Protocol I1F-MC-RHCU(b)

Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

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Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

Ixekizumab (LY2439821)

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1. Protocol Synopsis

Title of Study:
Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

Rationale:
Two studies (I1F-MC-RHCS [RHCS] and I1F-MC-RHCT [RHCT]) in healthy volunteers have been conducted for the purpose of selecting an alternative formulation to the currently marketed formulation. Study RHCS was conducted to investigate injection site pain following subcutaneous (SC) injections of 2 ixekizumab alternate formulations compared to the ixekizumab commercial formulation using a prefilled syringe (PFS). Study RHCT was conducted to compare the relative bioavailability, safety, and tolerability of 2 alternate formulations of ixekizumab to the commercial product when administered subcutaneously via PFS. The active ingredient concentration and the injection volume of the alternate formulations were the same as the commercial drug product.

Based on the results of Studies RHCS and RHCT, a formulation was selected to take forward into the present Study I1F-MC-RHCU (RHCU) which is being conducted to evaluate the bioequivalence of the selected ixekizumab alternate formulation (test), compared to the ixekizumab commercial formulation (reference) when administered using an autoinjector (AI).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To evaluate the bioequivalence of a single 80 mg SC dose of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference)	• C_{max}, AUC(0-∞), AUC(0-t_{last})
Secondary To describe the safety and tolerability of a single 80 mg SC dose of ixekizumab alternate formulation (test) compared to the commercial formulation (reference)	• TEAEs, SAEs

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

Summary of Study Design:
Study RHCU is a Phase 1, subject-blind, 2-arm, randomized, parallel-design study in healthy subjects.

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and stratified into weight, formulation, and injection site categories as described in the treatment arms and planned

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

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, temperature, recording of adverse events (AEs), physical examination (PE)/medical assessments, Columbia Suicide Severity Rating Scale (C-SSRS), and immunogenicity.

Treatment Arms and Planned Duration for an Individual Subject:
At screening, subjects will be stratified into 1 of 3 weight categories (<70.0 kg, 70.0 to 80.0 kg, >80.0 kg). Within the 3 weight categories, subjects will be randomized 1:1 to either 80-mg ixekizumab commercial formulation (reference) or 80-mg ixekizumab alternate formulation (test) and subrandomized 1:1:1 to injection site (arm, thigh, or abdomen). On Day 1, subjects will receive a single SC dose according to the randomization plan. Subjects will participate for up to 16 weeks.

Number of Subjects:
Up to approximately 240 subjects may be enrolled so that approximately 216 subjects complete the study (108 in the 80-mg ixekizumab commercial formulation [reference] group and 108 in the 80-mg ixekizumab alternate formulation [test] group).

Statistical Analysis:
Pharmacokinetic parameters will be evaluated to determine the bioequivalence of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference). Log-transformed maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) parameters will be evaluated in a linear mixed-effects model with fixed effects for formulation and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI). Bioequivalence will be concluded if the 90% CI is completely contained within the interval (0.80, 1.25).

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

Safety laboratory parameters and vital signs data will be listed and summarized using standard descriptive statistics, where possible. Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by subject. Only subjects that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be included in the listing (i.e., if a subject's answers are all 'no' for the C-SSRS, then that subject will not be displayed). Hospital Anxiety Depression Scale (HADS) item scores will be listed for subjects with HADS depression subscale ≥11 at any time.

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

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

2. Schedule of Activities

Study Schedule Protocol I1F-MC-RHCU

	Screening	Days															Comments
Procedure	-28 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	85/ED ±3d	
Informed Consent	X																	
Medical History and Demographics	X																	
Review/Confirm Inclusion/Exclusion Criteria	X	X																
Subject Admission to CRU		X																
Subject Discharge from CRU			X															Subjects may be discharged after completion of the 4-hour safety assessments on Day 1, at the investigator's discretion.
Outpatient Visit				X	X	X	X	X	X	X		X		X		X	X	
Safety Assessment (Telephone Call)											X		X		X			
Randomization			X															
C-SSRS Lilly Self-Harm Supplement	X	X				X				X							X	At screening, 'Baseline - Screening' questionnaire to be used; all other time points use 'Since Last Visit' questionnaire.
HADS Depression Subscale	X	X				X				X							X	
Height, Weight, and BMI	X																X	Weight only at Day 85/ED.
Body Temperature		X	P	X	X	X	X	X	X	X		X		X		X	X	

	Screening	Days															Comments
Procedure	-28 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	85/ED ±3d	
Physical Examination /Medical Assessment		X															X	Full physical examination/medical assessment at Day -1 and at Day 85/ED. Symptom-directed examinations/assessments may be conducted at other visits, as deemed necessary by the investigator.
Vital Signs (sitting) (hours)	X	X	P, 2-4			X		X		X		X					X	Vital signs can be taken at any time during the 2- to 4-hour window of Day 1. Time points may be added if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X	X						X		X							X	See Appendix 2, Clinical Laboratory Tests, for details.
Serology	X																	See Appendix 2, Clinical Laboratory Tests, for details.
QuantiFERON®-TB Gold Test/TST	X																	
Ethanol Test and Urine Drug Screen	X	X																May be repeated at the discretion of the investigator.
FSH Test	X																	Females only, if applicable (see Section 6.1, criterion 1b see 3ii).
Pregnancy Test	X	X															X	Females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at other indicated times.

	Screening	**Days**															**Comments**
Procedure	-28 to -2 days prior to Day 1	-1	1	3	5 ±1d	8 ±1d	11 ±1d	15 ±2d	22 ±2d	29 ±2d	36 ±2d	43 ±2d	50 ±2d	57 ±3d	64 ±3d	71 ±3d	85/ED ±3d	
Single 12-lead ECG	X																X	
Ixekizumab Administration			X															Subjects will fast (water is permitted) from 1 hour before until 1 hour postdose.
Ixekizumab PK Sample			P	X	X	X	X	X	X	X		X		X		X	X	
Immunogenicity Sample			P					X		X							X	A time-matched PK should be taken at each immunogenicity sample time point.
Pharmacogenetic Sample			P															
AEs and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	If an AE of ISR is reported, the investigator or designee will complete a supplemental ISR AE form.

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; C-SSRS = Columbia Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; ISR = injection site reaction; P = predose; PK = pharmacokinetics; TB = tuberculosis; TST = tuberculin skin test.

3. Introduction

3.1. Study Rationale

Ixekizumab is administered subcutaneously and is available commercially as an injectable solution in either a manual prefilled syringe (PFS) or an autoinjector (AI). Each PFS or AI contains 80 mg ixekizumab in 1 mL. Two studies (I1F-MC-RHCS [RHCS] and I1F-MC-RHCT [RHCT]) in healthy volunteers have been conducted for the purpose of selecting an alternative formulation to the currently marketed formulation.

Study RHCS was conducted to investigate injection site pain following subcutaneous (SC) injections of 2 ixekizumab alternate formulations compared to the ixekizumab commercial formulation using a PFS. Study RHCT was conducted to compare the relative bioavailability, safety, and tolerability of 2 alternate formulations of ixekizumab to the commercial product when administered subcutaneously via PFS. The active ingredient concentration and the injection volume of the alternate formulations were the same as the commercial drug product.

Based on the results of Studies RHCS and RHCT, a formulation was selected to take forward into the present Study I1F-MC-RHCU (RHCU) which is being conducted to evaluate the bioequivalence of the selected ixekizumab alternate formulation (test), compared to the ixekizumab commercial formulation (reference) when administered using an AI.

3.2. Background

Ixekizumab (LY2439821, Taltz®) is a humanized immunoglobulin G subclass 4 monoclonal antibody that binds with high affinity and specificity to interleukin 17A (IL-17A), a proinflammatory cytokine. Ixekizumab is marketed in the US and EU for the treatment of moderate-to-severe plaque psoriasis (Ps) at a dose of 160 mg at Week 0, followed by 80 mg every 2 weeks up to Week 12, then maintenance dosing of 80 mg every 4 weeks, and for psoriatic arthritis (PsA) at a dose of 160 mg at Week 0 followed by 80 mg every 4 weeks. Ixekizumab is also marketed in the US for treatment of ankylosing spondylitis with a recommended dose of 160 mg (two 80-mg injections) at Week 0, followed by 80 mg every 4 weeks.

In the ixekizumab clinical program, injection site pain was reported by 2.4% of patients with moderate-to-severe Ps and 1.5% of patients with PsA. Most injection site pain occurred shortly after drug administration and the incidence rate declined with subsequent injections. Post approval reports along with insights from customers have shown that pain is a clear concern and issue for patients, thus the rationale for evaluating an alternate formulation to help reduce injection site pain.

3.3. Benefit/Risk Assessment

As this study will enroll healthy subjects, there is no anticipated therapeutic benefit for the subjects.

On the basis of the 21 Mar 2019 data cutoff dates for the current investigator's brochure (IB) (approved on 7 June 2019), approximately 9848 patients were treated with at least 1 dose of

ixekizumab in clinical trials (6721 patients with Ps, 532 patients with rheumatoid arthritis, 1413 patients with PsA, 253 healthy subjects, and an estimated 929 patients with axial spondyloarthritis (includes both radiographic and nonradiographic axial spondyloarthritis).

Four previous studies have administered ixekizumab to healthy subjects. These include Study I1F-MC-RHCA (RHCA) where 41 subjects were administered ixekizumab by PFS (160 mg [2 × 80 mg] followed by 80 mg 2 weeks later). All treatment-emergent adverse events (TEAEs) in Study RHCA were mild in severity. The most commonly reported adverse events (AEs) were headache (4 events in 4 subjects), injection site erythema (4 events in 2 subjects), and fatigue (3 events in 3 subjects). With the exception of fatigue, this is consistent with commonly reported AEs reported in Phase 3 studies. An additional 78 healthy subjects were administered ixekizumab by PFS, marketed AI, and modified AI (3 single 80 mg doses) in Study I1F-MC-RHCK (RHCK). In Study RHCK, all TEAEs were mild in severity and the most commonly reported Medical Dictionary for Regulatory Activities (MedDRA) preferred term was injection site reaction (ISR) (which represented solicited AEs) with injection site pruritus, nausea, diarrhea, upper respiratory tract infection, and injection site erythema (nonsolicited AEs) also reported by at least 2 subjects each.

Study RHCS was a 3-period crossover design, hence each subject received three 80 mg injections, each separated by 7 days (1 injection from each of the 2 alternate ixekizumab formulations [test] and 1 injection from the commercial ixekizumab formulation [reference]). Safety data collected during the study, including AEs, clinical laboratory tests, and vital signs, indicated that all 3 treatments administered were consistent with previous studies with ixekizumab in healthy subjects. The percentage of subjects reporting TEAEs (all causalities) was generally similar following administration of each treatment (17.5% to 26.2%). The most commonly reported treatment-related TEAEs (all causalities) were in the General Disorders and Administration Site Conditions system organ class, with ISRs being the most frequently reported TEAE overall (18 events in 13 subjects). Injection site rash, injection site hemorrhage, nasal congestion, productive cough, upper respiratory tract infection, headache, pain in extremity, and breast mass were each also reported by at least 2 subjects. Infections and infestations that were considered to be treatment related were reported by 6 subjects overall. The majority of TEAEs were mild in severity.

In Study RHCT, 99 healthy subjects received a single 80-mg SC ixekizumab injection (33 in each group of either the commercial or 2 test formulations). Safety data collected during the study, including AEs, clinical laboratory tests, and vital signs, indicated that all 3 treatments administered had similar safety profiles. The percentage of subjects reporting treatment-related TEAEs was similar following administration of each treatment (30.3% to 45.5%). The most commonly reported treatment-related TEAEs were in the General Disorders and Administration Site Conditions system organ class, with ISRs being the most frequently reported TEAE overall (5 events in 4 subjects). Injection site erythema, abdominal pain, upper respiratory tract infection, and headache were each also reported by at least 2 subjects. The majority of TEAEs were mild in severity. Antidrug antibody response observed in Study RHCT with healthy subjects was approximately 9.1% to 12.1% with a low incidence of neutralizing antibodies.

In Study RHCT, 2 subjects had a neutrophil count lower than the reference range at 1 postdose time point each during the study; neither of these decreases were clinically significant. A decrease in neutrophil count is known to occur with IL-17 antagonism. One death was reported in Study RHCT in a hospitalized study participant who had 4 serious AEs (SAEs) (sinusitis, cerebral vein thrombophlebitis/cerebral vein thrombosis, periorbital abscess, and phaeohyphomycotic brain abscess). These 4 SAEs were deemed unrelated to ixekizumab.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of ixekizumab are to be found in the IB and the United States Product Insert (drug label).

4. Objectives and Endpoints

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

Table RHCU.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the bioequivalence of a single 80 mg SC dose of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference)	• C_{max}, AUC(0-∞), AUC(0-t_{last})
Secondary To describe the safety and tolerability of a single 80 mg SC dose of ixekizumab alternate formulation (test) compared to the commercial formulation (reference)	• TEAEs, SAEs

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

5. Study Design

5.1. Overall Design

Infection risk

Participants should follow local guidance and clinical research unit (CRU) precautions to minimize risk for COVID-19 infection.

Study RHCU is a Phase 1, subject-blind, 2-arm, randomized, parallel-design study in healthy subjects.

All subjects will be screened within 28 days prior to enrollment. Eligible subjects will be admitted to the CRU on Day -1. At screening, subjects will be stratified into 1 of 3 weight categories (<70.0 kg, 70.0 to 80.0 kg, >80.0 kg). Within the 3 weight categories, subjects will be randomized 1:1 to either 80-mg ixekizumab commercial formulation (reference) or 80-mg ixekizumab alternate formulation (test) and subrandomized 1:1:1 to injection site (arm, thigh, or abdomen) (Table RHCU.2). On Day 1, subjects will receive a single SC dose according to the randomization plan (Table RHCU.2 and Schedule of Activities, Section 2).

The desire is to have approximately equal numbers of subjects in each weight category to avoid a large difference in mean weight between the test and reference formulation groups. A subject population of 72 per weight group is an approximate target with the recommended weight categories selected based on the distribution of weights in the prior studies, RHCS and RHCT. The number of subjects assigned to each formulation and the number of subjects assigned to each site of injection location is desired to be balanced.

Table RHCU.2. Study RHCU Stratification and Randomization Plan

Weight Category (Subjects)	Formulation (80-mg ixekizumab)	Subcutaneous Injection Location[a]	Desired Number of Subjects
Low <70.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12
Medium 70.0 kg – 80.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12
High >80.0 kg (72 subjects)	Commercial (reference)	Arm	12
	Alternate (test)		12
	Commercial (reference)	Abdomen	12
	Alternate (test)		12
	Commercial (reference)	Thigh	12
	Alternate (test)		12

Abbreviations: RHCU = I1F-MC-RHCU; SC = subcutaneous.

[a] A dose of investigational product will consist of 1 SC injection of 80-mg ixekizumab into the arm, thigh, or abdomen. All doses will be administered by trained site staff.

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

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, temperature, recording of AEs, physical examination (PE)/medical assessments, Columbia Suicide Severity Rating Scale (C-SSRS), and immunogenicity.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to approximately 240 subjects may be enrolled so that approximately 216 subjects complete the study (108 in the 80-mg ixekizumab commercial formulation [reference] group and 108 in the 80-mg ixekizumab alternate formulation [test] group).

As described in Section 5.1, eligible subjects will be admitted to the CRU on Day -1. At screening, subjects will be stratified and randomized as described in Section 5.1 and Table RHCU.2. On Day 1, subjects will receive a single SC dose (Schedule of Activities, Section 2) according to the randomization plan. The number of subjects in each weight category and assigned to each formulation is desired to be approximately equal. The number of subjects assigned to each site of injection location is desired to be balanced.

For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities have been finished.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients. A population of healthy subjects is frequently used in the assessment of the bioequivalence of both small and large molecules.

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

A parallel-group design is chosen because a crossover design is impractical for ixekizumab, which has a half-life of approximately 13 days. Additionally, a crossover study could confound PK data if subjects develop neutralizing antidrug antibodies (ADAs).

5.5. Justification for Dose

The recommended dose for Ps patients is 160 mg by SC injection (two 80-mg injections) at Week 0, followed by an 80-mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. A dose of 80-mg ixekizumab was selected for Study RHCU to match the approved individual dose unit strength administered during treatment in clinical practice.

6. Study Population

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

The nature of any conditions present at the time of the PE and any preexisting conditions will be documented. Screening and/or Day -1 laboratory testing may be repeated once at the discretion of the investigator for any out-of-range results.

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

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or Day -1:

[1] are overtly healthy males or females, as determined by screening medical history and PE, or are males or females with chronic, stable medical problems that, in the investigator's opinion, will not place the subject at increased risk by participating in the study, and will not interfere with interpretation of the data

[1a] male subjects:

agree to use a reliable method of birth control and to not donate sperm during the study and for 3 months following ixekizumab dosing.

Examples of reliable methods of birth control,

- for male subjects condoms with spermicide or male sterilization,
- for female partners of childbearing potential, a highly effective birth control method,
    - oral or implanted contraceptives,
    - intrauterine device or
    - a combination of 2 effective methods (for example, female condom with spermicide).

Male subjects who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either maintain abstinence or stay in a same-sex relationship without sexual relationships with females. Periodic abstinence, declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception.

[1b] female subjects:

1) Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception.

2) Otherwise, women of child-bearing potential must agree to use 1 highly effective method (less than 1% failure rate) of contraception or a combination of 2 effective methods of contraception for the entirety of the study and for 3 months following ixekizumab dosing.

    i. Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test on Day -1.

    ii. Either 1 highly effective method of contraception (e.g., combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

3) Women not of child-bearing potential may participate and include those who are:

    i. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, tubal ligation, or permanent tubal occlusion such as Essure®), a congenital anomaly such as mullerian agenesis, or

    ii. postmenopausal, defined as either:

        a) a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:

            - cessation of menses for at least 1 year, or

- at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone level >40 mIU/mL

b) a woman 55 years or older, not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea;

c) a woman 55 years or older with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are aged at least 18 to 75 years at the time of screening

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

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

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

[6] are able and willing to give informed consent

6.2. Exclusion Criteria

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

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

[8] are employees of Eli Lilly and Company (Lilly), Covance, or a third-party organization involved in the study

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

[10] have participated, within the last 30 days in a clinical study involving an IP. If the previous IP has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed

[11] have previously completed or withdrawn from this study or any other study investigating ixekizumab, and have previously received the IP or have been administered other anti-IL-17 agents

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

[13] have self-perceived dullness or loss of sensation on either side of their arm, thigh, or abdomen

[14] have uncontrolled arterial hypertension characterized by a systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg

Note: if an initial blood pressure reading exceeds this limit, the reading may be repeated once after the subject has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.

[15] have a significant history of, or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or hematologic disorders, that in the opinion of the investigator poses an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data

[16] have presence of significant uncontrolled neuropsychiatric disorder; have lifetime history of suicidal behavior (yes to any suicidal behavior question from the "Suicidal Behavior" portion of the C-SSRS from screening and between screening and baseline [Day -1]); have history of active suicidal ideation within the past year (yes to question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS from screening and between screening and baseline [Day -1]); and/or are clinically judged by the investigator to be at risk for suicide

[17] have recent history (past 30 days) of depression; have Hospital Anxiety Depression Scale (HADS) Depression subscale score of ≥11

[18] have current or history of inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis), signs or symptoms indicative of ulcerative colitis or Crohn's disease (based on investigator determination), or knowledge of a family history of IBD in first degree relatives

[19] Infections:

[19a] have had a serious infection (e.g., pneumonia, cellulitis, and sepsis), have been hospitalized, or have received intravenous antibiotics for an infection within 12 weeks prior to Day 1; have had a serious bone or joint infection within 24 weeks prior to Day 1, or have ever had an infection of an artificial joint; or are immunocompromised to an extent such that participation in the study would pose an unacceptable risk to the subject

[19b] have or have had an infection typical of an immunocompromised host and/or that occurs with increased incidence in an immunocompromised host (including, but not limited to, pneumocystis jiroveci pneumonia, histoplasmosis, or coccidioidomycosis), or have a known immunodeficiency

[19c] have or have had a herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks of Day 1

[19d] have had any other active or recent infection within 4 weeks of Day 1 that, in the opinion of the investigator, would pose an unacceptable risk to the subject if participating in the study; these subjects may be rescreened (once) ≥4 weeks after documented resolution of symptoms

[20] have a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new-onset ischemic heart disease or other serious cardiac disease, within 12 weeks prior to Day 1

[21] have clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant, and/or have any of the following specific abnormalities:

- neutrophil count <1500 cells/μL
- lymphocyte count <800 cells/μL
- platelet count <100,000 cells/μL
- total white blood cell count <3000 cells/μL

Note: Screening and/or Day -1 laboratory testing may be repeated (once) at the discretion of the investigator for any out of range results. Thereafter, laboratory tests may not be repeated unless there is a documented technical error or clinical reason to believe a result may need to be retested within the screening period

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

[23] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies

[24] show evidence of hepatitis C or positive hepatitis C antibody

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

[26] are women who are lactating

[27] have donated blood of more than 500 mL within the last month prior to dosing or intend to donate blood during the course of the study

[28] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females up to and over 65, and males over 65), or are unwilling to stop alcohol consumption for 48 hours prior to admission to the CRU until CRU discharge, plus 48 hours prior to admission to the CRU for the 12-week follow-up visit until final discharge from the CRU, or are unwilling to restrict alcohol intake to 3 units per day (males) and 2 units per day (females) during the outpatient period (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[29] show evidence of active or latent tuberculosis (TB), as documented by medical history and examination, any recent chest x-rays (if obtained in the previous 6 months; x-rays will not be taken for the sole purpose of determining eligibility for this study), and TB testing

[30] had a vaccination with Bacillus Calmette-Guérin (BCG), other live vaccines, or attenuated live vaccines within 12 months prior to admission to the CRU, or intend to have a vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study

[31] 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

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

[33] have a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk to the subject if participating in this study

[34] have had 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

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

[36] have excessive tattoos or scars over the arm, thigh, or abdomen or other factors (e.g., rash, excessive folds of skin) that, in the investigator's opinion, would interfere with injection site assessments

[37] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [7] and [8] prevent conflict of interest in study participants. Exclusion Criteria [9] through [37] exclude items including, but not limited to, medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

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

6.3.2. Alcohol and Tobacco

Alcohol consumption is not permitted while at the CRU and for 48 hours prior to each study visit. Alcohol intake during outpatient periods should not exceed 3 units per day (males up to age 65)

and 2 units per day (females up to and over 65, and males over 65). In addition, subjects must abide by the CRU smoking restrictions during study visits and while resident in the CRU.

6.3.3. Activity

Subjects will be encouraged to maintain their regular exercise; however, they should not undertake vigorous or prolonged exercise within 48 hours prior to each CRU visit.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened (once) at the investigator's discretion (See Section 6).

7. Treatment

7.1. Treatment Administered

A dose of IP will consist of 1 SC injection of 80-mg ixekizumab in a 1-mL volume into the arm, thigh, or abdomen. All doses will be administered by trained site staff.

This study involves a comparison of:

- 80-mg ixekizumab commercial formulation (reference) administered subcutaneously via AI
- 80-mg ixekizumab alternate formulation (test) administered subcutanenously via AI

Prior to the injection using the AI, the investigator or his/her designee will clean the subject's skin. The injection will be administered by trained site staff, according to the instructions provided by the sponsor.

Table RHCU.3 shows the treatment regimens.

Table RHCU.3. Treatments Administered

Treatment Name	Alternate Formulation (Test)	Commercial Formulation (Reference)
Formulation	solution for injection	solution for injection
Dose	80-mg ixekizumab	80-mg ixekizumab
Route of Administration	SC injection	SC injection
Delivery Method	AI	AI

Abbreviations: AI = autoinjector; SC = subcutaneous.

The investigator or designee is responsible for:

- explaining the correct use of the IPs to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study where appropriate

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. Retention samples must be kept as instructed by Lilly.

7.1.1. Packaging and Labeling

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

designed to deliver 80 mg of ixekizumab. The following products will be supplied by Lilly, with study-specific labels, for use in the study:

- ixekizumab commercial formulation (reference; solution for injection) in an AI (80-mg ixekizumab in a 1-mL volume)
- ixekizumab alternate formulation (test; solution for injection) in an AI (80-mg ixekizumab in a 1-mL volume)

Unblinded site personnel will be responsible for handling and administering IP. Unblinded site personnel are also responsible to make sure subjects remain blinded to treatment. Site personnel may create blinding processes and precautions as they deem necessary to maintain injection site assessor blinding.

The IP will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

The randomization table will be prepared by the statistician (or appropriate delegate) for the study and provided to the CRU pharmacists or pharmacy staff involved in dose preparation.

As described in Section 5.1, eligible subjects will be admitted to the CRU on Day -1. At screening, subjects will be stratified into 1 of 3 weight categories (<70.0 kg, 70.0 to 80.0 kg, >80.0 kg). Within the 3 weight categories, subjects will be randomized 1:1 to either 80-mg ixekizumab commercial formulation (reference) or 80-mg ixekizumab alternate formulation (test) and subrandomized 1:1:1 to injection site (arm, thigh, or abdomen) (Table RHCU.2).

7.2.1. Selection and Timing of Doses

The actual time of dose administration will be recorded in the subject's case report form (CRF).

7.3. Blinding

Study RHCU is a subject-blind study.

7.4. Dose Modification

Dose adjustments are not allowed in this study.

7.4.1. Special Treatment Considerations

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to skin rash, pruritus (itching), urticaria (hives), angioedema (e.g., swelling of the lips and/or tongue), and anaphylactic reaction. Sometimes these reactions can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all subjects should be closely monitored for signs or symptoms that could result from such reactions, be educated on the signs or symptoms of these types of reactions, and be instructed to contact the study site immediately if any of the symptoms are experienced after discharge from the CRU.

If a subject experiences an acute allergic/hypersensitivity reaction after an injection of IP, he or she should be managed appropriately and receive relevant supportive care. The event should be recorded as an AE. In case of systemic hypersensitivity reactions, defined as anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event (Section 9.2.1.3). Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The lab results are provided to the sponsor via the central laboratory.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Subjects on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Permitted concomitant medications, at the discretion of the investigator, include hormonal contraceptives, hormone replacement therapy, and thyroid replacement. In addition, occasional acetaminophen is acceptable at the discretion of the investigator. However, acetaminophen should not be administered on the dosing day within 4 hours prior to the injection and until at least 4 hours after the injection. No more than 3 g of acetaminophen will be permitted in any 24-hour period. Inclusion of subjects on any other concomitant medication (e.g., statins and anti-hypertensives) is contingent upon approval following consultation with the sponsor.

Subjects will be restricted from applying any creams or lotions on the arm, thigh, or abdominal skin within 24 hours prior to or after the injection.

If the need for any additional concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly Clinical

Pharmacologist (CP) or Clinical Research Physician (CRP). Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the treatment prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Not applicable.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

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

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

The investigator will record all relevant AE and SAE information in the electronic CRF (eCRF). After the informed consent form is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above
- when a condition related to the auto injector necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

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

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

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

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

9.2.1.1. Adverse Events of Special Interest

The following AEs of special interest will be used to determine the safety and tolerability of ixekizumab administered by AI in this clinical study.

Adverse events of special interest for ixekizumab are:

- cytopenias (leukopenia, neutropenia, and thrombocytopenia)
- liver function test changes/enzyme elevations (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin level [TBL], and alkaline phosphatase [ALP]) that are considered to be clinically relevant by the principle investigator/investigator)
- infection
- ISRs (see Section 9.4.5.1)
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- depression
- IBD (Crohn's disease and ulcerative colitis)
- interstitial lung disease

If infections, or allergic/hypersensitivity reactions are reported, these will be recorded as AEs. Investigators will also educate subjects about the symptoms of allergic/hypersensitivity reactions and will provide instructions on dealing with these reactions. A blood sample will be collected when possible for any subject who experiences an AE of systemic hypersensitivity reaction during the study.

Data on cerebrocardiovascular events (defined as death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, coronary revascularization procedure, peripheral revascularization procedure, cardiogenic shock due to myocardial infarction, resuscitated sudden death, serious arrhythmia, hospitalization for hypertension, and peripheral arterial event) will be collected and the events may be adjudicated by an external Clinical Events Committee (CEC) made up of a chair, 2 cardiologists, and a neurologist.

Data on suspected IBD, as identified by events possibly indicative of ulcerative colitis and Crohn's disease, will be collected. The events may be adjudicated by an external CEC composed of gastroenterologists with expertise in IBD.

The role of the CECs is to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CECs is to ensure that all events that have been reported are evaluated uniformly by a single group.

9.2.1.2. Suspected Unexpected Serious Adverse Reactions

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

9.2.1.3. Systemic Hypersensitivity Reactions

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

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In case of systemic hypersensitivity reactions, defined as anaphylaxis or generalized urticaria, additional blood samples should be collected as described in Appendix 6. Laboratory results are provided to the sponsor via the central laboratory.

9.2.2. Complaint Handling

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

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

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

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

If the investigator is asked to return the product for investigation, he/she will return a copy of the Product Complaint Form with the product.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of ixekizumab is considered any dose higher than the dose assigned through randomization. Autoinjectors used in this study can deliver only 1-mL volume of ixekizumab.

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

Refer to the Taltz Product Label (FDA resources page [WWW]).

9.4. Safety

Safety will be assessed throughout the course of the study at site visits and via telephone calls in between site visits.

9.4.1. Laboratory Tests

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

See Appendix 6 for further laboratory testing and instructions for hypersensitivity events.

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

9.4.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 2 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each subject, a single12-lead digital ECG will be collected according to the Schedule of Activities (Section 2).

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

Electrocardiograms will be interpreted by a qualified investigator (physician or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

9.4.4. Temperature

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

9.4.5. Other Tests

9.4.5.1. Injection Site Assessments

Injection site reactions will be captured on the ISR AE form and the eCRF as an AE. The findings of ISR (including induration, pain, edema, pruritus, and erythema) for a specific injection will be captured as a single AE, even if more than 1 of the findings is positive, and the

severity that is recorded on the ISR AE form will be the highest severity across the findings at each applicable visit.

If injection site pain is reported at any time during the study, the intensity of pain will be quantified using the 100-mm validated visual analog scale (VAS) pain score. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually "no pain" and "worst possible pain." The subject will be asked to rate any pain at the injection site on a scale of 0 to 100 mm on the line as soon as is practical following reporting of the event.

Injection site assessments should be conducted at the next planned visit following the reporting of an injection-related AE.

9.4.5.2. Bleeding/Bruising Assessment

The presence of visible bleeding at the injection site will be recorded on the eCRF as applicable. A bandage may be placed on the injection site after assessment.

9.4.5.3. Columbia Suicide Severity Rating Scale

Columbia Suicide Severity Rating Scale: A scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. Any occurrence of suicide-related thoughts and behaviors will be assessed at the times indicated in the Schedule of Activities (Section 2) using the C-SSRS. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed. The first time the scale is administered in this study, the C-SSRS 'Baseline – Screening' version will be used, and the findings will constitute the baseline assessment. The C-SSRS 'Since Last Visit' scale will be used for all subsequent assessments. The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If there are positive findings on the Self-Harm Supplement, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.5.3.1. Hospital Anxiety Depression Scale

The HADS depression subscale is a 7-item assessment scale that determines the levels of depression that a subject is experiencing over the past week. The HADS depression subscale utilizes a 4-point Likert scale (e.g., 0 to 3) for each question and is intended for ages 12 to 65 years (Zigmond and Snaith 1983; White et al. 1999). The score can range from 0 to 21, with higher scores indicating greater depression (Zigmond and Snaith 1983; Snaith 2003).

9.4.6. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review trends in safety data, laboratory analytes, and AEs.

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

9.4.6.1. Hepatic Safety

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

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

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

9.5. Pharmacokinetics

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

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of ixekizumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the

bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

9.6. Pharmacodynamics

Not applicable.

9.6.1. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against ixekizumab. Antibodies may be further characterized for their ability to neutralize the activity of ixekizumab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of ixekizumab. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent ADAs (TE-ADAs) are defined in Section 10.3.3. If the immunogenicity titer at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the signal returns to baseline (i.e., no longer TE-ADA positive) or for up to 1 year after dosing.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the IP. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample (10 mL) will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to ixekizumab and to investigate genetic variants thought to play a role in autoimmune disorders. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period 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 ixekizumab.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, multiplex assays, and candidate gene studies.

Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Not applicable.

9.9. Health Economics

Not applicable.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to approximately 240 subjects may be enrolled so that approximately 216 subjects (108 in the 80-mg ixekizumab commercial formulation [reference] group and 108 in the 80-mg ixekizumab alternate formulation [test] group) complete the study.

A sample size of 108 subjects per treatment group will provide approximately 90% power that the 90% confidence interval (CI) of the geometric mean ratio of maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) between groups will fall within equivalence range of 0.8 to 1.25. This sample size calculation was based on the assumptions that the PK parameters have log-normal distribution, the percent coefficients of variation (%CV) of C_{max} and AUC are less or equal to 48% (from study RHCT), the expected ratio of geometric means is between 0.997 to 1.04, and the %CV are the same for subjects from each treatment group.

Subjects who are randomized but not administered treatment and subjects who do not complete PK sampling (including day 85) may be replaced so that approximately 216 subjects (108 for each treatment) complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

Pharmacokinetic (PK) analyses will be conducted on data from all subjects who receive the complete single dose of ixekizumab and have sufficient evaluable PK. Only subjects who complete the PK sampling schedule to Day 85 will be included in the statistical analysis of PK parameters.

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

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.1.2.1. Statistical Evaluation of Other Safety Parameters

Safety laboratory parameters and vital signs data will be listed and summarized using standard descriptive statistics, where possible. Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by subject. Only subjects that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be included in the listing (i.e., if a subject's answers are all 'no' for the C-SSRS, then that subject will not be displayed). Hospital Anxiety Depression Scale item scores will be listed for subjects with HADS depression subscale ≥11 at any time. Additional analysis may be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for ixekizumab will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, AUC(0-t_{last}) and AUC(0-∞) of ixekizumab. Other noncompartmental parameters, such as time to maximum drug concentration (t_{max}), half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), apparent clearance, and apparent volume of distribution may be reported.

Pharmacokinetic parameters may also be normalized by body weight for summarizing the data and may be summarized by site of injection location using descriptive statistics.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to determine the bioequivalence of ixekizumab alternate formulation (test) compared to the ixekizumab commercial formulation (reference). Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model

with fixed effects for formulation and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

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

Bioequivalence will be concluded if the 90% CI is completely contained within the interval (0.80, 1.25).

10.3.3. Evaluation of Immunogenicity

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

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

10.3.4. Interim Analyses

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

11. References

Snaith RP. The Hospital Anxiety and Depression Scale. Health Qual Life Outcomes. 2003;1:29.

Taltz (ixekizumab) Injection Label. Food and Drug Administration web site. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125521s016lbl.pdf. Accessed October, 22 2019.

White D, Leach C, Sims R, Atkinson M, Cottrell D. Validation of the Hospital Anxiety and Depression Scale for use with adolescents. Br J Psychiatry. 1999;175:452-454.

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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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
%CV	percent coefficients of variation
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AI	autoinjector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BCG	Bacillus Calmette-Guérin
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his/her staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/or his/her staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
CEC	Clinical Events Committee
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

CP	Clinical Pharmacologist
CRF	case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
GCP	good clinical practice
HADS	Hospital Anxiety and Depression Scale
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IL	interleukin
IL-17A	interleukin 17A
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

ISR	injection site reaction
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Lilly	Eli Lilly and Company
MedDRA	Medical Dictionary for Regulatory Activities
randomize	The process of assigning subjects/patients to an experimental group on a random basis.
PE	physical examination
PFS	prefilled syringe
PK	pharmacokinetic
Ps	plaque psoriasis
PsA	psoriatic arthritis
RHCA	Study I1F-MC-RHCA
RHCK	Study I1F-MC-RHCK
RHCS	Study I1F-MC-RHCS
RHCT	Study I1F-MC-RHCT
RHCU	Study I1F-MC-RHCU
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
t_{max}	time to maximum drug concentration

ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

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

Differential WBC absolute counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

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

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

Clinical Chemistry
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorus
- Glucose random
- Blood urea nitrogen (BUN)
- Uric acid
- Total protein
- Albumin
- Total bilirubin level (TBL)
- Direct bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine

Other tests
- Ethanol testing[a]
- Urine drug screen[a]
- Pregnancy test (females only)[b]
- FSH (females only, if applicable)[c,d]
- QuantiFERON®-TB Gold[d] or TST[d]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; TB = tuberculosis; TST = tuberculin skin test; WBC = white blood cells.

a Urine drug screen and ethanol (breath test) level will be performed locally at screening and at admission to the clinical research unit. Test may be repeated at additional time points at the discretion of the investigator.

b Serum pregnancy test to be performed at screening. Urine pregnancy test to be performed at all other times.

c FSH test performed for women ≥50 and <55 years of age who have an intact uterus and are not on hormone therapy, and have had spontaneous amenorrhea for ≥6 months but <1 year to confirm nonchildbearing potential (>40 mIU/mL).

d Performed at screening only.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Recruitment

Eli Lilly and Company (Lilly) or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study specific recruitment material should be approved by Lilly.

Ethical Review

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

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

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

Protocol Signatures

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

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

Final Report Signature

The lead investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate case report form (CRF) data and/or use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Eli Lilly and Company or its designee clinical research physician.

Hepatic Monitoring Tests

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

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

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

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol I1F-MC-RHCU Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	28	1	28
Clinical laboratory tests[a]	15.2	4	60.8
Pharmacokinetics	3	15[b]	45
Immunogenicity	10	4	40
Pharmacogenetics	10	1	10
Total			183.8
Total for clinical purposes [rounded up to nearest 10 mL]			190

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

[b] Includes an additional 3 samples, if required.

Appendix 6. Recommended Laboratory Testing for Hypersensitivity Events

Lab testing should be performed at the time of a Systemic Hypersensitivity Event. Important information about why, when, and what to test for is provided below. The management of the adverse event may warrant lab testing beyond that described below and should be performed as clinically indicated.

When should labs be obtained?
In the presence of generalized urticaria or if anaphylaxis is suspected, after the subject has been stabilized:

- obtain a sample within 1-2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- obtain a follow up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

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

Hypersensitivity Tests[a]

Anti-LY2439821 antibodies (immunogenicity)	Tryptase[b]
LY2439821 concentration (PK)	N-methylhistamine
	Drug-specific IgE[c]
	Basophil activation Test[c]
	Complements[d]
	Cytokine panel[e]

Abbreviations: Ig= immunoglobulin; LY2439821 = ixekizumab; PK = pharmacokinetics.

[a] Assayed by Lilly-designated laboratory. These labs are bundled in the Clinical Laboratory Operations Hypersensitivity Lab Testing Kit.

[b] If a tryptase sample is obtained more than 2 hours after the event (i.e., within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for *N*- methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

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

[d] C3a and C5a.

[e] IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines).

Appendix 7. Protocol Amendment I1F-MC-RHCU(b) Summary Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects

Protocol I1F-MC-RHCU, Bioequivalence of an Alternate Ixekizumab Formulation Compared to the Commercial Formulation in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes made to this protocol are as follows:

- Modified Exclusion Criterion [8] in Section 6.2 to consider employees of third-party organizations, in addition to employees of Lilly and Covance who are involved in the study.
- Minor editorial changes and formatting corrections were made but are not necessarily documented in the revision below.
- Added in verbiage to Section 5.1 for COVID 19 related precautions to be taken by the CRU.
- Removed verbiage in Section 10.3.1 on safety analyses in enrolled patients

Revised Protocol Sections

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

6.2. Exclusion Criteria

[8] ~~are Eli Lilly and Company (Lilly) or Covance employees~~ are employees of Eli Lilly and Company (Lilly), Covance, or a third-party organization involved in the study.

5. Study Design

5.1 Overall Design

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

10.3. Statistical Analysis

10.3.1 Safety Analysis

~~Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.~~

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Approver: PPD

Approval Date & Time: 28-Sep-2020 20:02:30 GMT

Signature meaning: Approved

Approver: PPD

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