0 to 28.0 kg/m^2, inclusive, who are native Chinese and born in l Ć (((((((4 ((((grandparents are of Chinese origin. Due to effect of body weight on PK, enrolment of participants with similar body weights between the cohorts is preferred.

Number of Participants:

Approximately 24 healthy Chinese participants who have satisfied the entry criteria and completed all screening assessments will be enrolled to ensure at least 20 evaluable participants complete the study.

Intervention Groups and Duration:

The duration of the study is approximately 21 weeks, and will consist of 3 periods:

Screening period: Day -28 to Day -2

Inpatient period: Day -1 to Day 8

- single SC dose of 250 mg or 500 mg lebrikizumab, or placebo, on Day 1

Follow-up period: discharge until Day 120 ± 3 days.

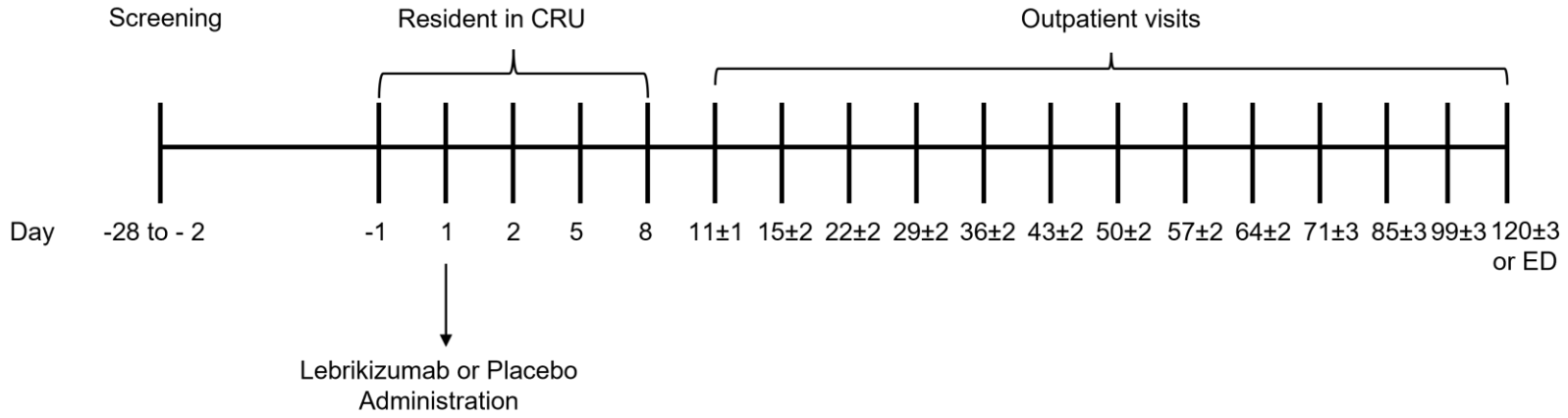
Ethical Considerations of Benefit/Risk:

No clinically significant safety concerns have been identified to date for lebrikizumab up to the highest SC dose given of 500 mg. The highest SC dose of 500 mg has been investigated in Study J2T-DM-KGAS/ILR4660g, a Phase 2 dose-ranging study to evaluate 125, 250, or 500 mg SC of lebrikizumab in adult participants with stable asthma. The safety findings from Study KGAS showed that lebrikizumab was generally well tolerated. Although there was a greater proportion of lebrikizumab-treated participants in the 500 mg dose group, 75% had 1 or more AEs compared with the 2 lower dose groups, 64.2% in both the 125- and 250-mg dose groups; most AEs were mild or moderate in severity, and of the AEs with the highest severity, most were considered not related to the study drug. No SAEs related to the drug or deaths were reported in the 500-mg dose group.

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.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: CRU = clinical research unit; ED = early discontinuation.

1.3. Schedule of Activities (SoA)

	Screening	Inpatient Period					Follow-up Period													Comments
Visit	**1**	**2**					**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
Day	-28 to -2	-1	1	2	5	8	11 ± 1	15 ± 2	22 ± 2	29 ± 2	36 ± 2	43 ±2	50 ±2	57 ±2	64 ±2	71 ±3	85 ±3	99 ±3	120 ±3 or ED	
Procedure																				
Informed consent	X																			
Medical history and demographics	X																			
Review and confirm inclusion/ exclusion criteria	X	X																		
Admission to CRU		X																		
Discharge from CRU						X														
Outpatient visit	X						X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X																	.
Height	X																			
Weight and BMI	X	X																	X	
Ultrasound examination	X																			Ultrasound examination (for example, abdominal) as deemed clinically necessary.
Serology	X																			See Section 10.2
TB testing	X																			See Section 10.2
Chest x-ray (posterior-anterior view)	X																			A lateral chest x-ray may be performed if clinically or radiologically indicated.

Ethanol test and urine drug screen	X	X																X	May be repeated at additional time points at (discretion.
FSH (females only)	X																		See Sections 10.2 and 10.4.
Pregnancy test (WOCBP only)	X	X																X	Serum test at screening only. Urine test at all other time points. See Sections 10.2 and 10.4.
Lebrikizumab or placebo administration			X																See Section 6.1.
Physical examination	X	X		X														X	Full physical examination at screening or Day -1. Symptom-directed examinations at other times, and at (discretion.
Vital signs (sitting pulse rate and blood pressure) and body temperature	X	X	P, 3h	24h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Predose D1 conducted within 2h predose. Postdose assessment 3±1h. Time points may be added at (discretion.

Single 12-lead ECG (supine)	X		P, 3h	24h														X	May be obtained at additional times, if deemed clinically necessary.
Hematology, chemistry, and urinalysis	X	X	P	X	X			X		X		X		X		X	X		X	D1 collected within 2h predose. See Section 10.2.
AE and concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If an AE of an ISR is reported, see Section 8.2.6.2.
Lebrikizumab PK sample			P	24h	X	X	X	X	X	X		X		X		X	X		X	D1 collected within 2h predose.
Immunogenicity sample			P					X		X							X		X	D1 collected within 2h predose.

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; h = hour; ISR = injection site reaction; PK = pharmacokinetic; P = predose; TB = tuberculosis; WOCBP = women of childbearing potential.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

2. Introduction

2.1. Study Rationale

Study J2T-MC-KGBV (KGBV) will assess the safety, tolerability, and PK of 250- and 500-mg SC single doses of lebrikizumab (LY3650150) in healthy Chinese participants. CCI

2.2. Background

Lebrikizumab (LY3650150) is a 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

- atopic dermatitis (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 IB.

Safety summary

As of the IB cutoff date of 01 May 2023, 552 healthy participants and an estimated 6360 participants have been exposed to at least 1 dose of lebrikizumab. Single IV doses up to 10 mg/kg and multiple SC doses up to 500 mg have been administered to humans in clinical trials without dose-limiting toxicity.

Healthy participants

Lebrikizumab has been evaluated in 6 healthy participant studies. Single IV doses administered comprised 0.1, 0.3, 1.0, 3.0, and 5.0 mg/kg. Single SC doses administered comprised 1 mg/kg, and 37.5, 125, 250, and 375 mg.

No deaths were reported in healthy participant studies. Eight treatment-emergent SAEs were reported in lebrikizumab-treated participants. All events were assessed by the investigator as not related to lebrikizumab. No SAE preferred term was reported in more than 1 participant. No participants discontinued the study treatment due to AEs. The most commonly reported TEAE in

greater than 5% of participants was headache. The majority of events were mild or moderate in severity.

Participants with atopic dermatitis, asthma, and other indications

Lebrikizumab has been evaluated in 2562 participants with AD, 3321 participants with asthma, and 477 participants with other indications. Multiple SC doses administered included 37.5 to 500 mg, and IV doses of 0.1 to 10 mg/kg. In participants with AD, the overall frequency of participants with at least 1 TEAE was similar in the lebrikizumab and placebo groups. Conjunctivitis, nasopharyngitis, and headache were the most frequently reported events for lebrikizumab-treated participants. Most TEAEs were mild or moderate in severity. The frequency of participants reporting at least 1 SAE was 1.1% in the lebrikizumab group and 1.8% in the placebo group. No SAEs were reported by more than 1 participant. Four deaths were reported in the lebrikizumab treatment group, none of which were assessed by the investigator as related to treatment. The overall safety profile of lebrikizumab in other indications was consistent with the safety profile of lebrikizumab in the AD population, with the exception of events that have been observed in the underlying disease state being studied or known associated comorbidities.

Pharmacokinetic summary

In clinical studies to date, lebrikizumab has exhibited linear PK in humans with no target-mediated drug disposition over a dose range of 37.5 to 500 mg. A 2-compartment population PK model with first-order absorption and linear clearance best described the PK of lebrikizumab in participants with AD and healthy participants over this dose range. Maximal serum concentrations were generally achieved 7 to 8 days after SC administration. Based on the population PK model, the elimination half-life of lebrikizumab was approximately 25 days, the estimated bioavailability following SC administration was 86%, and exposure was dose proportional over a dose range of 37.5 to 500 mg SC. Clearance was approximately 0.154 L/day, with 24.7% inter-individual variability.

The PK profiles were compared for the 2 maintenance dosing regimens studied in Phase 3, lebrikizumab 250 mg Q2W and 250 mg Q4W, following the 500 mg loading doses at Weeks 0 and 2. The median lebrikizumab concentrations were approximately 50% lower for 250 mg Q4W dosing compared to 250 mg Q2W. Some overlap in lebrikizumab concentrations was predicted in comparison of the 5^{th} and 95^{th} percentiles between 250 mg Q2W and 250 mg Q4W.

Based on the evaluation of the influence of intrinsic and extrinsic factors on lebrikizumab PK across time, no significant effects of the following covariates were identified: age, sex, race, injection site location, disease state, and markers of hepatic and renal function (ALT, AST, and estimated glomerular filtration rate). Body weight was the only factor identified as a significant covariate on lebrikizumab PK, but the Exposure-Response model suggests no dose adjustment on the basis of body weight is needed for the population in the AD studies.

The PK of lebrikizumab in Japanese and White healthy participants was investigated in a Phase 1 study J2T-DM-KGAZ (KGAZ)/GB25741 following single SC administration of 125, 250, and

375 mg doses. Based on this study, there were no meaningful differences in PK between Japanese and White participants at all 3 dose levels.

Anti-lebrikizumab antibodies

In the completed studies of participants with AD, 2.8% to 3.4% of participants developed ADA. 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. In a completed Phase 1 study of healthy participants, the incidence of TE ADA+ participants ranged between 4.2% and 5.0% depending on the adopted injection system, autoinjector or prefilled syringe, respectively. Due to the low immunogenicity, no conclusion could be drawn on the impact of TE ADA on safety.

2.3. Benefit/Risk Assessment

This study will evaluate single SC doses of 250 and 500 mg lebrikizumab. The justification of these doses can be found in Section 4.3.

No clinically significant safety concerns have been identified to date for lebrikizumab up to the highest SC dose given of 500 mg as described in Section 2.2. The highest SC dose of 500 mg has been investigated in Study J2T-DM-KGAS/ILR4660g, a Phase 2 dose-ranging study to evaluate 125, 250, or 500 mg SC of lebrikizumab in adult participants with stable asthma (Noonan et al, 2013). The safety findings from Study KGAS showed that lebrikizumab was generally well tolerated. Although there was a greater proportion of lebrikizumab-treated participants in the 500 mg dose group, 75% had 1 or more AEs compared with the 2 lower dose groups, 64.2% in both the 125- and 250-mg dose groups; most AEs were mild or moderate in severity, and of the AEs with the highest severity, most were considered not related to the study drug. No SAEs related to the drug or deaths were reported in the 500-mg dose group.

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.

Detailed information about the known and expected benefits, risks, and reasonably expected AEs of lebrikizumab may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the safety of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	Incidence of TEAEs and SAEs
Secondary	
To evaluate the PK of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	C_{max}, AUC(0-t_{last}) of lebrikizumab
Exploratory	
To assess the immunogenicity of single SC doses of 250 mg and 500 mg lebrikizumab in healthy Chinese participants	Incidence of TE ADA

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

4. Study Design

4.1. Overall Design

This is a Phase 1, participant- and investigator-blinded, randomized, placebo-controlled, single-dose study to investigate the safety, tolerability, and PK of lebrikizumab in healthy Chinese participants.

Approximately 24 healthy Chinese participants who have satisfied the entry criteria and completed all screening assessments will be enrolled to ensure at least 20 evaluable participants complete the study. Due to effect of body weight on PK, enrolment of participants with similar body weights between the cohorts is preferred. Participants will be assigned sequentially into 1 of 2 cohorts, each with 12 participants. Within each cohort, participants will be randomized in a blinded manner to lebrikizumab or placebo. The planned doses are as follows:

- Cohort 1: single 250 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)
- Cohort 2: single 500 mg dose of lebrikizumab or placebo via SC injection (n=12; 10 lebrikizumab, 2 placebo)

The duration of the study is approximately 21 weeks, and will consist of 3 periods:

- Screening period: Day -28 to Day -2
- Inpatient period: Day -1 to Day 8
    - single SC dose on Day 1
- Follow-up period: discharge until Day 120 ± 3 days.

Screening period

All participants will be screened within 28 days prior to enrollment.

Inpatient period

Eligible participants will be admitted to the CRU on Day -1. On Day 1, participants will be randomized, and will receive either lebrikizumab or placebo via SC injection.

Participants may be allowed to leave the CRU after completing assessments on Day 8, or later at the investigator's discretion.

Follow-up period

Participants will return for PK and immunogenicity sampling and safety assessments at predefined times up to approximately 120 days postdose.

Safety and tolerability will be assessed through safety laboratory assessments, 12-lead ECGs, vital sign measurements, recording of AEs, and physical examinations.

4.2. Scientific Rationale for Study Design

CCI [redacted]

CCI

[redacted]

4.3. Justification for Dose

CCI

[redacted]

4.4. End of Study Definition

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

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA for the last participant.

5. Study Population

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

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 18 to 65 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Are overtly healthy as determined by medical evaluation including medical history, physical examination, safety laboratory assessments, ECGs, and vital signs.
3. Participants must be native Chinese and born in China(((((parents and all 4 (((((((l (.
4. Have safety laboratory assessment 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.
5. Have venous access sufficient to allow for blood sampling as per the protocol.
6. Agree not to donate blood or plasma until after the end of their participation in the study.
7. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Weight

8. Have a body mass index within the range of 18.0 to 28.0 kg/m^2, inclusive.

Sex and contraceptive/barrier requirements

9. Male or female

   Males may participate in this study. No male contraception is required except in compliance with specific local government study requirements.
   Females of childbearing potential and females not of childbearing potential may participate in this study.

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

Informed consent

10. Are capable of giving signed informed consent as described in 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

11. 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).
12. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis.
13. Have an abnormal blood pressure or pulse rate as determined to be clinically significant by the investigator.
14. 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.
15. Have a history or presence of psychiatric disorders deemed clinically significant by the investigator.
16. Have significant allergies to monoclonal antibodies.
17. Clinically significant multiple or severe drug allergies, 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.
18. 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, (₡ ₡’ (₡ -1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the investigator.
19. Known hepatic or biliary abnormalities, with the exception of Gilberts syndrome or asymptomatic gallstones.
20. Have donated blood of more than 500 mL within the previous 4 weeks of study screening.
21. 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.
22. Have had breast cancer within the past 10 years.
23. Are females who are pregnant or intend to become pregnant, or lactating.

Prior/concomitant therapy

24. Have received treatment with biologic agents, such as monoclonal antibodies, including marketed drugs, within 3 months or 5 half-lives, whichever is longer, prior to dosing.
25. Have previously completed or withdrawn from this study or any other study investigating lebrikizumab.
26. Have used or intend to use over-the-counter, prescription medication including herbal medications and traditional Chinese medicines within 7 days, or 14 days if the drug is a potential enzyme inducer, or 5 half-lives, whichever is longer, prior to dosing. Stable doses of hormone contraceptives, hormone-replacement therapy or thyroid replacement are permitted, at the discretion of the investigator. Supplements, for example vitamin supplements, may be permitted at the discretion of the investigator.
27. Have received a live vaccine, including attenuated live vaccines, within 12 weeks prior to screening or plan to receive such vaccines during the study. It is suggested that participants do not receive non-live or inactivated vaccinations from 2 weeks prior to until 2 weeks after lebrikizumab dosing.

Prior or concurrent clinical study experience

28. 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.
29. 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 dosing.

Diagnostic assessments

30. Regularly use known drugs of abuse or show positive findings on drug screening.
31. Show evidence of human immunodeficiency virus infection or positive human immunodeficiency virus antibodies.
32. Have a positive HCV antibody test. Participants with a positive HCV antibody test at screening can be included only if a confirmatory HCV RNA test is negative.
33. Show evidence of hepatitis B and/or positive hepatitis B surface antigen or hepatitis B core antibody.
34. Show evidence of active or latent TB, as documented through
    medical history
    examination
    posterior to anterior chest x-rays read by a radiologist, pulmonologist, or designee; a lateral chest x-ray may be performed if clinically or radiologically indicated, or
    positive, not indeterminate, QuantiFERON®-TB Gold test or T-SPOT® TB test or have had household contact with a person with active TB, unless appropriate and documented prophylaxis treatment has been given. If a repeat test is also indeterminate, the participant will not be eligible. Participants with any history of

active TB are excluded from the study, regardless of previous or current TB treatments. The choice to perform a QuantiFERON-TB Gold test or a T-SPOT TB test will be made by the investigator according to local standard of care.

35. ALT or AST greater than 1.5 × ULN.
36. Total bilirubin greater than 1.5 × ULN. Isolated bilirubin greater than 1.5 × ULN is acceptable if TBL is fractionated and direct bilirubin is less than 35%.
37. Absolute eosinophil count greater than ULN.

Infections

38. 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; 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.
39. Have or have had an infection typical of an immunocompromised host or that occurs with increased incidence in an immunocompromised host, including, but not limited to, Pneumocystis jirovecii pneumonia, histoplasmosis, or coccidioidomycosis, or have a known immunodeficiency.
40. 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.
41. 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.

Other exclusion criteria

42. Are Lilly employees or are employees of a third-party organization involved with the study.
43. Are investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
44. Have an average weekly alcohol intake exceeding greater than 21 units for males or greater than 14 units for females. One unit is equivalent to 8 g of alcohol, which is equivalent to a half pint, approximately 240 mL, of beer, one 125 mL glass of wine, or one 25 mL measure of spirits.
45. Are unwilling to stop alcohol consumption 24 hours prior to each study visit.
46. Smoke more than 10 cigarettes per day or the equivalent including electronic cigarettes or are unable to abide by CRU smoking restrictions.
47. 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.
48. In the opinion of the investigator, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

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
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5.3.2. Substance Use: 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

Exercise

Participants will be advised to maintain their regular levels of physical activity or exercise; however, they should not undertake vigorous or prolonged exercise within 48 hours prior to any visit in which laboratory safety tests will occur. While certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

Blood or blood products donation

Study participants should be instructed not to donate blood or blood products during the study until the end of study participation.

5.4. Screen Failures

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

Rescreening is not permitted. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Randomization of a Participant

Not applicable.

6. Study Interventions and Concomitant Therapy

Study intervention is defined as any medicinal products or medical devices intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This table lists the interventions used in this clinical study.

Intervention Name	Lebrikizumab	Placebo
Dosage Formulation	250 mg (125 mg/mL), 2 mL solution for injection in a prefilled syringe with needle safety device	Placebo solution in a prefilled syringe with needle safety device
Dosage Levels	Cohort 1: 250 mg (1 injection of 250 mg) Cohort 2: 500 mg (2 injections of 250 mg)	Not applicable
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	Single dose administration	Single dose administration
Packaging and Labeling	Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.	

6.1.1. Administration Details

Lebrikizumab or placebo will be administered by the investigator or designee, using a prefilled syringe with needle safety device. Each prefilled syringe is intended for a single 2 mL dose, 250 mg, administered subcutaneously in the abdomen, thigh, or back of the upper arm. Whenever possible, study drug administration should be carried out by the same personnel. The location of the injection(s) will be recorded. Multiple injections making up a single dose for Cohort 2 should be apart from each other, so ISRs, if any, can be observed separately. Administration of placebo will match that for lebrikizumab as either 1 or 2 injections. Participants may stay in the semi-recumbent position for 2 hours following study drug administration, where possible.

6.2. Preparation, Handling, Storage, and Accountability

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

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

All study intervention must be stored in a secure, environmentally controlled, and monitored, manual or automated, area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

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

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

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

6.3. Assignment to Study Intervention

On Day 1, participants will be assigned a unique randomization number in ascending numerical order. The randomization number will indicate ((((lebrikizumab or placebo, according to the randomization schedule generated prior to the study by the statistics department at the sponsor or its designee. Due to effect of body weight on PK, enrolment of participants with similar body weights between the cohorts is preferred. Each participant will be (((₡ ((((((number.

6.4. Blinding

This is a participant- and investigator-blind study. The sponsor will not be blinded to treatment assignment; however, to preserve the blinding of the study, a minimum number of Lilly personnel and staff at the CRU, namely, CRU pharmacy staff, will see the randomization table before the study is complete. Individuals involved in the blinding of the study intervention will not be involved in any of the clinical aspects of the study, including study intervention administration and AE assessments.

Participants will be randomly assigned in a 5:1 ratio to receive lebrikizumab and placebo. All study site personnel, except staff who prepare or dispense study medication, will remain blinded (((((((((((₡

To maintain this blind, an otherwise uninvolved third party, unblinded site or CRU pharmacy staff, will be responsible for the removal of the tear-off portion of the label and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

In the event of a quality assurance audit, the auditor will be allowed access to unblinded study intervention records at the site to verify that randomization or dispensing has been done accurately.

Emergency codes will be available to the investigator. A code, which reveals the study intervention for a specific study participant, may be opened during the study only if the (- (((((((E

In case of an emergency, the investigator has the sole responsibility for determining if unblinding

Where feasible and when timing of the emergent situation permits, the investigator should

assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician or clinical pharmacologist for the participant to continue in the study.

6.5. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.6. Dose Modification

Dose adjustments are not permitted in this study.

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

Study intervention will not be made available after conclusion of the study to participants.

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than the dose of study intervention assigned through randomization will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE or SAE and laboratory abnormalities as medically appropriate, and
- obtain a blood sample for PK analysis if requested by the medical monitor, determined on a case-by-case basis.

6.9. Prior and Concomitant Therapy

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

reason for use

dates of administration including start and end dates, and

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

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

Participants must abstain from taking over-the-counter, prescription medication including herbal medications and traditional Chinese medicines within 7 days, or 14 days if the drug is a potential enzyme inducer, or 5 half-lives, whichever is longer, prior to dosing and throughout the study. In addition, prior to dosing, the participant must also abstain from taking

biologic agents, such as monoclonal antibodies, including marketed drugs, within 3 months or 5 half-lives, whichever is longer, and

live vaccines, including attenuated live vaccines, within 12 weeks prior to screening.

Stable doses of hormone contraceptives, hormone-replacement therapy or thyroid replacement are permitted, at the discretion of the investigator. Supplements, for example vitamin supplements, may be permitted at the discretion of the investigator.

Acetaminophen, at doses of less than or equal to 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor, if required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.

7.1. Discontinuation of Study Intervention

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

at any time at (own request for any reason or without providing any reason

at the request of (designee, for example, parents or legal guardian

at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or

if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

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

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

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.

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.

Section 10.2 lists the laboratory tests that will be performed for this study and Section 10.2.1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. See Section 10.1.9 for details about sample retention and custody.

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Physical examinations will be conducted according to Section 1.3.

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, single vital sign measurements should be conducted according to Section 1.3. If warranted, additional vital signs may be measured.

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

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

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

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

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to Section 1.3. All single ECGs recorded should be stored at the investigational site.

ECGs may be obtained at additional times when deemed clinically necessary, for example, to
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ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 minutes before ECG collection, and remain supine and awake during ECG collection.

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

ECGs will be interpreted by the investigator, a physician or qualified designee, at the site as soon after the time of ECG collection as practical, to determine whether the participant meets entry criteria.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical safety laboratory assessments to be performed and the SoA in 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. l (
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All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and local laboratory procedures and requirements.

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

8.2.4.1. Tuberculosis Testing

Participants will be tested, using either a QuantiFERON or T-spot test, and a chest x-ray conducted as indicated in the SoA in Section 1.3 for evidence of active or latent TB. If the test is indeterminate, one retest is allowed. If the retest is indeterminate, the participant will be excluded from the study.

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

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

8.2.5. Pregnancy Testing

Pregnancy testing will be conducted according to Section 1.3.

8.2.6. Safety Monitoring

8.2.6.1. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Discontinuation

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

I I I I I		
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**
ALT or AST greater than or equal to 3×ULN	X	
ALP greater than or equal to 2×ULN	X	
TBL greater than or equal to 2×ULN[b]	X	
ALT or AST greater than or equal to 5×ULN	X	X
ALP greater than or equal to 2.5×ULN	X	X
ALT or AST greater than or equal to 3×ULN with hepatic signs or symptoms[a]	X	X
ALT or AST greater than or equal to 5×ULN for more than 2 weeks	X	X
ALT or AST greater than or equal to 8×ULN	X	X
ALT or AST greater than or equal to 3×ULN and TBL greater than or equal to 2×ULN[b]	X	X
ALP greater than or equal to 3×ULN	X	X
ALP greater than or equal to 2.5×ULN and TBL greater than or equal to 2×ULN[b]	X	X
ALP greater than or equal to 2.5×ULN with hepatic signs or symptoms[a]	X	X

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

[b] r (((p (, the threshold for TBL may be higher.

8.2.6.1.1. Close Hepatic Monitoring

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

ALT or AST greater than or equal to 3×ULN or
ALP greater than or equal to 2×ULN or
TBL greater than or equal to 2×ULN[a]

[a] r (((p (, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

Laboratory tests detailed in Section 10.5, including ALT, AST, ALP, TBL, direct bilirubin, complete blood count with differential, gamma-glutamyl transferase, and creatine kinase should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.

In addition to laboratory tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include

- physical examination and a thorough medical history, including current symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- concomitant medications including over-the-counter
- herbal and dietary supplements
- history of alcohol drinking, and
- other substance abuse.

8.2.6.1.2. Comprehensive Hepatic Evaluation

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

ALT or AST greater than or equal to 5×ULN **or**
ALP greater than or equal to 2.5×ULN **or**
ALT or AST greater than or equal to 3×ULN with hepatic signs or symptoms[a] **or**
ALT or AST greater than or equal to 5×ULN for more than 2 weeks **or**

ALT or AST greater than or equal to 8×ULN **or**
ALT or AST greater than or equal to 3×ULN and TBL greater than or equal to 2×ULN[b] or INR greater than or equal to 1.5

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

[b] r (((p (, the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for

- prothrombin time-INR
- viral hepatitis A, B, C, and E
- autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or computed tomography scan.

k (((((((((((((((in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- urine toxicology screen
- ” (
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and t (((((((condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including

- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or
- a liver biopsy.

Clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until levels normalize or return to approximate baseline values.

All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.6.2. Injection Site Reactions

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

If an ISR is reported by a participant or site staff, it will be recorded as an AE of a local ISR, and the ISR 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).

8.2.6.3. Hypersensitivity Reactions

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

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

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

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

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

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

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

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

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

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

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

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; PC = product complaint; N/A = not applicable; SAE = serious adverse event
* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

– ((((((((((((((partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

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

will obtain a consent to release information from the pregnant female partner directly, and

within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

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

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status, presence or absence of anomalies, or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion, occurring at less than 20 weeks gestational age, or still birth, occurring at greater than or equal to 20 weeks gestational age, is always considered to be an SAE and will be reported as such.

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

8.3.3. Adverse Events of Special Interest

Adverse events of special interest for this program include

conjunctivitis

keratitis

ISRs, and

hypersensitivity reactions.

If these AEs of special interest are reported, sites will be prompted to collect additional details and data.

8.4. Pharmacokinetics

Blood samples will be collected for measurement of serum concentrations of lebrikizumab as specified in the SoA in Section 1.3.

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

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.4.1. 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.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Antibodies to lebrikizumab will be evaluated in blood samples collected from all participants according to the SoA in Section 1.3. 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.

TE ADA are defined in Section 9.3.4.

Immunogenicity will be assessed by CCI [redacted] Antidrug antibody samples will be stored as per local regulation or IRB/IEC requirements. Samples will be immediately destroyed once lebrikizumab is launched or there is no further request on testing the samples from China authority.

8.9. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary objective of this study is to describe the safety of a single dose of 250 mg and 500 mg lebrikizumab in healthy Chinese participants. There will be no formal hypothesis testing.

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled	All participants who were assigned to study intervention, regardless of whether they take any doses. Participants will be analyzed according to the treatment group to which they have been assigned.
Safety analysis	All participants randomly assigned to study intervention and who receive study intervention. Participants will be analyzed according to the intervention they actually received.
Immunogenicity analysis	Same as safety population.
Pharmacokinetic analysis	All enrolled participants who receive a full dose of lebrikizumab and have evaluable PK data.

9.3. Statistical Analyses

9.3.1. General Considerations

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

PK analyses will be conducted on data from all enrolled participants who receive a full dose of lebrikizumab and have evaluable PK data.

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

Summary statistics, data tabulations, and data graphs will be provided as deemed appropriate.

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

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

9.3.2. Safety Analysis

The primary endpoint is the incidence of TEAEs and SAEs to investigate the safety of lebrikizumab versus placebo following SC administration of a single dose in Chinese healthy participants.

Safety data will be listed and summarized by treatment group.

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

Other safety parameters that will be assessed include safety laboratory parameters and vital signs. Safety parameters will be listed and summarized using standard descriptive statistics as appropriate.

The incidence of AEs for each treatment will be presented by severity and by association with the study intervention as perceived by the investigator. AEs reported to have occurred prior to randomization will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of TEAEs and SAEs will be reported.

9.3.3. Pharmacokinetic Analysis

Noncompartmental analysis will be conducted, and PK parameters such as maximum observed drug concentration, time to maximum observed drug concentration, area under the concentration versus time curve from time zero to infinity, and area under the concentration versus time curve from time zero to t, where t is the last time point with a measurable concentration will be reported for lebrikizumab. Other noncompartmental parameters such as apparent clearance, apparent volume of distribution, and half-life may be reported, as appropriate.

Exploratory graphical analyses relating lebrikizumab serum exposure and immunogenicity may be conducted.

9.3.4. Immunogenicity Analysis

The frequency and percentage of participants with pre-existing ADA and with TE ADA to lebrikizumab may be tabulated by treatment. TE ADA are defined as those with a titer 2-fold, 1 dilution, greater than the minimum required dilution if no ADA were detected at baseline, treatment-induced ADA, or those with a 4-fold, 2 dilutions, increase in titer compared to baseline if ADA were detected at baseline, treatment-boosted ADA.

The frequency of neutralizing antibodies and distribution of maximum titers may also be tabulated in TE ADA+ participants by treatment.

The relationship between the presence of antibodies to lebrikizumab and safety may be assessed.

9.4. Interim Analysis

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

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.5. Sample Size Determination

Approximately 24 participants will be enrolled in 2 dosing cohorts for at least 20 evaluable participants to complete the study. The sample sizes described are customary for Phase 1 studies evaluating safety and PK parameters and are not powered on the basis of statistical hypothesis testing. Each cohort will comprise approximately 12 participants with a randomization ratio of 5:1 between lebrikizumab and placebo. Participants who discontinue the study before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant can complete the entire study period.

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 CIOMS International Ethical Guidelines

Applicable ICH GCP Guidelines, and

Applicable laws and regulations.

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

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

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

The investigator will be responsible for the following:

providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, if applicable, and all other applicable local regulations, and

reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

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

10.1.2. Informed Consent Process

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

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

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

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

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

10.1.3. Data Protection

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

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

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

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

The transfer of personal data is subject to appropriate safeguards through contractual agreements ((((((((((((legislations including the General Data Protection Regulation.

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 study due to safety findings, this decision will be communicated by Lilly to all investigators, for example, by phone or email, as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly

personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

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

Data

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

10.1.5. Data Quality Assurance

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

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

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

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

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

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

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

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in

accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

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

Data Capture System

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

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

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

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

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

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the ((((E (((((E

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

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

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

for study termination due to discontinuation of further study intervention development
for site termination due to

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

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

10.1.8. Publication Policy

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for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Participant Visit
Pharmacokinetic	Sponsor or designee	1 year
Immunogenicity	Sponsor or designee	Per local regulation or the IECs/IRBs requirements. Samples will be immediately destroyed once lebrikizumab is launched or there is no further request on testing the samples from China authority.
Hematology, chemistry, urinalysis, and hepatic monitoring (both central and local laboratory)	Sponsor or designee	These samples are destroyed after protocol-specific tests are performed, based on the requirements for the laboratory procedures, laws, regulations, or internal laboratory certification standard.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the laboratories listed in Section 10.7.

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

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

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

Investigators must document their review of the laboratory safety results.

Laboratory or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

I I		Comments
Hematology		
Hematocrit	Cell morphology (RBC and WBC)	
Hemoglobin	Differential counts (% and absolute) of:	
Erythrocyte count (RBC)	Neutrophils	
Mean cell volume	Lymphocytes	
Mean cell hemoglobin	Monocytes	
Mean cell hemoglobin concentration	Eosinophils	
Leukocytes (WBC)	Basophils	
Platelets		
Clinical Chemistry		
Sodium	Total cholesterol	
Potassium	Total protein	
Chloride	Albumin	
Calcium	Total bilirubin	
Phosphorus	Direct bilirubin	
Glucose	Alkaline phosphatase	
Blood urea nitrogen or urea	Aspartate aminotransferase	
Creatinine	Alanine aminotransferase	
Uric acid	Gamma-glutamyl transferase	
Urinalysis		
Specific gravity	Urobilinogen	
pH	Blood	
Protein	Nitrite	
Glucose	Microscopic examination of sediment	
Ketones		
Bilirubin		
Other Tests		
Ethanol testing	Urine drug screen	Tests may be repeated locally at additional time points at the discretion of the investigator.
QuantiFERON®-TB Gold or T-SPOT®	Urine and serum pregnancy test (women of childbearing potential only)	
FSH (females only)		
Serology		
Hepatitis B surface antigen	HIV	
Hepatitis B core antibody	Hepatitis C antibody	

Pharmacokinetic Samples		Results will not be provided to the investigative sites.
Lebrikizumab concentration		
Immunogenicity (ADA) Samples		Results will not be provided to the investigative sites.
Anti-LY3650150 antibodies	Anti-LY3650150 antibodies neutralization	

Abbreviations: ADA = anti-drug antibody; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; TB = tuberculosis; 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.

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18.5	1	18.5
Hematology and chemistry[a]	5.5	11	60.5
Pharmacokinetics	3	13	39
Immunogenicity	10	5	50
Total			168
Total for clinical purposes			170

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

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection, ideally prior to the next dose after the event, to assess post-event return-to-baseline values.

Timing	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase complements (C3, C3a, and C5a) cytokine panel (IL-V(ru L (ru LI((((panel that includes these 3 cytokines)
Collect only if not already collected on the same day as the event. Note: If collecting, collect up to 12 hours after the start of the event.	LY3650150 anti-drug antibodies LY3650150 concentration

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

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

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

Events meeting the AE definition

Any abnormal laboratory test results, hematology, clinical chemistry, or urinalysis, or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
Medication error, misuse, or abuse of investigational medicinal product, including signs, symptoms, or clinical sequelae.

Events <u>NOT</u> 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
(((((((((E
The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, un (((((((((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 or convenience admission to a hospital.
Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

Results in death

Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

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

Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

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

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

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

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and product complaint recording

When an AE/SAE/product complaint 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/product complaint information in the (((((((((AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

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

It is **not** acceptable for the investigator to send photocopies of the partic (((to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

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

Assessment of intensity

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

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

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

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

j ((((((((((₵ ₵ G (arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

The investigator will also consult the IB in their assessment.

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

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

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

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

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible.

This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor 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 Global Patient Safety Clinical Trial Serious Adverse Event Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they have a congenital anomaly such as Müllerian agenesis are infertile due to surgical sterilization, or are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

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

	I
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation declare abstinence just for the duration of a trial, or use the withdrawal method

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

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

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	female sterilization[a] (including fallopian tube ligation, hysteroscopic sterilization) combination oral contraceptive pill progestin-only contraceptive pill (mini-pill) implanted contraceptives injectable contraceptives contraceptive patch (only women <198 pounds or 90 kg) total abstinence vasectomy (for men in clinical trials and for female partner if only sexual partner) fallopian tube implants (if confirmed by hysterosalpingogram) combined contraceptive vaginal ring, or intrauterine devices
Effective contraception	male or female condoms with spermicide diaphragms with spermicide or cervical sponges barrier method with use of a spermicide

Methods	Examples
	○ condom with spermicide ○ diaphragm with spermicide, or ○ female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	spermicide alone periodic abstinence fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) withdrawal postcoital douche, or lactational amenorrhea

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

10.4.2.2. Male Participants

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

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See Section 8.2.6.1 for guidance on appropriate test selection.

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

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing, in the table below.

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

The local laboratory must be qualified in accordance with applicable local regulations.

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

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

[a] Not required if anti-actin antibody is tested.

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.6. Appendix 6: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

r (((₡ (((((₡ ((implement changes if permitted by local regulations.

After approval by local IRBs/IECs, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study, and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section (“ C
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, AE and concomitant medications.

Other alternative locations - Participants may visit local hospital other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include but are not limited to safety monitoring (physical examination, vital signs, ECG, body temperature, neurological examinations) and sample collections for clinical laboratory tests.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 28 days.

The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances.

If screening is interrupted for less than 28 days from screening to randomization visit, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 28 days from first screening.
– (((((((((((((Ꞓ
and the site should document the reason for delay.
The site should a (((((((((
confirmation in the source documentation.

If screening is interrupted for more than 28 days from screening to randomization visit, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

” ((((((₡ ((((((₡ (should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study. For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the inves source documentation and should be transferred to the site in a secure and timely manner.

10.7. Appendix 7: Clinical Laboratories and Specimen Disposal Units

CCI

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10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AD	atopic dermatitis
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRU	clinical research unit
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HCV	hepatitis C virus
IB	r (k
ICF	informed consent form

ICH International Council for Harmonisation

IEC independent ethics committee

IL interleukin

informed consent A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are ((((((E(r (((((means of a written, signed and dated informed consent form.

investigational product A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

IRB institutional review board

ISR injection site reaction

IV intravenous

medication error Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more ((((((c(((C(((C(e right dose, right route, at the right time.

In addition to the core five rights, the following may also represent medication errors:

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(((on past the recommended in-use date

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(((((((((((((medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or

((((C((C((E

misuse Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription

participant n ((l mr∞l ((c((((((((C(either as recipient of an investigational medicinal product or as a control

PK pharmacokinetics

Q2W every 2 weeks

Q4W every 4 weeks

SAE serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TB	tuberculosis
TBL	total bilirubin
TE ADA	treatment-emergent anti-drug antibody
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WOCBP	women of childbearing potential

11. References

Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol*. 2013 Sep;132(3):567-574.e12. doi: 10.1016/j.jaci.2013.03.051.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397. doi:10.1016/j.jaci.2005.12.1303

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

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