Protocol I1F-MC-RHBU(a)

Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

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Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Confidential Information

Ixekizumab (LY2439821)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 25 August 2016
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1. Protocol Synopsis

Title of Study:
Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Rationale:
Psoriasis is a chronic inflammatory skin disease in which elevated levels of proinflammatory cytokines are observed. Elevated proinflammatory cytokines can lead to disease-drug interactions by reducing the expression and activity of some cytochrome P450 (CYP) enzymes, thereby theoretically altering the systemic exposure of CYP substrates. Thus, treatment of psoriasis with biological products that reduce inflammation could theoretically reduce elevations in cytokines and in turn affect CYP activity. It is currently unknown if treatment with a biologic agent affecting the interleukin (IL)-17 pathway has the potential to influence CYP activity as has been seen with anti-IL-6 or anti-Tumor Necrosis Factor α agents.

In vitro assays demonstrated that IL-17 inhibition by ixekizumab had little or no influence on mRNA CYP expression; however, while the use of in vitro assays to predict risk of clinical drug-drug interactions (DDI) is well established for small molecule chemical entities, the utility of in vitro assays to predict clinical DDI with biologic agents has been inconsistent and thus not yet routinely accepted by global regulatory agencies in lieu of clinical studies for biologic agents that may affect cytokines. This study therefore seeks to evaluate the effect of single and multiple doses of ixekizumab on the single–dose pharmacokinetics (PK) of CYP3A, CYP2C9, CYP2D6, CYP2C19, and CYP1A2 substrates midazolam, warfarin, dextromethorphan, omeprazole, and caffeine, respectively, in patients with moderate-to-severe psoriasis.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To assess the effects of single and multiple doses of ixekizumab on the PK of a drug cocktail of CYP substrates in patients with moderate-to-severe psoriasis.	Ratio of geometric least squares means between each CYP substrate administered alone and in combination with ixekizumab for maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity (AUC[0-∞]) of parent drug.
Secondary To evaluate the tolerability of ixekizumab in patients with moderate-to-severe psoriasis.	Incidence of treatment-emergent adverse events (TEAEs).

Summary of Study Design:

This is a 2-period, fixed-sequence, open-label, multi-center, Phase 1 study to assess the effects of single and multiple doses of ixekizumab on the PK of a drug cocktail of CYP substrates (midazolam, warfarin, dextromethorphan, omeprazole, and caffeine) in patients with moderate-to-severe psoriasis.

Patients will be admitted to the clinical research unit (CRU) on Day -1 of Period 1 and receive the drug cocktail on the morning of Day 1. Patients will reside at the CRU until Day 2 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 3 (48 hours post-drug cocktail dose), Day 4 (72 hours post-drug cocktail dose), and Day 5 (96 hours post-drug cocktail dose).

Patients will attend the CRU as outpatients on Day 1 of Period 2 (3 to 7 days after Day 5 of Period 1) and receive a 160-mg dose of ixekizumab (administered as two 80-mg subcutaneous [SC] injections).

Patients will be admitted to the CRU on Day 7 (±2 days) of Period 2 and receive the drug cocktail on the following morning (Day 8; Week 1). Patients will reside at the CRU until Day 9 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 10 (48 hours post-drug cocktail dose), Day 11 (72 hours post-drug cocktail dose), and Day 12 (96 hours post-drug cocktail dose).

Patients will receive single 80-mg doses of ixekizumab on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10) of Period 2. Patients will be admitted to the CRU on Day 84 (±2 days) and receive 80 mg ixekizumab and the drug cocktail on the following morning (Day 85; Week 12). Patients will reside at the CRU until Day 86 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of additional drug cocktail PK samples and safety assessments, as applicable, on Day 87 (48 hours post-drug cocktail dose), Day 88 (72 hours post-drug cocktail dose), and Day 89 (96 hours post-drug cocktail dose). Patients will attend a follow-up visit on Day 113 (±4 days; Week 16).

Safety will be monitored throughout the study by recording of adverse events (AEs), clinical laboratory parameters, vital signs, physical examination, Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS-SR16), Columbia-Suicide Severity Rating Scale (C-SSRS) and Lilly Self-Harm Supplement responses, and electrocardiograms (ECGs).

Treatment Arms and Duration:

In Period 1, patients will receive a single oral dose of drug cocktail (with single oral doses of 1 mg midazolam, 10 mg warfarin [+ 10 mg vitamin K], 30 mg dextromethorphan, 20 mg omeprazole, and 100 mg caffeine) on Day 1 and PK sampling will be conducted up to 96 hours post-drug cocktail dose (Day 5).

In Period 2, patients will receive a 160-mg SC dose of ixekizumab (administered as 2 x 80-mg SC injections) on Day 1, followed by 80-mg SC doses every 2 weeks from Day 15 (Week 2) through Day 85 (Week 12). On Day 8 and Day 85, patients will receive a single oral dose of drug cocktail and PK sampling will be conducted up to 96 hours post-drug cocktail dose (Days 12 and 89).

Patients will attend a follow-up visit at Week 16.

Number of Patients:
Approximately 30 patients will be enrolled with the assumption that 21 patients complete the study.

Statistical Analysis:

Pharmacokinetic parameter estimates for midazolam and 1-hydroxymidazolam, S-warfarin, dextromethorphan and dextrorphan, omeprazole and 5-hydroxyomeprazole, and caffeine and paraxanthine will be calculated by standard noncompartmental methods of analysis.

Pharmacokinetic parameter estimates will be evaluated to delineate the effects of drug interaction. Midazolam, warfarin, dextromethorphan, omeprazole, and caffeine administered in the absence of ixekizumab will represent the reference treatments and will be analyzed separately. Each drug administered with ixekizumab will represent the test treatments and will be analyzed separately. Data for each drug will also be analyzed separately after single or multiple doses of ixekizumab. For the primary analysis, log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for patient. The treatment differences will be back-transformed to present ratios of geometric least squares means and the corresponding 90% confidence intervals (CIs).

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, and C-SSRS scores. The parameters will be listed, and summarized using standard descriptive statistics.

2. Schedule of Activities

Study Schedule Protocol I1F-MC-RHBU – Period 1

	Screening	Baseline					
Procedure	**D -29 to -2**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**
Informed Consent	X						
Medical History	X						
Review of AEs		X					
Review Concomitant Medications		X					
TB Test[a]	X						
Chest X-ray	X[f]						
Height	X						
Weight	X	X					
Patient Admission to CRU		X					
Patient Discharge from CRU				X[g]			
Outpatient Visit	X				X	X	X
Urine Drug Screen	X	X					
Ethanol Breath Test	X	X					
Vital Signs (Supine and Standing Blood Pressure and Pulse Rate and Body Temperature)	X	X					X
Clinical Laboratory Tests[b]	X	X			X		X
Pregnancy Test[c]	X	X					
Physical Examination/ Medical Assessment[d]	X	X					X
12-Lead ECG	X	X					X
QIDS-SR16	X						
C-SSRS and Self-Harm Supplement	X	X		X			
PASI	X	X					
sPGA	X	X					
% BSA Assessment	X	X					
Drug Cocktail Administration			X				

	Screening	Baseline					
Procedure	**D -29 to -2**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**
Midazolam and 1-hydroxymidazolam PK Sample[e]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h			
Warfarin PK Sample[e]			Predose, 1, 2, 4, 6, 8, 10 h	24 h	48 h	72 h	96 h
Dextromethorphan and Dextrorphan PK Sample[e]			Predose, 1, 2, 4, 6, 8, 10 h	24 h	48 h	72 h	
Omeprazole and 5-hydroxyomeprazole PK Sample[e]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h		
Caffeine and Paraxanthine PK Sample[e]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h		
Pharmacogenetic Sample		X					

Abbreviations: AE = adverse event; BSA = body surface area; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; PPD = purified protein derivative; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); sPGA = static Physicians Global Assessment; TB = tuberculosis; W = Week.

a TB test(s) include PPD, QuantiFERON®-TB Gold, and T-SPOT®.

b Screening samples tested at a local laboratory, all other clinical laboratory test samples tested at a central laboratory. Additional samples for coagulation parameters (Appendix 2) may be collected and tested at a local laboratory at the discretion of the investigator.

c Females only. Serum pregnancy test to be performed at screening. Serum or urine pregnancy test may be performed locally at all other times, at the discretion of the investigator.

d One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All medical assessments throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.

e Sample times are relative to administration of the drug cocktail. The PK sample collection times are nominal; actual times should be recorded. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).

f A chest X-ray will be taken at screening unless one has been obtained within the last 6 months (provided the x-ray and/or report are available for review).

g Patients may be discharged after collection of the 24 hour PK sample, at the discretion of the investigator.

Study Schedule Protocol I1F-MC-RHBU – Period 2

	W 0	Check-in for W 1	W 1					W 2	W 4	W 6	W 8	W 10
	D 1[e]	D 7[g] ±2d	D 8[g]	D 9[g]	D 10[g]	D 11[g]	D 12[g]	D 15 ±2d	D 29 ±2d	D 43 ±2d	D 57 ±2d	D 71 ±2d
Procedure												
Patient Admission to CRU		X										
Patient Discharge from CRU				X[h]								
Outpatient Visit	X				X	X	X	X	X	X	X	X
Review of AEs	X											
Review Concomitant Medications	X											
Urine Drug Screen		X										
Ethanol breath test		X										
Vital Signs (Supine and Standing Blood Pressure and Pulse Rate and Body Temperature)	Predose[f]	X					X	Predose[f]	Predose[f]	Predose[f]	Predose[f]	Predose[f]
Clinical Laboratory Tests[a]	Predose[f]	X			X		X		Predose[f]			
Pregnancy Test[b]	Predose[f]											
Medical Assessment[c]							X					
12-Lead ECG	Predose[f]											
QIDS-SR16		X										
C-SSRS and Self-Harm Supplement	Predose[f]	X		X				Predose[f]	Predose[f]	Predose[f]	Predose[f]	Predose[f]
PASI	Predose[f]		X						X		X	
sPGA	Predose[f]		X						X		X	
% BSA Assessment	Predose[f]		X						X		X	
Inflammatory Biomarker Sample	Predose[f]		X						Predose[f]		Predose[f]	
Ixekizumab	160 mg							80 mg	80 mg	80 mg	80 mg	80 mg

	W 0	Check-in for W 1	W 1					W 2	W 4	W 6	W 8	W 10
	D 1[e]	D 7[g] ±2d	D 8[g]	D 9[g]	D 10[g]	D 11[g]	D 12[g]	D 15 ±2d	D 29 ±2d	D 43 ±2d	D 57 ±2d	D 71 ±2d
Procedure												
Administration												
Drug Cocktail Administration			X									
Ixekizumab PK Sample	Predose[f]		X					Predose[f]	Predose[f]		Predose[f]	
Midazolam and 1-hydroxymidazolam PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8,12 h	24 h								
Warfarin PK Sample[d]			Predose, 1, 2, 4, 6, 8, 10 h	24 h	48 h	72 h	96 h					
Dextromethorphan and Dextrorphan PK Sample[d]			Predose, 1, 2, 4,6, 8, 10 h	24 h	48 h	72 h						
Omeprazole and 5-hydroxyomeprazole PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h							
Caffeine and Paraxanthine PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h							
Ixekizumab Immunogenicity Sample	Predose[f]		X					Predose[f]	Predose[f]		Predose[f]	

Abbreviations: AE = adverse event; BSA = body surface area; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; ED = early discontinuation; PASI = Psoriasis Area Severity Index; PK = pharmacokinetics; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); sPGA = static Physicians Global Assessment; W = Week.

[a] All clinical laboratory test samples tested at a central laboratory. Additional samples for coagulation parameters (Appendix 2) may be collected and tested at a local laboratory at the discretion of the investigator.

[b] Females only. Serum or urine pregnancy test may be performed locally, at the discretion of the investigator.
[c] All medical assessments throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.
[d] Sample times are relative to administration of the drug cocktail. The PK sample collection times are nominal; actual times should be recorded. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).
[e] Day 1 of Period 2 will be 3 to 7 days after Day 5 of Period 1.
[f] Time is relative to that day's ixekizumab dose.
[g] Drug cocktail administration and drug cocktail PK sampling days must run consecutively from admission to CRU (on Day 5 to Day 9).
[h] Patients may be discharged after collection of the 24 hour PK sample, at the discretion of the investigator.

Study Schedule Protocol I1F-MC-RHBU –Period 2 continued

	Check-in for W 12	W 12					Follow-up/ED
	D 84[f] ±2d	D 85[f]	D 86[f]	D 87[f]	D 88[f]	D 89[f]	W 16
Procedure							D 113 ±4d
Patient Admission to CRU	X						
Patient Discharge from CRU			X[g]				
Outpatient Visit							X
Review of AEs		X					
Review Concomitant Medications		X					
Urine Drug Screen	X						
Ethanol breath test	X						
Vital Signs (Supine and Standing Blood Pressure and Pulse Rate and Body Temperature)	X				X		X
Clinical Laboratory Tests[a]	X			X		X	X
Pregnancy Test[b]							X
Medical Assessment[c]						X	X
12-lead ECG							X
C-SSRS and Self-Harm Supplement	X		X				X
PASI		Predose[e]					
sPGA		Predose[e]					
% BSA Assessment		Predose[e]					
Inflammatory Biomarker Sample		Predose[e]					
Ixekizumab Administration		80 mg					
Drug Cocktail Administration		X					
Ixekizumab PK Sample		Predose[e]					X

	Check-in for W 12	W 12					Follow-up/ED
	D 84[f] ±2d	D 85[f]	D 86[f]	D 87[f]	D 88[f]	D 89[f]	W 16
Procedure							D 113 ±4d
Midazolam and 1-hydroxymidazolam PK Sample[d]		Predose, 0.5, 1, 2, 3, 4, 6, 8,12 h	24 h				
Warfarin PK Sample[d]		Predose, 1, 2, 4, 6, 8, 10 h	24 h	48 h	72 h	96 h	
Dextromethorphan and Dextrorphan PK Sample[d]		Predose, 1, 2, 4,6, 8, 10 h	24 h	48 h	72 h		
Omeprazole and 5-hydroxyomeprazole PK Sample[d]		Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h			
Caffeine and Paraxanthine PK Sample[d]		Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h			
Ixekizumab Immunogenicity Sample		Predose[e]					X

Abbreviations: AE = adverse event; BSA = body surface area; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; ED = early discontinuation; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); sPGA = static Physicians Global Assessment; W = Week.

[a] All clinical laboratory test samples tested at a central laboratory. Additional samples for coagulation parameters (Appendix 2) may be collected and tested at a local laboratory at the discretion of the investigator.

[b] Females only. Serum or urine pregnancy test may be performed locally, at the discretion of the investigator.

[c] All medical assessments throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.

[d] Sample times are relative to administration of the drug cocktail. The PK sample collection times are nominal; actual times should be recorded. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).

[e] Time is relative to that day's ixekizumab dose.

[f] Drug cocktail administration and drug cocktail PK sampling days must run consecutively from admission to CRU (on Day 82 to Day 86).

[g] Patients may be discharged after collection of the 24 hour PK sample, at the discretion of the investigator.

3. Introduction

3.1. Study Rationale

Psoriasis is a chronic inflammatory skin disease in which elevated levels of proinflammatory cytokines are observed. Elevated proinflammatory cytokines can lead to disease-drug interactions by reducing the expression and activity of some cytochrome P450 (CYP) enzymes, thereby theoretically altering the systemic exposure of CYP substrates (Wang et al. 2014). Thus, treatment of psoriasis with biological products that reduce inflammation could theoretically reduce elevations in cytokines and in turn affect CYP activity. It is currently unknown if treatment with a biologic agent affecting the interleukin (IL)-17 pathway has the potential to influence CYP activity as has been seen with anti-IL-6 or anti-Tumor Necrosis Factor α agents.

In vitro assays demonstrated that IL-17 inhibition by ixekizumab had little or no influence on mRNA CYP expression; however, while the use of in vitro assays to predict risk of clinical drug-drug interactions (DDI) is well established for small molecule chemical entities, the utility of in vitro assays to predict clinical DDI with biologic agents has been inconsistent, and thus not yet routinely accepted by global regulatory agencies in lieu of clinical studies for biologic agents that may affect cytokines. This study therefore seeks to evaluate the effect of single and multiple doses of ixekizumab on the pharmacokinetics (PK) of CYP3A, CYP2C9, CYP2D6, CYP2C19, and CYP1A2 substrates midazolam, warfarin, dextromethorphan, omeprazole, and caffeine, respectively, in patients with moderate-to-severe psoriasis.

3.2. Background

Ixekizumab (LY2439821) is an immunoglobulin subclass 4 (IgG4) monoclonal antibody that binds with affinity (<3 pM) and specificity to IL-17A, a proinflammatory cytokine. Elevated levels of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases, including psoriasis.

Ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and is administered by subcutaneous (SC) injection. The recommended dose is 160 mg (two 80-mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks thereafter.

In psoriasis patients, the mean (geometric coefficient of variation [CV%]) half-life was 13 days (40%) as determined from a population PK analysis. Following a single SC dose of 160 mg in subjects with plaque psoriasis, ixekizumab reached peak mean concentrations by approximately 4 days postdose.

3.3. Benefit/Risk Assessment

As of the cut-off date for the current investigator's brochure (IB), more than 4950 patients (4209 psoriasis patients, 532 rheumatoid arthritis patients, and 209 psoriatic arthritis patients) have received at least 1 dose of ixekizumab.

There were 11 deaths among all ixekizumab-treated patients (8 among psoriasis patients), with none of these considered to be related to ixekizumab treatment. In an integrated analysis of data

from all psoriasis studies, a total of 411 ixekizumab-treated patients (9.8%) reported at least 1 serious adverse event (SAE). The individual SAE preferred terms with an incidence ≥0.2% included: cellulitis (0.4%), fall (0.3%), myocardial infarction (0.3%), osteoarthritis (0.3%), acute myocardial infarction (0.2%), chronic obstructive pulmonary disease (0.2%), nephrolithiasis (0.2%), suicide attempt (0.2%), prostate cancer (0.2%), and coronary artery disease (0.2%).

The percentage of psoriasis patients reporting at least 1 treatment-emergent adverse event (TEAE) was greater for each ixekizumab treatment group than for that of the placebo group; 46.8% of placebo-treated patients reported ≥1 TEAE, compared to 58.6% of patients treated with 80 mg ixekizumab either once every 2 weeks or once every 4 weeks. Individual TEAEs reported at a significantly greater frequency in ixekizumab-treated patients than in placebo-treated patients were injection site reaction, injection site erythema, nausea, and oropharyngeal pain. Most TEAEs were mild or moderate in severity. Overall, severe TEAEs were similar across the ixekizumab and placebo-treated group.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated adverse events (AEs) of ixekizumab are to be found in the IB and the Package Insert. Information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs for each of the cocktail drugs are to be found in each drug's respective Package Insert.

4. Objectives and Endpoints

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

Table RHBU.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the effects of single and multiple doses ixekizumab on the pharmacokinetics (PK) of a drug cocktail of cytochrome P450 (CYP) substrates in patients with moderate-to-severe psoriasis.	Ratio of geometric least squares means between each CYP substrate administered alone and in combination with ixekizumab for maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity (AUC[0-∞]) of parent drug.
Secondary To evaluate the tolerability of ixekizumab in patients with moderate-to-severe psoriasis.	Incidence of treatment-emergent adverse events (TEAEs).
Exploratory • To explore the effects of ixekizumab on the PK of a drug cocktail of CYP substrates in the subgroups of patients with moderate-to-severe psoriasis who respond to ixekizumab treatment at Week 12 and those who do not respond. • To evaluate the effects of ixekizumab treatment over time on inflammatory biomarker concentrations in patients with moderate-to-severe psoriasis. • To determine the PK of metabolites and metabolite to parent ratios where appropriate.	• Ratio of geometric least squares means between each CYP substrate administered alone and in combination with ixekizumab for C_{max} and AUC(0-∞) of parent drug in responders and nonresponders. • Change from baseline in inflammatory biomarker concentrations over time during 12 weeks of ixekizumab treatment. • C_{max} and AUC(0-∞) of CYP substrate metabolites, where appropriate, and metabolite to parent ratios.

5. Study Design

5.1. Overall Design

This is a 2-period, fixed-sequence, open-label, multi-center, Phase 1 study to assess the effects of single and multiple doses of ixekizumab on the PK of a drug cocktail of CYP substrates (midazolam, warfarin, dextromethorphan, omeprazole, and caffeine) in patients with moderate-to-severe psoriasis.

Patients will be admitted to the clinical research unit (CRU) on Day -1 of Period 1 and receive the drug cocktail, with single oral doses of 1 mg midazolam, 10 mg warfarin (+ 10 mg vitamin K), 30 mg dextromethorphan, 20 mg omeprazole, and 100 mg caffeine on the morning of Day 1. Patients will reside at the CRU until Day 2 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 3 (48 hours post-drug cocktail dose), Day 4 (72 hours post-drug cocktail dose), and Day 5 (96 hours post-drug cocktail dose).

Patients will attend the CRU as outpatients on Day 1 of Period 2 (3 to 7 days after Day 5 of Period 1) and receive a 160-mg dose of ixekizumab (administered as two 80-mg SC injections).

Patients will be admitted to the CRU on Day 7 (±2 days) of Period 2 and receive the drug cocktail on the following morning (Day 8; Week 1). Patients will reside at the CRU until Day 9 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of PK samples and safety assessments, as applicable, on Day 10 (48 hours post-drug cocktail dose), Day 11 (72 hours post-drug cocktail dose), and Day 12 (96 hours post-drug cocktail dose).

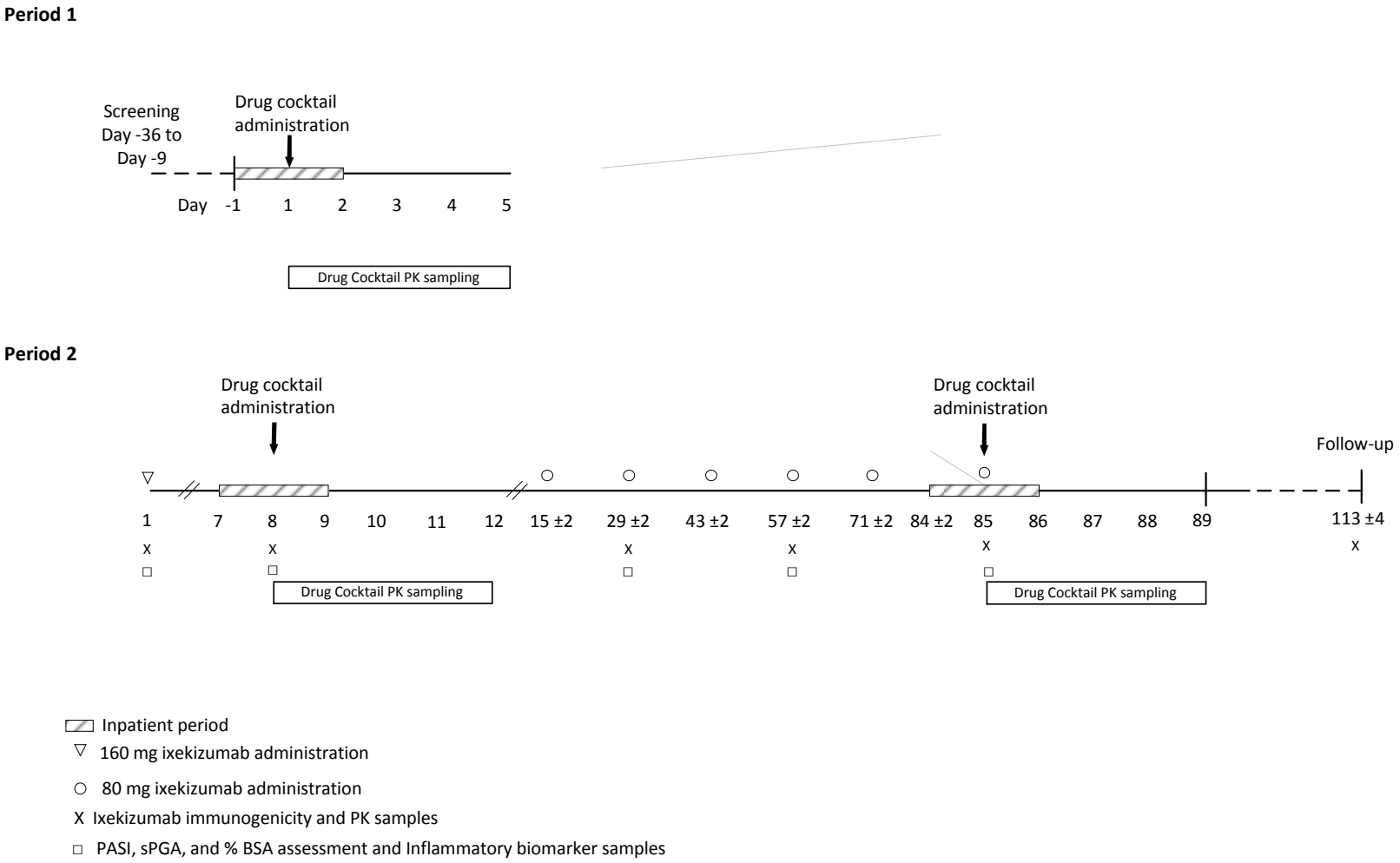
Patients will receive single 80-mg doses of ixekizumab on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10) of Period 2. Patients will be admitted to the CRU on Day 84 (±2 days) and receive 80 mg ixekizumab and the drug cocktail on the following morning (Day 85; Week 12). Patients will reside at the CRU until Day 86 and may be discharged from the CRU following collection of the 24 hour PK samples, at the discretion of the investigator. Patients will return to the CRU as outpatients for collection of additional drug cocktail PK samples and safety assessments, as applicable, on Day 87 (48 hours post-drug cocktail dose), Day 88 (72 hours post-drug cocktail dose), and Day 89 (96 hours post-drug cocktail dose).

Blood sampling for assessment of inflammatory biomarkers (IL-1β, IL-6, IL-19, and Tumor Necrosis Factor α) and ixekizumab PK and immunogenicity will be conducted at prespecified visits. Concentrations of IL-17A will not be measured as it complexes with ixekizumab, and therefore correlates with the PK of ixekizumab. Interleukin-17A drives production of IL-19 in keratinocytes of psoriatic skin. C-reactive protein will also be used as an inflammatory biomarker and is collected as part of the clinical laboratory testing. Efficacy will be evaluated using static Physicians Global Assessment (sPGA), Psoriasis Area Severity Index (PASI), and percentage of body surface area (BSA) assessments at prespecified visits.

All patients will attend a follow-up visit on Day 113 (±4 days; Week 16).

Safety will be monitored throughout the study by recording of AEs, clinical laboratory parameters, vital signs, physical examination, Quick Inventory of Depressive Symptomatology-Self Report (16 items) (QIDS-SR16), Columbia-Suicide Severity Rating Scale (C-SSRS) and Lilly Self-Harm Supplement responses, and electrocardiograms (ECGs).

Figure RHBU.1 illustrates the study design.



Abbreviations: BSA = body surface area; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; sPGA = static Physicians Global Assessment.

Figure RHBU.1. Illustration of study design for I1F-MC-RHBU.

5.2. Number of Participants

Approximately 30 patients will be enrolled with the assumption that 21 patients complete the study.

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 patient.

5.4. Scientific Rationale for Study Design

This is an open-label study. Blinding is not necessary because the primary endpoint is PK and thus not vulnerable to patient or investigator bias. The fixed-sequence design is used due to the long half-life of ixekizumab.

This study will be conducted in patients with moderate-to-severe plaque psoriasis as this is the patient population for whom ixekizumab treatment is indicated; conducting the study in this population allows the assessment of the effect of ixekizumab on CYP enzymes expressed at clinically relevant levels.

Regulatory agencies recommend conducting a clinical drug interaction study using a drug cocktail approach when interactions with multiple CYPs are investigated (European Medicines Agency [EMA] Guideline 2012; Food and Drug Administration [FDA] 2012, PMDA Draft Guideline 2013). Drugs used in such a cocktail should be selective for the specific CYP enzymes, should not interact with each other, and ultimately should be safe when administered. One such drug cocktail is a modified 5+1 Cooperstown cocktail which includes midazolam (CYP3A), warfarin (CYP2C9), dextromethorphan (CYP2D6), omeprazole (CYP2C19), caffeine (CYP1A2), and vitamin K (to counter the anticoagulant effect of warfarin), and has been administered in previous studies (Goh et al 2010; Ma et al 2006). The drug cocktail will be administered prior to initiation of ixekizumab dosing and again on Day 8 (Week 1) of Period 2, to assess the effect of a single dose of ixekizumab, and on Day 85 (Week 12) of Period 2, when steady-state concentrations of ixekizumab should be achieved. The total required blood volume of 650 mL is considered acceptable given that blood samples are taken during the course of the study which has a minimum duration of approximately 17 weeks.

5.5. Justification for Dose

Drug cocktail containing 1 mg midazolam, 10 mg warfarin (+ 10 mg vitamin K), 30 mg dextromethorphan, 20 mg omeprazole, and 100 mg caffeine has been chosen as these are clinically relevant doses considered safe to administer and have been used concomitantly in previous clinical studies.

The 1 mg oral dose of midazolam used for this study is lower than the 5 mg oral dose that has been used in some published cocktail studies. Use of 1 mg benefits patient safety since this dose does not result in conscious sedation yet still provides sufficient exposure to midazolam to assess midazolam PK.

The dosing regimen for ixekizumab is consistent with that recommended in the United States Package Insert.

6. Study Population

Eligibility of patients for study enrollment will be based on the results of screening medical history, physical examination, vital signs, QIDS-SR16, C-SSRS, clinical laboratory tests, and ECG.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment. Patients 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

Patients are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] Males or females.

[1a] Male patients:

agree to use a reliable method of contraception and not donate sperm for the duration of the study

[1b] Female patients:

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

a) Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
b) Postmenopausal – postmenopausal is defined as women with an intact uterus who have not taken hormones or oral contraceptives within 1 year, who have had either cessation of menses for at least 1 year, or 6 to 12 months of spontaneous amenorrhea with follicle-stimulating hormone consistent with menopause (>40 mIU).

Women of child-bearing potential may participate, and include those who test negative for pregnancy prior to initiation of treatment based on a serum pregnancy test and agree to use a reliable method of contraception during the study and until 3 months after the last dose of ixekizumab received in the study.

[2] Are 18 years or older at the time of screening.

[3] Have a body mass index (BMI) of 18.5 to 40.0 kg/m2, 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] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

[7] Present with chronic plaque psoriasis based on a confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to screening.

[8] Have ≥10% BSA involvement at screening and first admission to the CRU.

[9] Have both an sPGA score of ≥3 and PASI score ≥12 at screening and first admission to the CRU.

[10] Are a candidate for phototherapy and/or systemic therapy.

6.2. Exclusion Criteria

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

[11] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[12] Are employees of Lilly or Covance.

[13] Are currently enrolled in, or discontinued from a clinical trial involving an investigational product or nonapproved use of a drug or device, within the last 4 weeks or a period of at least of 5 half-lives of the last administration of the drug, whichever is longer, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the patient if participating in the study.

[15] Have allergy to rubber or latex.

[16] Have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

[17] Have donated more than 500 mL of blood within the last 4 weeks, or intend to donate blood during the course of the study.

[18] Are women who are lactating.

[19] Are unwilling to comply with the dietary requirements/restrictions during the study: (i) consume only the meals provided during the inpatient visits, and (ii) refrain from consuming grapefruit, Seville oranges, star fruit, pomelos, or products containing these fruits, for at least 14 days prior to the first administration of the drug cocktail through the end of Week 12 assessments.

[20] Are currently or have been smokers or users of tobacco or nicotine replacement products within 1 month prior to first admission to the CRU.

[21] Intend to consume caffeine- or xanthine-containing food or beverages from 5 days prior to each administration of the drug cocktail and until collection of the 48 hour drug cocktail PK samples in each period.

[22] Have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption for at least 24 hours prior to each visit to the CRU, and while resident in the CRU (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).

[23] Require treatment with inhibitors of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2, with inducers of CYP3A or CYP1A2, or with rifampin (inducer of multiple CYPs) within 14 days prior to the first administration of the drug cocktail through the end of Week 12 assessments.

[24] Require treatment with substrates of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 with narrow therapeutic indices within 14 days prior to the first administration of the drug cocktail through the end of Week 12 assessments, at the discretion of the investigator and by agreement with the Lilly clinical research physician (CRP), or clinical pharmacologist (CP), or designee.

[25] Require ongoing treatment with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine, or require treatment with a drug contraindicated with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine (per the prescribing label and Package Insert for each drug) within 14 days prior to the first administration of the drug cocktail through the end of Week 12 assessments.

[26] Have pustular, erythrodermic, and/or guttate forms of psoriasis.

[27] Have a history of drug-induced psoriasis.

[28] Have received systemic nonbiologic psoriasis therapy (including, but not limited to, oral psoralen and ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; methotrexate; oral retinoids; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; azathioprine; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues), or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to first admission to the CRU

-or-

Had topical prescription psoriasis treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, and emollients) within the previous 14 days prior to first admission to the CRU. Exceptions: Class 6 (mild, such as desonide) or Class 7 (least potent, such as hydrocortisone) topical steroids will be permitted for use limited to the face, axilla, and/or genitalia.

[29] Cannot avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to first admission to the CRU and during the study.

[30] Have concurrent use or have received any of the following biologic agents within the last year: human growth hormone (hGH), interferons, rituximab, efalizumab, tocilizumab or other agents that target interleukin-6, interferons, basiliximab or other agents that target IL-2, muromonab or other agents that target CD3, canakinumab or other agents that target IL-1, or Cimzia (certolizumab pegol); or have concurrent use or have received any of the following biologic agents with the following washout periods: alefacept, or any agents that target Tumor Necrosis Factor α (such as Remicade [infliximab], Humira [adalimumab], or Enbrel [etanercept]), (<60 days), ustekinumab or other agents that target IL-12 or IL-23, (<8 months), Simponi (golimumab) (<90 days); or any other biologic agent <5 half-lives prior to first admission to the CRU.

[31] Have ever received natalizumab or other agents that target alpha-4-integrin.

[32] Have previously completed or withdrawn from this study, or have participated in any other study with ixekizumab or other IL-17 antagonists such as secukinumab or brodalumab, or have been prescribed ixekizumab or secukinumab.

[33] Have a known allergy or hypersensitivity to any component of the drug cocktail that would pose an unacceptable risk to the patient if participating in this study.

[34] Had a live vaccination within 12 weeks prior to first admission to the CRU, or intend to have a live vaccination during the course of the study, or within 12 months of completing treatment in this study, or have participated in a vaccine clinical study within 12 weeks prior to first admission to the CRU. Investigators should review the vaccination status of their patients and follow the local guidelines for adult vaccination with nonlive vaccines intended to prevent infectious disease prior to therapy.

(Note: Killed/inactive or subunit vaccines are expected to be safe)

[35] Had a vaccination with Bacillus Calmette-Guérin (BCG) 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.

[36] Had any major surgery within 8 weeks prior to first admission to the CRU, or will require such during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.

[37] Have current or a history of lymphoproliferative disease; or signs or symptoms of lymphoproliferative disease; or have active or history of malignant disease.

(Note: Patients with successfully treated basal-cell carcinoma [no more than 3], squamous-cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to first admission to the CRU may participate in the study.)

[38] Have presence of significant uncontrolled cerebrocardiovascular disorder (for example, myocardial infarction [MI], unstable angina, moderate-to-severe [New York Heart Association Class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders, or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the patient if participating in the study or of interfering with the interpretation of data.

[39] Have a history of uncompensated heart failure, fluid overload, or MI, or evidence of new-onset ischemic heart disease or other serious cardiac disease, within 12 weeks prior to first admission to the CRU.

[40] Presence of significant uncontrolled neuropsychiatric disorder; have a recent history of a suicide attempt (30 days within screening visit and any time between screening visit and baseline); or have a score of 3 on Item 12 (Thoughts of Death or Suicide) of the QIDS-SR16 at screening, or are clinically judged by the investigator to be at risk for suicide.

[41] Had a serious infection (for example, pneumonia, cellulitis), have been hospitalized, or have received intravenous antibiotics for an infection, within 12 weeks prior to first admission to the CRU, or had a serious bone or joint infection within 24 weeks prior to first admission to the CRU, 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 patient.

[42] Have or had an infection typical of an immunocompromised host, and/or that occurs with increased incidence in an immunocompromised host (including, but not limited to, Pneumocystis jirovecii pneumonia, histoplasmosis, or coccidioidomycosis); or have a known immunodeficiency.

[43] Have or had a herpes zoster or any other clinically apparent varicella-zoster virus infection within 12 weeks of first admission to the CRU.

[44] Have any other active or recent infection within 4 weeks of first admission to the CRU that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study; these patients may be rescreened (1 time) ≥4 weeks after documented resolution of symptoms.

[45] Have a body temperature ≥38 °C (100.5 °F) at first admission to the CRU; these patients may be rescreened (1 time) ≥4 weeks after documented resolution of elevated temperature.

[46] Show evidence of active or latent tuberculosis (TB), as documented by medical history and physical examination, chest x-rays (posterior anterior and lateral), and TB testing: lack of TB will be demonstrated by either a negative purified protein derivative (PPD) test (defined as a skin induration <5 mm at 48 to 72 hours, regardless of BCG or other vaccination history) or a negative (not indeterminate) QuantiFERON-TB Gold test or T-SPOT. The choice to perform a PPD, QuantiFERON-TB Gold test, or T-SPOT 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.

Patients who test positive for latent TB at screening may be rescreened following appropriate treatment (see Section 6.4).

[47] Have uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg.

(Note: Determined by 2 consecutive elevated readings. If an initial BP reading exceeds this limit, the BP may be repeated once after the patient has rested sitting for ≥10 minutes. If the repeat value is less than the criterion limits, the second value may be accepted.)

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

[49] Show evidence of hepatitis B and/or positive hepatitis B surface antigen or positive hepatitis B core antibody (HBcAb+).

[50] Show evidence of hepatitis C and/or positive hepatitis C antibody.

[51] 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:

[51a] Neutrophil count <1500 cells/µL.

[51b] Lymphocyte count <500 cells/µL.

[51c] Platelet count <100,000 cells/µL.

[51d] Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN).

[51e] Total white blood cell count <3000 cells/μL.

[51f] Hemoglobin <8.5 g/dL (85 g/L) for male patients and <8.0 g/dL (80 g/L) for female patients.

[51g] Serum creatinine >2.0 mg/dL.

(Note: The AST and ALT may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be used to assess eligibility. Other laboratory tests should not be repeated unless there is a technical error or clinical reason to believe a result may be erroneous.).

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Patients will be provided with standard meals while resident in the CRU. Patients should not consume food from 1 hour before until 1 hour after each administration of drug cocktail.

Patients must refrain from consuming grapefruit, Seville oranges, star fruit, pomelos, or products containing these fruits, within 14 days prior to first administration of the drug cocktail until the last drug cocktail PK sample is collected.

6.3.2. Caffeine, Alcohol, and Tobacco

No caffeine- or xanthine-containing food or beverages will be allowed within 5 days of each administration of the drug cocktail (Day 1 of Period 1, Day 8, and Day 85 of Period 2) and until collection of the 48 hour drug cocktail PK samples for each administration.

No alcohol will be allowed from at least 24 hours prior to each CRU visit or while resident in the CRU.

Patients will not be permitted to use tobacco products from 1 month prior to first admission to the CRU until collection of the last drug cocktail PK samples in Period 2.

6.3.3. Activity

Patients 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 or while resident in the CRU.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened unless they failed due to having latent TB and have received appropriate treatment, an active or recent infection within 4 weeks of the first admission to the CRU, or a body

temperature ≥38 °C (100.5 °F) at first admission to the CRU. These individuals may be rescreened once. Rescreenings should occur at least 4 weeks after documented resolution of symptoms. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of the PK of oral doses of midazolam, warfarin, dextromethorphan, omeprazole, and caffeine when administered alone to that when administered following single and multiple doses of ixekizumab.

The timing of administration of study treatments will be consistent with the Schedule of Activities (Section 2). Administration of drug cocktail and ixekizumab up to Day 85 (Week 12) will be conducted by qualified staff at the CRU.

Ixekizumab

Each injection of ixekizumab should be administered according to the instructions for use. The 160-mg dose of ixekizumab will be administered on Day 1 of Period 2 as two 1.0-mL SC injections; 80 mg of ixekizumab per injection.

The 80-mg dose of ixekizumab will be administered on Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), Day 71 (Week 10), and Day 85 (Week 12) in Period 2, as one 1.0-mL SC injection.

Possible injection sites include the abdomen, thigh, and upper arm. The injection site should not be in a psoriatic lesion and should be rotated to another area for the subsequent dose.

Drug cocktail

The drug cocktail will contain midazolam, warfarin (plus vitamin K), dextromethorphan, omeprazole, and caffeine. Each study site will source cocktail drugs, and will ensure that the same package lot is used for each cocktail drug in each of the 2 periods for an individual patient. Administration of each cocktail drug will be according to the respective instructions for use. The following doses of cocktail drugs will be coadministered orally with approximately 240 mL of room temperature water, in a sitting position.

If a patient experiences clinically significant changes in coagulation parameters after receiving the second dose of drug cocktail, the patient may be administered the third dose of drug cocktail without warfarin.

Midazolam

A 1-mg oral dose of commercially available midazolam syrup.

Warfarin

A 10-mg oral dose of commercially available warfarin, plus a 10-mg oral dose of commercially available vitamin K.

Dextromethorphan

A 30-mg oral dose of commercially available dextromethorphan.

Omeprazole

A 20-mg oral dose of commercially available omeprazole.

Caffeine

A 100-mg (caffeine base) oral dose administered as a commercially available caffeine citrate solution (for example, if each mL of commercially available caffeine citrate solution contains 10 mg caffeine base then the dose would be 10 mL of caffeine citrate solution).

All study treatments

The investigator or designee is responsible for:

- explaining the correct use of the investigational products to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product 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 trial materials.

7.1.1. Packaging and Labeling

Ixekizumab will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practices (cGMP), labeled according to the country's regulatory requirements, and supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

Ixekizumab will be supplied as injectable solution in 1-mL, single-dose, prefilled, disposable, manual syringes with study-specific labels. Each syringe of ixekizumab is designed to deliver ixekizumab 80 mg. Syringes will be supplied in cartons, with the appropriate quantity of syringes specific to the planned dispensing schedule of the investigational product.

Commercially available midazolam, warfarin, vitamin K, dextromethorphan, omeprazole, and caffeine will be used in the drug cocktail.

All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

7.2. Method of Treatment Assignment

This study is not subject to randomization.

7.2.1. Selection and Timing of Doses

The selected dosing regimen for ixekizumab is that recommended for the treatment of adults with moderate-to-severe plaque psoriasis.

Doses of cocktail drugs are clinically relevant and considered safe to administer. In Period 2, the drug cocktail will be administered on Day 8, to assess the effect of a single dose of ixekizumab, and Day 85 (Week 12), at which time steady-state concentrations of ixekizumab should be achieved.

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose reductions or adjustments will not be allowed during this study.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer study treatment while the patient is attending the CRU. All study treatments 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.

Ixekizumab is to be stored at 2°C to 8°C (36°F to 46°F) in its original carton to protect from light. Ixekizumab must not be frozen or shaken. Sites will be required to monitor temperature of the on-site storage conditions of the investigational product.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Investigational products will be administered at the clinical site and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Treatment with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine will not be allowed during the study.

Drugs that are known inhibitors of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2, inducers of CYP3A or CYP1A2, or rifampin (inducer of multiple CYPs) will not be allowed within 14 days prior to the first administration of the drug cocktail through the end of the Week 12 assessments.

Drugs that are known substrates of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2, with narrow therapeutic indices, will not be allowed within 14 days prior to the first administration of

the drug cocktail through the end of the Week 12 assessments, at the discretion of the investigator, and by agreement with the Lilly CRP or designee.

Drugs that are contraindicated with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine (per the prescribing label and Package Insert for each drug) will not be allowed within 14 days prior to the first administration of the drug cocktail through the end of the Week 12 assessments.

Patients should not receive systemic nonbiologic psoriasis therapy (including, but not limited to, oral PUVA light therapy; cyclosporine; corticosteroids; methotrexate; oral retinoids; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; azathioprine; fumaric acid derivatives; or 1, 25 dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, or self-treatment with tanning beds or therapeutic sunbathing) within 4 weeks prior to first admission to the CRU and during the study.

Patients should not receive topical prescription psoriasis treatment (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, and emollients) within the previous 14 days prior to first admission to the CRU or during the study. Class 6 (mild, such as desonide) or Class 7 (least potent, such as hydrocortisone) topical steroids will be permitted for use limited to the face, axilla, and/or genitalia.

The following drugs will not be allowed within 1 year of screening or during the study: hGH, interferons, rituximab, efalizumab, tocilizumab or other agents that target IL-6, interferons, basiliximab or other agents that target IL-2, muromonab or other agents that target CD3, canakinumab or other agents that target IL-1, or Cimzia (certolizumab pegol).

The following drugs will not be allowed without the following washout before screening: alefacept, any agents that target Tumor Necrosis Factor α (such as Remicade [infliximab], Humira [adalimumab], or Enbrel [etanercept]) (<60 days), ustekinumab or other agents that target IL-12 or IL-23, (<8 months), Simponi (golimumab) (<90 days); or any other biologic agent <5 half-lives prior to first admission to the CRU.

The investigator may approve administration of acetaminophen at doses not to exceed a total of 2 g in any 24-hour period, without consultation with Lilly. The investigator should consult with Lilly if a total dose >2 g in a 24-hour period is desired; however, the maximum total dose cannot exceed 3 g in any 24-hour period.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Any additional 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 to this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

- Alanine aminotransferase or AST >5× ULN.
- ALT or AST >3× ULN along with one of the following criteria:
  - sustained for more than 2 weeks or
  - total bilirubin level (TBL) >2× ULN or
  - prothrombin time >1.5× ULN or
  - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3× ULN.
- ALP>2.5× ULN and TBL >2× ULN.
- ALP>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

In addition, patients will be discontinued from the investigational product in the following circumstances:

- The patient becomes pregnant.
- Neutrophil (segmented) counts:
  - <500 cells/μL.
  - ≥500 and <1000 cells/μL (based on 2 test results; the second test performed within 1 week of knowledge of the initial result).
  - ≥1000 and <1500 cells/μL and the patient has a concurrent infection that requires systemic anti-infective therapy.
- Total white blood cell count <2000 cells/μL.
- Lymphocyte count <200 cells/μL.
- Platelet count <50,000 cells/μL.

Patients will be evaluated for discontinuation if a suicide-related thought or behavior is identified at any time during the study, or if during the study a patient gives:

- a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS; or
- a “yes” answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS; or

- a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

It is recommended that the patient also be assessed by a psychiatrist or appropriately trained professional to assist the investigator in deciding whether the patient should be discontinued from the study.

In addition, patients will also be evaluated for discontinuation if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior. It is recommended that a patient be assessed by a psychiatrist or appropriately trained professional to assist the investigator in deciding whether the patient should be discontinued from the study.

Patients who discontinue the investigational product early will have early discontinuation procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or investigator identifies a patient 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 patient 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 patient to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this 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 patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Patient Decision
    - the patient requests to be withdrawn from the study

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Patients Lost to Follow-up

A patient 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 patients 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.

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.

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

Efficacy will be evaluated using sPGA, PASI, and percentage of BSA assessments (see Section 9.6) according to the Schedule of Activities (Section 2).

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient 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 ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each patient'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, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product 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.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

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
- events considered significant by the investigator based upon appropriate medical judgment

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Study site personnel must alert Lilly, 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 begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, 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 patients once they have discontinued from and/or completed the study (the patient summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient 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 investigational product) 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. 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 identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. 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 investigational products used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of ixekizumab is any dose above that assigned. Doses of up to 180 mg have been administered SC in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg SC have been reported without any SAEs. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Refer to the Package Insert of each cocktail drug for information on treatment of overdose.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

For each patient, vital sign measurements (standing and supine BP and pulse rate, and body temperature) should be conducted according to the Schedule of Activities (Section 2).

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

Additional vital signs may be assessed as clinically indicated as well as at the scheduled times. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 3 minutes. If the patient feels unable to stand, supine vital signs only will be recorded.

Additional scheduled vital signs may be added during each study period if warranted and agreed upon between the sponsor and investigator.

9.4.3. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Patients 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 or qualified designee assigned by the investigator at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QT corrected for heart rate interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Quick Inventory of Depressive Symptomatology-Self Report (16-Items)

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation. Additional information and the QIDS-SR16 questions can be found at the University of Pittsburgh IDS/QIDS internet page (http://www.ids-qids.org).

9.4.5. Columbia-Suicide Severity Scale

Any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2) using the C-SSRS. The C-SSRS is 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. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C CASA) categorization of suicidal events.

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.

Terms captured by the use of the C-SSRS can be mapped to C CASA (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Baseline" 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. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. It is recommended that a patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient should be discontinued from study treatment (Section 8.1). A patient does not necessarily have to be discontinued if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior. Of course, if this situation arises, it is recommended that the patient be referred to a psychiatrist or appropriately trained professional.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, 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.

9.4.6. Safety Monitoring

The Lilly CP or CRP/clinical research 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 research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data

- laboratory analytes
- AEs

If a study patient experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and compliance with regulatory guidance, the investigator is to consult with the Lilly designated CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 4).

9.4.7. Inflammatory Bowel Diseases Assessments

Data on suspected inflammatory bowel disease, as identified by events possibly indicative of ulcerative colitis and Crohn's disease, will be collected and the events will be adjudicated by an external Clinical Events Committee (CEC) made up of gastroenterologists with expertise in inflammatory bowel disease. The role of the CEC is to adjudicate defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of a study. The importance of the CEC is to ensure that all events that have been reported are evaluated uniformly by a single group.

9.4.8. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against ixekizumab. Additional samples may be collected if there is a possibility that an AE is immunologically mediated.

Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies in the presence of ixekizumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ixekizumab. Immunogenicity samples may also be analyzed for ixekizumab serum concentration to facilitate in the interpretation of the immunogenicity data.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and 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.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), separate venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam, S-warfarin, dextromethorphan and its metabolite dextrorphan, omeprazole and its metabolite 5-hydroxyomeprazole, and caffeine and its metabolite paraxanthine. Samples of approximately 3 mL will be collected to determine the serum concentrations of ixekizumab. 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 designated by the sponsor. Plasma concentrations of each analyte in the drug cocktail will be assayed using a validated method. Serum concentrations of ixekizumab will be measured using a validated enzyme-linked immunosorbent assay method.

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

9.6. Pharmacodynamics

The PASI, sPGA, and percent BSA are considered pharmacodynamic measures of disease activity in this study.

The PASI is the most commonly used primary endpoint and measure of psoriasis severity in clinical trials (EMA 2004; Menter et al. 2008). The PASI combines assessments of the extent of BSA involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for severe disease (Fredriksson and Pettersson 1978).

The static Physician Global Assessment (sPGA) is the physician's global assessment of the patient's psoriasis (Ps) lesions evaluated at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

Percent BSA will be evaluated as the percent involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation 2009).

Data will be collected at the times shown in the Schedule of Activities (Section 2).

9.7. Genetics

A blood sample 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 response to ixekizumab and to investigate genetic variants thought to play a role in psoriasis. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs/institutional review boards 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

Whole blood samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for measurement of the inflammatory biomarkers, IL-1β, IL-6, IL-19, and Tumor Necrosis Factor α. C-reactive protein is collected as part of the clinical laboratory testing panel and may also be used as an exploratory biomarker. Samples may also be used for research on the drug target, disease process, variable response to ixekizumab, pathways associated with psoriasis, mechanism of action of ixekizumab, and/or research method, or for validating diagnostic tools or assay(s) related to psoriasis. All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

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

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 30 patients will be enrolled with the assumption that 21 complete the study.

Midazolam

For midazolam AUC and C_{max}, the intrasubject variability (CV) was estimated to be 16.1% and 26.4%, respectively (derived from a previous study). Based on this assumption, 21 patients will provide a precision of 0.1 and 0.17 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 9.8% and 15.3%, respectively. .

Warfarin

For S-warfarin AUC and C_{max}, the intrasubject variability (CV) was estimated to be 7% and 8%, respectively (Steinijans et al. 1995). Based on these estimates, 21 patients will provide a precision of 0.045 and 0.049 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 4.4% and 4.8%, respectively.

Dextromethorphan

For dextromethorphan AUC and C_{max}, the intrasubject variability (CV) was estimated to be 33.5% and 32.1%, respectively (derived from a previous study). Based on these estimates, 21 patients will provide a precision of 0.206 and 0.197 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 18.6% and 17.9%, respectively.

Omeprazole

For omeprazole AUC and C_{max}, the intrasubject variability (CV) was estimated to be 21.8% and 29.8%, respectively (Public Assessment Report 1 Omeprazole "Copyfarm" Omeprazole). Based on these assumptions, 21 patients will provide a precision of 0.135 and 0.184 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 12.6% and 16.8%, respectively.

Caffeine

For caffeine AUC and C_{max}, the intrasubject variability (CV) was estimated to be 21.0% (Blanchard and Sawers 1983) and 23.4% (Turpault et al. 2009), respectively. Based on these estimates, 21 patients will provide a precision of 0.13 and 0.148 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means is no larger than 12.2% and 13.8%, respectively.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The patient's age, sex, race, weight, height, BMI, and other demographic characteristics will be recorded. Baseline disease severity (PASI and sPGA score, and percentage of BSA), age of psoriasis onset, and previous psoriasis therapy type will also be recorded and reported.

Patient characteristics will be summarized. The summaries will include descriptive statistics (mean, standard deviation, sample size, minimum, maximum, lower and upper quartiles) for the continuous parameters, and frequencies and percentages for the remaining categorical parameters.

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 the full analysis set. For drug cocktail PK, the full analysis set includes all data from all patients receiving at least one dose of drug cocktail, with evaluable PK data, according to the treatment the patients actually received. For ixekizumab PK, the full analysis set includes all data from all patients receiving at least one dose of ixekizumab with evaluable PK data.

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements. Pharmacodynamic and biomarker analyses will be conducted for all patients receiving at least one dose of ixekizumab with at least one postbaseline measurement in Period 2.

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. Pharmacokinetic Analyses

10.3.1.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for midazolam and 1-hydroxymidazolam, S-warfarin, dextromethorphan and dextrorphan, omeprazole and 5-hydroxyomeprazole, and caffeine and paraxanthine will be calculated by standard noncompartmental methods of analysis.

For ixekizumab, sparse sampling is conducted to obtain concentrations over the time course of the study which will be summarized using descriptive statistics.

For midazolam and 1-hydroxymidazolam, S-warfarin, dextromethorphan and dextrorphan, omeprazole and 5-hydroxyomeprazole, and caffeine and paraxanthine, the primary parameters

for analysis will be C_{max} and area under the concentration versus time curve from zero to infinity (AUC[0-∞]). Other noncompartmental parameters such as time of maximum observed drug concentration (t_{max}), area under the concentration versus time curve from time zero to the last time point with a measurable concentration (AUC[0-t_{last}]), half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), apparent clearance, and apparent volume of distribution may be reported.

Exploratory analyses of the metabolite to parent ratios may be conducted.

10.3.1.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates of cocktail drugs will be evaluated to delineate the effects of drug interaction. Midazolam, warfarin, dextromethorphan, omeprazole, and caffeine administered in the absence of ixekizumab will represent the reference treatments and will be analyzed separately. Each drug administered with ixekizumab will represent the test treatments and will be analyzed separately. Data for each drug will also be analyzed separately after single or multiple doses of ixekizumab. For the primary analysis, log-transformed C_{max} and AUC(0-∞) estimates will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for patient. The treatment differences will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

The AUC(0-t_{last}) will be analyzed using the same method described above.

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

10.3.2. Immunogenicity Analyses

Immunogenicity data will be listed for individual patients and the frequency of antibody detection will be reported at each time point.

10.3.3. Exploratory Analyses

The same model used for the primary analysis will be applied to the subgroups of responders to ixekizumab and nonresponders at Week 12. The treatment differences for each subgroup will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

A responder to ixekizumab will be defined as a patient with a sPGA equal to 0 or 1 at Week 12. A nonresponder will be defined as a patient with sPGA >1 at Week 12.

Change from baseline in percentage of BSA, percent change from baseline in PASI scores, sPGA (0,1) response, and PASI 75 response will be calculated at each time point and summarized using descriptive statistics.

10.3.4. Safety Analyses

10.3.4.1. Clinical Evaluation of Safety

All investigational product 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 investigational product as perceived by the investigator. Symptoms reported to occur prior to study treatment 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 investigational product-related SAEs will be reported.

10.3.4.2. Statistical Evaluation of Safety

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

10.3.5. Interim Analyses

No interim analysis is planned for this study.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
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 the last time point with a measurable concentration
BCG	Bacillus Calmette-Guérin
BMI	body mass index
BP	blood pressure
BSA	body surface area
C CASA	Columbia Classification Algorithm of Suicide Assessment
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 trial-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
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interactions
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
hGH	human growth hormone
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
MI	myocardial infarction
Non-investigational product	A product that is not being tested or used as a reference in the clinical trial, but is provided to patients 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.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PASI	Psoriasis Area Severity Index
PPD	purified protein derivative
PK	pharmacokinetic
PUVA	psoralen and ultraviolet A
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 items)
SAE	serious adverse event
SC	subcutaneous(ly)
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 trial.
sPGA	Static Physicians Global Assessment
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
TB	tuberculosis
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Phosphorus
Mean cell hemoglobin concentration	Glucose random
Leukocytes (WBC)	Blood urea nitrogen (BUN)
Cell morphology	Uric acid
Absolute counts of:	Total cholesterol
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
Platelets	Alanine aminotransferase (ALT)
	Creatinine
Coagulation parameters[a]	Gamma-glutamyl transferase (GGT)
aPTT	High sensitivity C-reactive protein (hsCRP)
PT	
INR	Additional tests[a]
	Ethanol breath testing
Inflammatory biomarkers[a,b]	Urine drug screen
IL-1β	PPD/QuantiFERON-TB Gold/T-SPOT[d]
IL-6	Hepatitis B surface antigen[d]
IL-19	Hepatitis B core antibody (HBcAb+)[d]
Tumor necrosis factor α	Hepatitis C antibody[d]
	HIV[d]
Urinalysis[a]	Pregnancy test[e]
Specific gravity	FSH (females, as appropriate)[d]
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine creatinine	
Leukocyte esterase	
Microscopic analysis of sediment[c]	

Abbreviations: aPTT = activated partial thromboplastin time; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IL = interleukin; INR = international normalized ratio; PPD = purified protein derivative; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

[a] Results will be validated by local or central laboratory at the time of initial testing (screening tests, pregnancy tests and ethanol and drug screen performed locally, all other tests performed at central laboratory).
[b] Samples obtained at time points detailed in the Schedule of Activities (Section 2).
[c] Test only if dipstick result is abnormal.
[d] Performed at screening only.
[e] Serum pregnancy test to be performed at screening. Serum or urine pregnancy test may be performed at all other times, at the discretion of the investigator.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study.
- ensuring that informed consent is given by each patient 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 investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the 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 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:

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 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 eCRFs, 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 eCRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient 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.

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 patients 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, segmented	
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	
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood 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. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I1F-MC-RHBU Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	35	1	35
Clinical laboratory tests[a]	12	12	144
Pharmacokinetics:			
Midazolam	2	30	60
Warfarin	2	33	66
Dextromethorphan	2	30	60
Omeprazole	2	33	66
Caffeine	2	33	66
Ixekizumab	3	7	21
Ixekizumab immunogenicity	7.5	7	52.5
Inflammatory biomarkers	7	5	35
Blood discard for cannula patency	1	33	33
Pharmacogenetics	10	1	10
Total			648.5
Total for clinical purposes [rounded up to nearest 10 mL]			650

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

Appendix 6. Protocol Amendment I1F-MC-RHBU(a) Summary
Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Overview

Protocol I1F-MC-RHBU, Evaluation of the Effect of Ixekizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- In Section 1, text in the "Treatment Arms and Duration" section a typographic error was correct to remove a minus sign and to indicate dose of drug cocktail occurs on Day 1.
- In Section 1, confidence interval related text in the "Statistical Analysis" section was deleted based upon regulatory feedback.
- In Section 2, the Schedule of Activities for Period 2 was updated to remove the ± 2d text from the D8, D9, D10, D11, and D12 columns; this change makes the schedule of activities consistent with footnote g.
- In Section 6.1, inclusion criterion 1 was updated to indicate that the use of reliable methods of contraception for women of child-bearing potential participating in the study will extend until 3 months after the last dose of ixekizumab received in the study and a typographic error was corrected.
- In Section 9.6, text describing how lesions are categorized by the sPGA was updated to be consistent with other ixekizumab studies in patients with psoriasis.
- In Section 10.1, a typographical error was corrected and text related to the confidence intervals was updated based upon regulatory feedback.
- In Section 10.3.1.2, text related to the confidence intervals for C_{max} and AUC(0-∞) was deleted based upon regulatory feedback.
- In Section 10.3.3, text was deleted in order to be consistent with the SAP.

Revised Protocol Sections

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

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

1. Protocol Synopsis

Treatment Arms and Duration:

In Period 1, patients will receive a single oral dose of drug cocktail (with single oral doses of 1 mg midazolam, 10 mg warfarin [+ 10 mg vitamin K], 30 mg dextromethorphan, 20 mg omeprazole, and 100 mg caffeine) on Day ~~minus~~ 1 and PK sampling will be conducted up to 96 hours post-drug cocktail dose (Day 5).

Statistical Analysis:

~~For each drug administered with ixekizumab, if the CIs for both C_{max} and AUC(0-∞) of parent drug are contained within the 0.7 and 1.43 limits, a no drug-drug interaction will be declared for that drug and ixekizumab.~~

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, and C-SSRS scores. The parameters will be listed, and summarized using standard descriptive statistics.

2. Schedule of Activities

Study Schedule Protocol I1F-MC-RHBU – Period 2

	W 0	Check-in for W 1	W 1					W 2	W 4	W 6	W 8	W 10
	D 1[e]	D 7[g] ±2d	D 8[g] ~~±2d~~	D 9[g] ~~±2d~~	D 10[g] ~~±2d~~	D 11[g] ~~±2d~~	D 12[g] ~~±2d~~	D 15 ±2d	D 29 ±2d	D 43 ±2d	D 57 ±2d	D 71 ±2d
Procedure												
Patient Admission to CRU		X										
Patient Discharge from CRU				X[h]								
Outpatient Visit	X				X	X	X	X	X	X	X	X
Review of AEs	X											
Review Concomitant Medications	X											
Urine Drug Screen		X										
Ethanol breath test		X										
Vital Signs (Supine and Standing Blood Pressure and Pulse Rate and Body Temperature)	Predose[f]	X					X	Predose[f]	Predose[f]	Predose[f]	Predose[f]	Predose[f]
Clinical Laboratory Tests[a]	Predose[f]	X			X		X		Predose[f]			
Pregnancy Test[b]	Predose[f]											
Medical Assessment[c]							X					
12-Lead ECG	Predose[f]											
QIDS-SR16		X										
C-SSRS and Self-Harm Supplement	Predose[f]	X		X				Predose[f]	Predose[f]	Predose[f]	Predose[f]	Predose[f]
PASI	Predose[f]		X						X		X	
sPGA	Predose[f]		X						X		X	
% BSA Assessment	Predose[f]		X						X		X	
Inflammatory	Predose[f]		X						Predose[f]		Predose[f]	

	W 0	Check-in for W 1	W 1					W 2	W 4	W 6	W 8	W 10
	D 1[e]	D 7[g] ±2d	D 8[g] ~~±2d~~	D 9[g] ~~±2d~~	D 10[g] ~~±2d~~	D 11[g] ~~±2d~~	D 12[g] ~~±2d~~	D 15 ±2d	D 29 ±2d	D 43 ±2d	D 57 ±2d	D 71 ±2d
Procedure												
Biomarker Sample												
Ixekizumab Administration	160 mg							80 mg	80 mg	80 mg	80 mg	80 mg
Drug Cocktail Administration			X									
Ixekizumab PK Sample	Predose[f]		X					Predose[f]	Predose[f]		Predose[f]	
Midazolam and 1-hydroxymidazolam PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8,12 h	24 h								
Warfarin PK Sample[d]			Predose, 1, 2, 4, 6, 8, 10 h	24 h	48 h	72 h	96 h					
Dextromethorphan and Dextrorphan PK Sample[d]			Predose, 1, 2, 4,6, 8, 10 h	24 h	48 h	72 h						
Omeprazole and 5-hydroxyomeprazole PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h							
Caffeine and Paraxanthine PK Sample[d]			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12 h	24 h	48 h							
Ixekizumab Immunogenicity Sample	Predose[f]		X					Predose[f]	Predose[f]		Predose[f]	

Abbreviations: AE = adverse event; BSA = body surface area; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; ED = early discontinuation; PASI = Psoriasis Area Severity Index; PK = pharmacokinetics; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); sPGA = static Physicians Global Assessment; W = Week.

[a] All clinical laboratory test samples tested at a central laboratory. Additional samples for coagulation parameters (Appendix 2) may be collected and tested at a local laboratory at the discretion of the investigator.
[b] Females only. Serum or urine pregnancy test may be performed locally, at the discretion of the investigator.
[c] All medical assessments throughout the study should include a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.
[d] Sample times are relative to administration of the drug cocktail. The PK sample collection times are nominal; actual times should be recorded. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).
[e] Day 1 of Period 2 will be 3 to 7 days after Day 5 of Period 1.
[f] Time is relative to that day's ixekizumab dose.
[g] Drug cocktail administration and drug cocktail PK sampling days must run consecutively from admission to CRU (on Day 5 to Day 9).
[h] Patients may be discharged after collection of the 24 hour PK sample, at the discretion of the investigator.

6.1. Inclusion Criteria

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

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

Women of child-bearing potential may participate, and include those who test negative for pregnancy prior to initiation of treatment based on a serum pregnancy test and agree to use a reliable method of contraception during the study and until 3 months after the last dose of ixekizumab received in the study.

9.6. Pharmacodynamics

The static Physician Global Assessment (sPGA) is the physician's global assessment of the patient's psoriasis (Ps) lesions evaluated at a given time point (European Medicines Agency [EMA] 2004 [WWW]). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of ~~The sPGA is a physician's assessment of the patient's psoriasis lesions overall at a given time point. The sPGA is recommended as an endpoint for assessing efficacy in the treatment of psoriasis (EMA 2004). Overall lesions are graded for induration, erythema, and scaling; and the sum of the 3 scores is divided by 3 to obtain a final sPGA score (range 0 to 5). For the analysis of responder rates, the sPGA scores are rounded to the nearest whole number, and the patient's psoriasis is assessed as~~ clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

10.1. Sample Size Determination

Approxim~~a~~ately 30 patients will be enrolled with the assumption that 21 complete the study. ~~For each of the following drugs, a lack of drug to drug interaction will be declared if the 90% confidence interval (CI) for the ratio of the least squares means for both area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) of parent drug are contained within the limits 0.7 and 1.43.~~

Midazolam

For midazolam AUC and C_{max}, the intrasubject variability (CV) was estimated to be 16.1% and 26.4%, respectively (derived from a previous study). Based on this assumption, 21 patients will provide a precision of 0.1 and 0.17 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 9.8% and 15.3%, respectively. ~~98% chance of declaring lack of drug interaction assuming a ratio equal to 1.05.~~

Warfarin

For S-warfarin AUC and C_{max}, the intrasubject variability (CV) was estimated to be 7% and 8%, respectively (Steinijans et al. 1995). Based on these estimates, 21 patients will provide a precision of 0.045 and 0.049 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 4.4% and 4.8%, respectively.~~greater than 99% chance of declaring lack of drug interaction assuming a ratio equal to 1.05.~~

Dextromethorphan

For dextromethorphan AUC and C_{max}, the intrasubject variability (CV) was estimated to be 33.5% and 32.1%, respectively (derived from a previous study). Based on these estimates, 21 patients will provide a precision of 0.206 and 0.197 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 18.6% and 17.9%, respectively..~~90% chance of declaring lack of drug interaction assuming a ratio equal to 1.05.~~

Omeprazole

For omeprazole AUC and C_{max}, the intrasubject variability (CV) was estimated to be 21.8% and 29.8%, respectively (Public Assessment Report 1 Omeprazole "Copyfarm" Omeprazole). Based on these assumptions, 21 patients will provide a precision of 0.135 and 0.184 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means for AUC and C_{max} is no larger than 12.6% and 16.8%, respectively. ~~a 95% chance of declaring lack of interaction assuming a ratio equal to 1.05.~~

Caffeine

For caffeine AUC and C_{max}, the intrasubject variability (CV) was estimated to be 21.0% (Blanchard and Sawers 1983) and 23.4% (Turpault et al. 2009), respectively. Based on these estimates, 21 patients will provide a precision of 0.13 and 0.148 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric means is no larger than 12.2% and 13.8%, respectively. ~~greater than 99% chance of declaring lack of drug interaction assuming a ratio equal to 1.05~~.

10.3.1.2 Pharmacokinetic Statistical Inference

~~For each drug administered with ixekizumab, if the CIs for both C_{max} and AUC(0-∞) of parent drug are contained within the 0.7 and 1.43 limits, a no drug-drug interaction will be declared for that drug and ixekizumab~~.

10.3.3. Exploratory Analyses

~~A repeated-measure mixed model will be used to summarize the changes over time in exploratory biomarkers after ixekizumab dosing in Period 2. The model may include baseline,~~

~~time, responder status (yes/no), and time*responder status interaction as fixed effects. Patient will be included as a random effect.~~

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