I1F-MC-RHCT (b) Clinical Pharmacology Protocol

Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

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Protocol I1F-MC-RHCT (b)
Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

Confidential Information

Ixekizumab (LY2439821)

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1. Protocol Synopsis

Title of Study:
Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

Rationale:
Changes in buffer composition are being investigated as a potential way to address injection-site pain reported for ixekizumab. Study I1F-MC-RHCT is therefore being conducted to compare the relative bioavailability and tolerability of ixekizumab administered using 2 new formulations compared to the marketed formulation.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To evaluate the relative bioavailability of a single 80 mg subcutaneous (SC) dose of ixekizumab Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference)	Maximum observed drug concentration (C_{max}), area under the concentrations versus time curve from time zero to infinity (AUC[0-∞]), area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}])
Secondary To evaluate the safety and tolerability of a single 80 mg SC dose of ixekizumab Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference)	Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), injection-site reactions (ISRs), and visual analog scale (VAS) pain score immediately after injection

Summary of Study Design:

Study I1F-MC-RHCT is a Phase 1, subject-blind, 3-arm, randomized, parallel-design study in healthy subjects.

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1:1 to 1 of 3 possible treatments. Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and will return for pharmacokinetic (PK) and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose. Subjects will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, temperature, recording of adverse events (AEs), physical examination/medical assessments, Columbia Suicide Severity Rating Scale (C-SSRS), Hospital Anxiety Depression Scale (HADS), immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site VAS.

Treatment Arms and Planned Duration for an Individual subject:
All subjects will be screened within 28 days prior to enrollment. On Day 1, subjects will receive a single subcutaneous (SC) dose of 1 of the following treatments, according to the randomization schedule:

- 80 mg ixekizumab Test Formulation 1
- 80 mg ixekizumab Test Formulation 2
- 80 mg ixekizumab Commercial Formulation (Reference).

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

Number of Subjects:
Up to 99 subjects may be enrolled so that 78 subjects (26 in each treatment arm) complete the study.

Statistical Analysis:

Pharmacokinetic parameters will be evaluated to estimate relative bioavailability. 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.

Safety parameters will be listed and summarized using standard descriptive statistics, where possible. Injection-site assessments, including induration, swelling, pruritis, bleeding/bruising, and erythema/redness, will also be assessed. The parameters will be listed and summarized using descriptive statistics. Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by subject. HADS item scores will be listed for subjects with HADS depression subscale ≥11 at any time. VAS pain score will be summarized using standard descriptive statistics. In addition, the severity of pain will be categorized by VAS pain score as: mild pain (≤ 30), moderate pain (> 30 and ≤ 70), and severe pain (> 70). The number and percentage of the subjects in each pain severity category will summarized by formulation and time point.

The frequency and percentage of subjects with preexisting anti-drug antibodies (ADA) and with treatment-emergent ADA (TE ADA) 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.

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

2. Schedule of Activities

Study Schedule Protocol I1F-MC-RHCT

	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 timepoints use 'Since Last Visit' questionnaire.
HADS Depression sub-scale	X	X				X				X							X	
Height, Weight, and BMI	X																X	Weight only at Day 85/ED.
Body Temperature (Oral)			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															X	Full physical examination/medical assessment at Screening. Symptom-directed examinations/assessments at other times, and as deemed necessary by the investigator.
Vital Signs (sitting) (hours)	X	X	P, 2-4					X				X					X	Day 1 2-4 hour assessment to be conducted at least 2 hours postdose and prior to discharge at approximately 4 hours postdose. Time points may be added if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X	X						X		X							X	See Appendix 2, Clinical Laboratory Tests, for details.
Serology	X																	See Appendix 2, Clinical Laboratory Tests, for details.
QuantiFERON®-TB Gold Test/TST	X																	
Urine Ethanol Test and Drug Screen	X	X																May be repeated at the discretion of the investigator.
FSH Test	X																	Females only, if applicable.
Pregnancy Test	X	X															X	Females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at all other times.
Single 12-lead ECG	X																	Single Screening ECG.
Ixekizumab			X															Subjects will fast (water only

	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	
Administration																		allowed) from 1 hour before until 1 hour after dosing.
Injection-Site Assessments (minutes)			0, 10, 20, 30, 60, 120, 240	X		X												Assessments of induration, swelling, pruritus, and erythema/redness (collected as described in Section 9.4.5.1). 0-minute time point should be done within ± 1 minute following injection; within ± 2 minutes of the 10, 20, and 30-minute time points; within ± 5 minutes of the 60, 120, and 240-minute time points.
Injection-site Bleeding/Bruising Assessment (minutes)			0, 10, 20, 30, 60, 120, 240	X		X												Observational assessment of injection-site bleeding and bruising. 0-minute time point should be done within ± 1 minute following injection; within ± 2 minutes of the 10, 20, and 30-minute time points; within ± 5 minutes of the 60, 120, and 240-minute time points.
Injection-site Pain Assessments using VAS (minutes)			0, 10, 20, 30, 60															Assessment of injection-site pain (VAS) at the 0-minute time point should be done within ± 1 minute following injection; within ± 2 minutes of the 10, 20, and 30-minute time points; within ± 5 minutes of the 60-minute time point.

	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	
Ixekizumab PK sample			P	X	X	X	X	X	X	X		X		X		X	X	
Immunogenicity Sample			P					X		X							X	
Pharmacogenetic Sample		X																
Adverse Events and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: BMI = body mass index; CRU = clinical research unit; C-SSRS – Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; ISR = injection-site reaction; P = predose; PK = pharmacokinetics; TB = tuberculosis; TST = tuberculin skin test; VAS = visual analog scale.

3. Introduction

3.1. Study Rationale

Ixekizumab is administered subcutaneously (SC), and is available 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.

Study I1F-MC-RHCK was conducted to assess acute pain and injection-site reactions (ISRs) following administration of ixekizumab via marketed AI (fast injection speed, visible needle), a modified AI (slow injection speed, hidden needle), the marketed PFS, and placebo administered using a device similar to the marketed AI (fast injection speed, visible needle). The results showed no statistically significant difference in intensity of injection-site pain following single injections administered via any of the methods tested. Safety profiles, including the frequency of injection-site reactions (ISRs) were also similar between treatments.

Several solution-associated factors may contribute to pain perception associated with injectable therapeutics, including active pharmaceutical ingredient, pH, buffer composition, and tonicity (Laursen et al. 2006).

Two new formulations of ixekizumab have therefore been developed using alternative approaches for buffer and tonicity agent; [redacted]

Study I1F-MC-RHCT (Study RHCT) is therefore being conducted to compare the relative bioavailability and tolerability of ixekizumab administered using the 2 new formulations, compared to the marketed formulation when administered using a PFS.

Study RHCT is being conducted in parallel with Study I1F-MC-RHCS which will provide further assessment of injection-site pain and ISRs associated with administration of the 3 ixekizumab formulations in a crossover study design.

3.2. Background

Ixekizumab (LY2439821, Taltz®) is a humanized immunoglobulin (Ig)G subclass 4 monoclonal antibody that binds with high affinity and specificity to interleukin (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 at a dose of 160 mg at Week 0 followed by 80 mg every 4 weeks.

3.3. Benefit/Risk Assessment

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

As of the cut-off date for the current investigator's brochure (IB; 22 March 2018), more than 8755 subjects and patients have received at least 1 dose of ixekizumab (5934 patients with Ps, 532 patients with rheumatoid arthritis, 1301 patients with psoriatic arthritis, 119 healthy subjects, and an estimated 869 patients with axial spondyloarthritis).

Forty-one healthy subjects were administered ixekizumab by PFS (160 mg [2 × 80 mg] followed by 80 mg 2 weeks later) in Study I1F-MC-RHCA (Study RHCA). All AEs in Study RHCA were mild in severity. The most commonly reported AEs were headache, injection-site erythema, and fatigue. 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. All TEAEs were mild in severity and the most commonly reported TEAEs were ISR, injection-site pruritus, nausea, diarrhea, upper respiratory tract infection, and injection-site erythema.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of ixekizumab are to be found in the IB and the Package Insert.

4. Objectives and Endpoints

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

Table RHCT.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the relative bioavailability of a single 80 mg SC dose of ixekizumab Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference)	C_{max}, AUC(0-∞), AUC(0-t_{last})
Secondary To evaluate the safety and tolerability of a single 80 mg SC dose of ixekizumab Test Formulation 1 and Test Formulation 2 formulations compared to the commercial formulation (Reference)	TEAEs, SAEs, ISRs, and VAS pain score immediately after injection
Exploratory To evaluate the effect of ixekizumab on immunogenicity	TE ADAs

Abbreviations: AUC(0-∞) = area under the concentrations 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; ISR = injection-site reaction; SAE = serious adverse events; TE ADA = treatment-emergent anti-drug antibodies; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

5. Study Design

5.1. Overall Design

Study I1F-MC-RHCT is a Phase 1, subject-blind, 3-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 clinical research unit (CRU) on Day -1 and randomized 1:1:1 to 1 of 3 possible treatments. On Day 1, subjects will receive a single SC dose of one of the following treatments, according to the randomization schedule:

- 80 mg ixekizumab Commercial Formulation (Reference)
- 80 mg ixekizumab Test Formulation 1
- 80 mg ixekizumab Test Formulation 2

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

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), immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site visual analog scale (VAS).

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 99 subjects may be enrolled so that 78 subjects (26 in each treatment arm) complete the study. For the purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

Single doses of 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 RHCT 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 a screening medical history, PE, vital signs, clinical laboratory tests, and 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 males and females with chronic stable medical problems that, in the investigators 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 the last dose of ixekizumab.

Examples of reliable methods of birth control are condoms with spermicide, oral contraceptives or intrauterine device used by the female partner, and male sterilization.

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 childbearing potential 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.

2) Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to

either remain abstinent or stay in a same sex relationship without sexual relationships with males, and agree to use a condom with spermicide should the situation change. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a study, and withdrawal are not acceptable methods of contraception.

3) Otherwise, women of childbearing 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 dosing with ixekizumab.

Highly effective methods of contraception include combination oral contraceptives, implanted contraceptives, or intrauterine device or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include the 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.

4) Women not of childbearing potential may participate and include those who are:

A. Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), a congenital anomaly such as mullerian agenesis, or

B. Post-menopausal – defined as either

i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

a) spontaneous amenorrhea for at least 1 year, or

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

ii. A woman 55 years or older, not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, or

iii. A woman 55 years or older with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] are aged 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.

[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 signed informed consent.

6.2. Exclusion Criteria

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

[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 Lilly or Covance employees.

[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 ixekizumab, or have ever been administered other IL-17 antagonists.

[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 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] 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 HADS Depression subscale score of ≥11.

[18] have current or history of inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis), or 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 post 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 re-screened (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: Laboratory tests may be repeated if there is a documented technical error, or once at the discretion of the investigator for any out of range results.

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

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

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

[25] show evidence of hepatitis B and/or positive hepatitis B surface antigen 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 each study visit and while at the CRU, or are unwilling to restrict alcohol intake to 3 units per day (males) and 2 units per day (females) during outpatient periods (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: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guérin [BCG] or other vaccination history) or a positive (not indeterminate) QuantiFERON®-TB Gold test. The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produce significant immunosuppression.

[30] had a vaccination with BCG, other live vaccines, or attenuated live vaccines within 12 months prior to first 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.

Note: killed/inactive or subunit vaccines are expected to be safe; however, their efficacy with concomitant ixekizumab is unknown.

[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 Day 1. Subjects on stable doses of other medications (for example, statins and anti-hypertensives) 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 abdomen, or other factors (eg, 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 will receive a light breakfast on the morning of 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) and 2 units per day (females). 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 rescreened once at the investigator's discretion (see Section 6).

7. Treatment

7.1. Treatment Administered

A dose of IP will consist of 1 injection of 80 mg ixekizumab into the abdomen. All doses will be administered by trained site staff.

This study involves a comparison of:

- 80 mg ixekizumab Commercial Formulation administered SC via PFS (Reference)
- 80 mg ixekizumab Test Formulation 1 administered SC via PFS (Test Formulation 1)
- 80 mg ixekizumab Test Formulation 2 administered SC via PFS (Test Formulation 2)

Table RHCT.2 shows the treatment regimens.

Table RHCT.2. Treatments Administered

Treatment Name	Reference	Test Formulation 1	Test Formulation 2
Formulation	solution for injection	solution for injection	solution for injection
Dose	80 mg ixekizumab	80 mg ixekizumab	80 mg ixekizumab
Route of Administration	SC injection	SC injection	SC injection
Delivery Method	PFS	PFS	PFS

Abbreviations: PFS = prefilled syringe; 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

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.

7.1.1. Packaging and Labeling

Ixekizumab will be supplied by the sponsor or its designee in accordance with current good manufacturing practice (GMP), labeled according to the country's regulatory requirements, and supplied with lot numbers, expiry dates, and certificates of analysis, as applicable. Each syringe of ixekizumab 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 1-mL single-dose, prefilled, disposable manual syringes

- ixekizumab Test Formulation 1 (solution for injection) in 1-mL single-dose, prefilled, disposable manual syringes
- ixekizumab Test Formulation 2 (solution for injection) in 1-mL single-dose, prefilled, disposable manual syringes

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 (i.e., subjects must not see the syringe before, during or after the drug administration).

7.2. Method of Treatment Assignment

Subjects will be randomly assigned to 1 of 3 treatments using a computer-generated allocation code.

7.2.1. Selection and Timing of Doses

The actual time of all injections will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Blinding will be in place for subjects and for site staff conducting injection-site assessments and injection-site bleeding/bruising assessments.

7.4. Dose Modification

Dose modification is not permitted in this study.

7.4.1. Special Treatment Considerations

All biological agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include, but are not limited to skin rash, pruritus (itching), urticaria (hives), angioedema (eg, 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.

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 include oral contraceptives, hormone replacement therapy, and thyroid replacement at the discretion of the investigator. 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 (for example, 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 abdominal skin the morning prior to injection and for 24 hours after 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

This section is not applicable for this study.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

Not applicable in this single-dose study.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

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
- 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 clinical 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 for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the subject to discontinue before completing 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.

After the informed consent form (ICF) is signed, study site personnel will record, initially via source documents and then via eCRF, the occurrence and nature of each subject's preexisting conditions. 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 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 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 (that is, 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.

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.

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 electronic case report form [eCRF] has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Adverse Events of Special Interest

The following AEs of special interest will be used to determine the safety and tolerability of ixekizumab injections administered by PFS 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])
- infection

- ISRs
- allergic reactions/hypersensitivities
- cerebrocardiovascular events
- malignancies
- depression
- inflammatory bowel disease (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 allergic/hypersensitivity reaction during the study.

Injection-site reactions will be recorded as described in Section 9.4.5.1

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 inflammatory bowel disease, 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 inflammatory bowel disease.

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.

9.2.2. Complaint Handling

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

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. Syringes 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.

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

9.4.2. Vital Signs

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

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

Electrocardiograms will be interpreted by a qualified physician (the investigator 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 (oral) 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 assessments will be performed at the times indicated in the Schedule of Activities (Section 2).

If the investigator determines that the ISR is clinically significant, or if a subject indicates symptoms are indicative of an ISR (unsolicited event; volunteered by subject), the event will be captured as an AE.

Induration, swelling, pruritus, and erythema/redness associated with study injection sites will be evaluated by the investigator or designee.

9.4.5.2. Bleeding/Bruising Assessment

All injection sites will be observed at the times indicated in the Schedule of Activities (Section 2) by the investigator or designee, and the presence of visible bleeding/bruising will be recorded on the eCRF. A bandage may be placed on the injection site after assessment.

9.4.5.3. Injection-Site Pain

Pain measurements will be quantified using the 100-mm VAS pain score for all subjects. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually “no pain” and “worst imaginable pain.” The subject will be asked to relate any pain at the injection site on a scale of 1 to 100 mm on the line immediately (within 1 minute) following injection and at the additional time points listed in the Schedule of Activities (Section 2).

9.4.5.4. Columbia Suicide Severity Rating Scale

Columbia Suicide Severity Rating Scale (C-SSRS): 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.

9.4.5.4.1. 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 ≥3 × upper limit of normal (ULN), ALP ≥2 × ULN, or elevated total bilirubin ≥2 × ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, conjugated bilirubin, gamma-glutamyl transferase, and creatine phosphokinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the serum concentrations of 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 method.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last subject visit for the study.

9.6. Pharmacodynamics

This section is not applicable for this study.

9.6.1. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against ixekizumab. To interpret the results of immunogenicity, venous blood samples will be collected at the same time points to determine the serum concentrations of ixekizumab. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Treatment-emergent ADAs (TE ADAs) are defined in Section 10.3.3.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of ixekizumab at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab and/or their ability to cross-react with endogenous counterparts.

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 ixekizumab. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), 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 Ps. 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 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

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 99 subjects may be enrolled to ensure that 78 subjects (26 for each treatment) complete the study.

[redacted]

Subjects who are randomized but not administered treatment may be replaced to ensure that 78 subjects (26 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, and other demographic characteristics will be recorded and summarized using descriptive statistics.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on data from all subjects who receive 1 dose of ixekizumab and have evaluable PK.

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

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

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 the medical regulatory dictionary.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

10.3.1.2.1. Injection-Site Pain

VAS pain score will be summarized using standard descriptive statistics. In addition, the severity of pain will be categorized by VAS pain score as: mild pain (≤30), moderate pain (>30 and ≤70), and severe pain (>70). The number and percentage of the subjects in each pain severity category will summarized by formulation and time point.

A mixed model for the repeating measures analysis model will be used to analyze the continuous injection-site pain VAS score. The model will include formulation and time post injection (0, 10, 20, 30, and 60 minutes) and formulation by time as fixed factors. The covariance structure of the model will be unstructured. Other covariance matrices may be explored if needed. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least squares means will be used for the statistical comparison; the treatment differences along with their corresponding 95% CIs will also be reported.

Additional analyses may be performed as deemed necessary.

10.3.1.2.2. Statistical Evaluation of Other Safety Parameters

Safety laboratory parameters and vital signs data will be listed and summarized using standard descriptive statistics, where possible. Injection-site assessments, including induration, swelling, pruritis, bleeding/bruising, and erythema/redness, will also be assessed. The parameters will be listed and summarized using descriptive statistics. 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 (ie, if a subject's answers are all 'no' for the C-SSRS, then that subject will not be displayed). HADS 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-∞), AUC(0-t_{last}) 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. PK parameters may also be

normalized by body weight in the event there are differences in body weight between the treatment groups.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate the relative bioavailability of Test Formulation 1 and Test Formulation 2 compared to the commercial formulation (Reference). Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with a fixed effect 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.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with TE ADA+ 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 PK parameters and of ixekizumab may be assessed.

10.3.4. Data Review During the Study

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

10.3.5. Interim Analyses

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

11. References

Laursen T, Hansen B, Fisker S. Pain perception after subcutaneous injections of media containing different buffers. *Basic Clin Pharmacol Toxicol*. 2006;98(2):218-221.

Medicines.org.uk. (2018) Taltz 80 mg solution for injection – Summary of Product Characteristics (SPC). [online] available at https://www.medicines.org.uk/emc/product/7233/smpc [Accessed 05 September 2018]

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

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
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(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is last the time point with a measurable concentration
BCG	Bacillus Calmette-Guérin
BMI	body mass index
CEC	Clinical Events Committee
CI	confidence interval
C_{max}	maximum 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
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
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
GMP	good manufacturing practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
Ig	immunoglobulin
IL	interleukin
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product (IP)	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.
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.
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.

Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
PE	physical examination
PFS	prefilled syringe
PK	pharmacokinetic
Ps	psoriasis
randomize	the process of assigning subjects to an experimental group on a random basis
RBC	red blood cell
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
$t_{1/2}$	terminal rate constant in noncompartmental analysis
TB	tuberculosis
TBL	total bilirubin level
TE ADA	treatment-emergent antidrug antibodies
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum drug concentration
TST	tuberculin skin test
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Glucose (random)
Leukocytes (WBC)	Blood urea nitrogen (BUN)
Platelets	Uric acid
	Total cholesterol
Differential WBC absolute counts of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin level (TBL)
Monocytes	Direct bilirubin
Eosinophils	Triglycerides
Basophils	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis	
Specific gravity	Phosphorus
pH	
Protein	
Glucose	**Other tests**
Ketones	Pregnancy test (females only)[b]
Bilirubin	FSH (females only, if applicable)[a,c]
Urobilinogen	QuantiFERON®-TB Gold[a] or TST
Blood	Ethanol testing[d]
Nitrite	Urine drug screen[d]
Microscopy (if dipstick abnormal)	
Serology	
Hepatitis B surface antigen[a]	
Hepatitis B core antibody[a]	
Hepatitis C antibody[a]	
HIV antibodies[a]	

Abbreviations: FSH = follicle-stimulating hormone; RBC = red blood cell; TB = tuberculosis; TST = tuberculin skin test; WBC = white blood cell.

[a] Performed at screening only.

[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 non-childbearing potential (>40 mIU/mL).

[d] Urine drug screen and ethanol 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.

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 ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for 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 site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). 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 Summary of Product Characteristics 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 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 investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (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 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 Lilly or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin level (TBL)	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**
CPK	**antibody)[a]**

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine 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, clinical laboratory, pharmacokinetics, immunogenicity, and bioanalytical assays) during the study.

Protocol I1F-MC-RHCT Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	26	1	26
Clinical laboratory tests[a]	15.2	4	60.8
Pharmacokinetics	3	15[b]	45
Immunogenicity	10	4	40
Pharmacogenetics	10	1	10
Total			181.8
Total for clinical purposes			190

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

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

Appendix 6. Protocol Amendment I1F-MC-RHCT (b) Summary: Relative Bioavailability of 2 Ixekizumab Test Formulations Compared to the Commercial Formulation in Healthy Subjects

Overview

Protocol I1F-MC-RHCT, Relative Bioavailability of 2 Ixekizumab Test Formulations 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.

A temperature assessment was added to each site visit. In addition, safety telephone calls were added in between outpatient visits as appropriate.

The additional study activities are being implemented to further monitor the health of subjects due to emerging data in response to a reporting of an SAE in this study.

Revised Protocol Sections

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

1. Protocol Synopsis

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1:1 to 1 of 3 possible treatments. Subjects may be allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and will return for pharmacokinetic (PK) and immunogenicity sampling and safety assessments at predefined times up to 12 weeks postdose. Subjects will be monitored for safety between outpatient visits by way of telephone assessment.

Safety and tolerability will be assessed by clinical laboratory tests, vital sign measurements, temperature, recording of adverse events (AEs), physical examination/medical assessments, Columbia Suicide Severity Rating Scale (C-SSRS), Hospital Anxiety Depression Scale (HADS), immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site VAS.

2. Schedule of Activities

	Screening	Study Day														
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
Safety Assessment (Telephone Call)											X		X		X		
Body Temperature (Oral)		P		X	X	X	X	X	X	X		X		X		X	X
Adverse Events and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

3.3 Benefit/Risk Assessment

As of the cut-off date for the current investigator's brochure (IB; 22 March 2018), more than 8755 subjects and patients have received at least 1 dose of ixekizumab (5934 patients with Ps, 532 patients with rheumatoid arthritis, 1301 patients with psoriatic arthritis, 119 healthy subjects, and an estimated 869 patients with axial spondyloarthritis).

5. Study Design

5.1 Overall Design

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

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), immunogenicity, and injection-site assessments. Pain assessments will be made using an injection-site visual analog scale (VAS).

9.4 Safety

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

9.4.4. Temperature

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