Protocol I6T-MC-AMBP (a)

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

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Protocol I6T-MC-AMBP
Evaluation of the Effect of Mirikizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Mirikizumab (LY3074828)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 27 June 2018.
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

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1. Protocol Synopsis

Title of Study:
Evaluation of the Effect of Mirikizumab 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 may be observed. Chronic inflammation can, in theory, lead to disease-drug interactions by reducing the expression and activity of some cytochrome P450 (CYP) enzymes, thereby altering the systemic exposure of CYP substrates. Therefore, treatment of psoriasis with biological products that reduce inflammation could result in changes in CYP activity.

Mirikizumab is an anti-interleukin (IL)-23 monoclonal antibody being developed for the treatment of autoimmune diseases, including psoriasis, in which the IL-23 pathway is thought to have a pathogenic role. This study seeks to determine whether mirikizumab affects CYP activity in patients with psoriasis by using a "probe cocktail" approach, whereby the pharmacokinetics (PK) of CYP3A, CYP2C9, CYP2D6, CYP2C19, and CYP1A2 substrates midazolam, warfarin, dextromethorphan, omeprazole, and caffeine, respectively, will be evaluated before and after multiple mirikizumab doses are administered to patients with moderate-to-severe psoriasis.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To assess the effects of multiple doses of mirikizumab on the PK of a drug cocktail of CYP substrates in patients with moderate-to-severe psoriasis.	• Ratio of geometric least squares means for C_{max} and AUC(0-∞) of parent drug between each CYP substrate administered alone and in combination with mirikizumab.
Secondary	
• To evaluate the tolerability of mirikizumab in patients with moderate-to-severe psoriasis.	• Incidence of TEAEs.
• To determine the PK of metabolites where appropriate.	• Ratio of geometric least squares means for the MR of AUC(0-∞) metabolite:AUC(0-∞) parent, as appropriate, between CYP substrate administered alone and in combination with mirikizumab.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CYP = cytochrome P450; MR = metabolic ratio; PK = pharmacokinetics; TEAE = treatment-emergent adverse event.

Summary of Study Design:
Study I6T-MC-AMBP is a Phase 1, multicenter, 2-period, fixed-sequence, open-label study to assess the effects of multiple doses of mirikizumab on the PK of a drug cocktail of CYP substrates (midazolam, warfarin, dextromethorphan, omeprazole, and caffeine) in patients with moderate-to-severe psoriasis.

Blood sampling for assessment of PK of the CYP substrates (and metabolites, as appropriate), inflammatory biomarkers, and mirikizumab PK and immunogenicity will be collected at prespecified visits. Efficacy will be evaluated using static Physician's Global Assessment (sPGA), Psoriasis Area Severity Index (PASI), and percentage of body surface area (BSA) assessments at prespecified visits. 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.

Treatment Arms and Planned Duration for Individual Patients:
Each patient will be administered:

- 2 oral doses (1 dose in each period) of drug cocktail containing: 1 mg midazolam, 10 mg warfarin, 10 mg vitamin K, 30 mg dextromethorphan, 20 mg omeprazole, 100 mg caffeine
- 5 subcutaneous (SC) doses of 250 mg mirikizumab once every 4 weeks in period 2

Planned duration for each patient:

- Screening visit: within 28 days prior to enrollment
- Period 1: 6 days; single dose of drug cocktail
- Period 2: 120 days; SC doses of mirikizumab once every 4 weeks for 16 weeks beginning Day 1 of Period 2, single dose of drug cocktail will be given 3 days (within 48 to 96 hours) after the final mirikizumab dose
- Follow-up visit: approximately 24 days after final PK sample is collected in Period 2

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

Statistical Analysis:
Pharmacokinetics: The PK 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. Drug cocktail administered in the absence of mirikizumab will represent the reference treatments. Drug cocktail administered with mirikizumab will represent the test treatments. For the primary analysis, log-transformed area under the concentration versus time curve from zero to infinity (AUC[0-∞]) and maximum observed drug concentration (C_{max}) 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). The area under the concentration versus time curve from time zero to the last time point with a measurable concentration (AUC[0-t_{last}]) and metabolic ratios will also be analyzed using this method. The time of maximum observed drug concentration (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. Mirikizumab concentrations will be listed and summarized using descriptive statistics.

Safety: All AEs will be listed and, if the frequency of events allows, will be summarized using descriptive methodology. The incidence of symptoms for each treatment will be presented by severity and by association with study treatment as perceived by the investigator. Each symptom will be classified by the most suitable term from the medical regulatory dictionary. Any study treatment-related serious AEs will be reported. Clinical chemistry and hematology data, vital signs, C-SSRS scores, Lilly Self-Harm Supplement responses, and QIDS-SR16 scores will be listed and summarized using standard descriptive statistics. Urinalysis data will be listed. Electrocardiograms and

physical examinations will be performed for safety monitoring purposes and will not be presented. Additional analysis will be performed if warranted upon review of the data.

Immunogenicity: The frequency and percentage of patients with preexisting antidrug antibodies (ADAs) and with treatment-emergent ADA (TE ADA+) to mirikizumab will be listed and summarized. The frequency of neutralizing antibodies will also be tabulated for TE ADA+ patients. The relationship between the presence of antibodies and the PK parameters and other responses, including safety and efficacy to mirikizumab, may be assessed.

Efficacy Assessments: The PASI scores, sPGA responses, and percent BSA evaluation results will be listed and summarized. The proportion of patients who achieved sPGA (0, 1) and sPGA (0), and PASI 75, PASI 90, and PASI 100 (at least a 75%, 90%, and 100% improvement from baseline in PASI score, respectively) will be summarized over time using descriptive statistics. The change from baseline in percent BSA will also be summarized over time using descriptive statistics.

Inflammatory Biomarkers: Concentrations of IL-19 and change from baseline will be listed and quantifiable concentrations will be summarized by treatment.

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMBP – Period 1

	Screening	Baseline					
Procedure	**D -28 to -2**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**
Outpatient Visit	X					X	X
Patient Admission to CRU		X[a]					
Patient Discharge from CRU					X[b]		
Informed Consent	X						
Screening Assessments							
Medical History	X						
TB Test[c]	X						
Chest X-ray[d]	X						
QIDS-SR16	X						
Height	X						
Weight	X	X					
Safety Assessments							
Urine Drug Screen	X	X					
Ethanol Breath Test		X					
Vital Signs (Sitting Blood Pressure and Pulse Rate)	X	X					X
Clinical Laboratory Tests[e]	X	X			X		X
Pregnancy Test[f]	X	X					
Physical Examination/Medical Assessment[g]	X	X					X
12-Lead ECG	X						X
C-SSRS	X	X			X	X	X
Self-Harm Supplement Form	X	X			X	X	X
Self-Harm Follow-up Form[h]	X	X			X	X	X
PASI	X	X					
sPGA	X	X					
% BSA Assessment	X	X					
Review of AEs[i]		X					
Review Concomitant Medications		X					
Other Samples							
Pharmacogenetic Sample			Predose				
hsCRP	X	X					

	Screening	Baseline					
Procedure	**D -28 to -2**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**
Drug Administration							
Drug Cocktail Administration			X				
PK Samples[j,k] (hours)							
Midazolam and 1'-hydroxymidazolam			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24			
S-Warfarin			Predose, 1, 2, 4, 6, 8, 10	24	48	72	96
Dextromethorphan and Dextrorphan			Predose, 1, 2, 4, 6, 8, 10	24	48	72	
Omeprazole and 5-hydroxyomeprazole			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48		
Caffeine and Paraxanthine			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48		

Abbreviations: AE = adverse event; BSA = body surface area; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; hsCRP = high sensitivity C-reactive protein; 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.

a Patients will be admitted at least 24 hours prior to dose administration to allow sufficient time for caffeine washout prior to dosing.

b Patients may be discharged after collection of the 48-hour PK sample, at the discretion of the investigator.

c Approved TB test(s) include PPD, QuantiFERON®-TB Gold, and T-SPOT®, one of which should be used.

d 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). The x-ray may be taken after the initial screening visit but before Day -1.

e 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.

f Serum pregnancy test to be performed at screening for all females. Serum or urine pregnancy test will be performed locally at all other times for females of childbearing potential. Additional tests may be performed at the discretion of the investigator.

g One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All other 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.

h Required if triggered by the Self-Harm Supplement Form per instructions (see Section 9.2.1.2.1).

i If an AE of injection site reaction is reported, then the investigator will complete a supplemental injection site reaction form.

j Sample times are relative to administration of the drug cocktail. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).

k Specified times are approximate and actual times will be recorded. Actual sampling time should not exceed acceptable windows indicated in Table AMBP.1.

Table AMBP.1. Acceptable Sampling Windows for Periods 1 and 2

Nominal Sample Time	Acceptable Sampling Window
Before study treatment administration (predose)	Within 60 minutes before dosing
0.5 to 2 hours after study treatment dose	± 5 minutes
3 to 6 hours after study treatment dose	± 10 minutes
8 to 12 hours after study treatment dose	± 20 minutes
24 to 72 hours after study treatment dose	± 30 minutes
>72 hours after study treatment dose	± 2 hours

Study Schedule Protocol I6T-MC-AMBP – Period 2

Note: There will be 3 to 7 days between Period 1 Day 5 and Period 2 Day 1.

	Period 2											FU/ED
	Week 1	Week 4	Week 8	Week 12	Week 16					Week 17		Week 20
Procedure	**D 1**	**D 29**	**D 57**	**D 85**	**D 113**	**D 115**	**D 116**	**D 117**	**D 118**	**D 119**	**D 120**	**D 144**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±1 day**	**± 1 day**	**±1 day**	**±1 day[m]**	**±1 day[m]**	**±1 day[m]**	**±1 day[m]**	**±4 days**
Outpatient Visit	X	X	X	X	X					X	X	X
Patient Admission to CRU						X[a]						
Patient Discharge from CRU									X[b]			
Safety Assessments												
Review AEs[c]	X											
Review Concomitant Medications	X											
Pregnancy Test[d]	Predose	Predose	Predose	Predose	Predose	X						X
Medical Assessment[e]	Predose					Predose					X	X
12-Lead ECG	Predose											X
Clinical Laboratory Tests[f]	Predose	Predose		Predose		X			X		X	X
Vital Signs (Sitting Blood Pressure and Pulse Rate)	Predose	Predose	Predose	Predose	Predose	X	Predose				X	X
C-SSRS	Predose	Predose	Predose	Predose	Predose	X			X	X	X	X
Self-Harm Supplement Form	Predose	Predose	Predose	Predose	Predose	X			X	X	X	X
Self-Harm Follow-up Form[g]	Predose	Predose	Predose	Predose	Predose	X			X	X	X	X
QIDS-SR16	Predose		Predose		Predose							
Urine Drug Screen						X						
Ethanol Breath Test						X						
Efficacy Assessments												
PASI	Predose	X	X	X	X		Predose					
sPGA	Predose	X	X	X	X		Predose					
% BSA Assessment	Predose	X	X	X	X		Predose					

	Period 2											FU/ED
	Week 1	Week 4	Week 8	Week 12	Week 16					Week 17		Week 20
Procedure	**D 1**	**D 29**	**D 57**	**D 85**	**D 113**	**D 115**	**D 116**	**D 117**	**D 118**	**D 119**	**D 120**	**D 144**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±1 day**	**± 1 day**	**±1 day**	**±1 day[m]**	**±1 day[m]**	**±1 day[m]**	**±1 day[m]**	**±4 days**
Other Samples[h]												
Exploratory Inflammatory Biomarkers	Predose	Predose	Predose	Predose	Predose		Predose					
IL-19	Predose	Predose	Predose	Predose	Predose		Predose					
hsCRP	Predose	Predose	Predose	Predose	Predose						X	X
Mirikizumab Immunogenicity[i]	Predose	Predose	Predose	Predose								X
Drug Administration												
250 mg Mirikizumab SC	X	X	X	X	X							
Drug Cocktail							X [j]					
PK Samples (hours)												
Mirikizumab[h]	Predose	Predose	Predose	Predose	Predose		Predose					X
Midazolam and 1'-hydroxymidazolam[k,l]							Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24				
S-Warfarin[k,l]							Predose, 1, 2, 4, 6, 8, 10	24	48	72	96	
Dextromethorphan and Dextrorphan[k,l]							Predose, 1, 2, 4, 6, 8, 10	24	48	72		
Omeprazole and 5-hydroxyomeprazole[k,l]							Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48			
Caffeine and Paraxanthine[k,l]							Predose, 0.5, 1, 2, 3, 4, 6, 8, 12	24	48			

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; FU = Follow-up; hsCRP = high sensitivity C-reactive protein; IL = interleukin; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; QIDS-SR16 = Quick Inventory of Depressive Symptomatology-Self Report (16 items); SC = subcutaneous; sPGA = static Physicians Global Assessment.

[a] Patients will be admitted at least 24 hours prior to dose administration to allow sufficient time for caffeine washout prior to dosing.

[b] Patients may be discharged after collection of the 48-hour PK sample, at the discretion of the investigator.

[c] If an AE of injection site reaction is reported, then the investigator will complete a supplemental injection site reaction form.

[d] Serum or urine pregnancy test will be performed locally for females of childbearing potential. Additional tests may be performed at the discretion of the investigator.
[e] Medical assessment includes a symptom directed physical as well as examination of heart, lungs, abdomen, and visual examination of the skin.
[f] Clinical laboratory 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.
[g] Required if triggered by the Self-Harm Supplement Form per instructions (see Section 9.2.1.2.1).
[h] Sample times are relative to that day's mirikizumab dose.
[i] Any unscheduled immunogenicity samples should be collected with a time-matched sample for mirikizumab concentration analysis.
[j] Drug cocktail will be administered approximately 3 days (within 48 to 96 hours) after the final mirikizumab dose.
[k] Sample times are relative to administration of the drug cocktail. Separate blood samples will be collected for each of the cocktail drugs (caffeine, omeprazole, warfarin, dextromethorphan, and midazolam).
[l] Specified times are approximate and actual times will be recorded. Actual sampling time should not exceed acceptable windows indicated in Table AMBP.1.
[m] Study days are relative to the day of drug cocktail administration.

3. Introduction

3.1. Study Rationale

Psoriasis is a chronic inflammatory skin disease in which elevated levels of proinflammatory cytokines may be observed. Chronic inflammation can, in theory, lead to disease-drug interactions by reducing the expression and activity of some cytochrome P450 (CYP) enzymes, thereby altering the systemic exposure of CYP substrates (Wang et al. 2014). Therefore, treatment of psoriasis with biological products that reduce inflammation could result in changes in CYP activity.

Mirikizumab is an anti-interleukin (IL)-23 monoclonal antibody being developed for the treatment of autoimmune diseases, including psoriasis, in which the IL-23 pathway is thought to have a pathogenic role. This study seeks to determine whether mirikizumab affects CYP activity in patients with psoriasis by using a "probe cocktail" approach, whereby the pharmacokinetics (PK) of CYP3A, CYP2C9, CYP2D6, CYP2C19, and CYP1A2 substrates midazolam, warfarin, dextromethorphan, omeprazole, and caffeine, respectively, will be evaluated before and after multiple mirikizumab doses are administered to patients with moderate-to-severe psoriasis.

3.2. Background

Mirikizumab is a humanized IgG4-variant monoclonal antibody that binds with high affinity and specificity to IL-23, a naturally occurring proinflammatory cytokine critically involved in the maintenance and amplification of T helper (Th)17 cells. Th17 cells play a central role in the pathogenesis of multiple autoimmune and chronic inflammatory diseases, and neutralization of IL-23 using mirikizumab results in clinical improvement.

Results from Study I6T-MC-AMAE (Study AMAE), in which healthy subjects received 250-mg mirikizumab doses in prefilled syringes [PFS], showed that the maximum observed drug concentration (C_{max}) of mirikizumab was observed 3 days postdose and the half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$) was 11.6 days. Preliminary analyses of data in patients with ulcerative colitis (UC) and psoriasis indicate that the PK of mirikizumab in these patients is similar to healthy subjects, and there are no patient factors that have a clinically relevant impact on PK.

3.3. Benefit/Risk Assessment

As of 02 February 2018, there were approximately 819 participants in studies of mirikizumab (including 245 patients with psoriasis, 248 patients with UC, 85 patients with Crohn's disease, and 241 healthy subjects) exposed to either placebo or mirikizumab at single doses ranging from 5 to 1200 mg and multiple doses up to a maximum of 1000 mg intravenously (IV) once every 4 weeks for 12 weeks and up to 300 mg subcutaneous (SC) once every 8 weeks for 16 weeks. Although the mirikizumab SC dose regimen of 250 mg once every 4 weeks has not yet been administered in humans, the drug exposure in this study is expected to be less than that of 1000 mg IV once every 4 weeks for 12 weeks, which has been well tolerated.

In completed or ongoing clinical pharmacology studies, no dose-related safety or tolerability issues were observed. Injection site pain, of short duration (usually hours), has been reported. Data from completed Study AMAE and preliminary data from Study I6T-MC-AMAL (Study AMAL) showed that most injection site reactions were mild or moderate in severity and primarily related to mild erythema and pain, with severe injection site pain reported in 2% of injection site reactions in the 250-mg SC test formulation group. Approximately 6% of subjects reported diarrhea following administration of placebo and both the 250-mg test and 250-mg reference SC formulations of mirikizumab in Studies I6T-MC-AMAA, I6T-JE-AMAD, AMAL, and AMAE.

As of 02 February 2018, Phase 2 Study I6T-MC-AMAF (Study AMAF) examining SC mirikizumab doses in patients with moderate-to-severe plaque psoriasis was still ongoing. In the induction period (the first 16 weeks) of this study, patients were randomized to 1 of the 4 treatment arms (30 mg mirikizumab, 100 mg mirikizumab, 300mg mirikizumab, or placebo) and received correspondent doses at Week 0 and Week 8. At Week 16, patients entered the maintenance period (88 weeks) where they were dosed as needed (no higher than 300 mg and no more frequent than Q8W) based on the Psoriasis Area Severity Index (PASI) responses. To date, evaluation of the unblinded safety data from Study AMAF has not revealed any dose-related safety or tolerability issues. At the 32-week interim analysis, reported treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and the most common TEAE was viral upper respiratory tract infection. One death attributed to lung cancer has been reported during the maintenance period; however, the death was not considered related to study treatment. Three patients had a serious adverse event (SAE) in the placebo-controlled induction period: 2 patients had suicidal ideation and 1 patient had both increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST). One patient had an SAE (endocarditis bacterial) in the maintenance period. Two patients discontinued treatment early due to an adverse event (AE) (maternal exposure during pregnancy and suicidal ideation [an SAE]) in the placebo-controlled induction period; 4 patients discontinued treatment early due to an AE (maternal exposure during pregnancy, psoriatic arthropathy, rash, and bacterial endocarditis [an SAE]) in the maintenance period.

To assess the nonclinical toxicity of mirikizumab and establish a margin of safety for clinical studies, 4-week and 6-month general toxicity studies in healthy, normal cynomolgus monkeys were conducted for the evaluation of immunotoxicity, toxicokinetics, safety pharmacology (as part of the 4-week study), and fertility (as part of the 6-month study). The weekly administration of mirikizumab to cynomolgus monkeys resulted in no adverse mirikizumab-related findings at doses of 0 mg/kg (vehicle), 1 and 30 mg/kg (SC), or 100 mg/kg (IV) for 4 weeks, or 0, 10, and 100 mg/kg (SC) for 6 months. Based on the lack of any toxicity at exposures exceeding the highest clinical exposure and lack of any tissue cross-reactivity, the nonclinical safety profile of mirikizumab supports clinical development. The exposure to mirikizumab in monkeys at the no-observed-adverse-effect-level in the 4-week and 6-month studies provided 52- and 22-fold margin of safety, respectively, relative to the predicted human exposure of the proposed mirikizumab dose in the present study (250 mg administered SC every 4 weeks).

Given the published literature supporting positive clinical activity following blocking IL-23 in autoimmune/inflammatory diseases including psoriasis, the favorable safety and PK profile of mirikizumab, and the initial clinical activity observed for mirikizumab in patients with psoriasis, the potential benefits of participating in Study AMBP are expected to outweigh the potential risks.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of mirikizumab are to be found in the Investigator's Brochure (IB).

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 AMBP.2 shows the objectives and endpoints of the study.

Table AMBP.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effects of multiple doses of mirikizumab on the PK of a drug cocktail of CYP substrates in patients with moderate-to-severe psoriasis.	• Ratio of geometric least squares means for C_{max} and AUC(0-∞) of parent drug between each CYP substrate administered alone and in combination with mirikizumab.
Secondary	
• To evaluate the tolerability of mirikizumab in patients with moderate-to-severe psoriasis.	• Incidence of TEAEs.
• To determine the PK of metabolites where appropriate.	• Ratio of geometric least squares means for the MR of AUC(0-∞) metabolite:AUC(0-∞) parent, as appropriate, between CYP substrate administered alone and in combination with mirikizumab.
Exploratory	
• To explore the effects of mirikizumab on the PK of a drug cocktail of CYP substrates in the subgroups of patients with moderate-to-severe psoriasis who respond to mirikizumab treatment at Week 16 and those who do not respond.	• Ratio of geometric least squares means between each CYP substrate administered alone and in combination with mirikizumab for C_{max} and AUC(0-∞) of parent drug in responders and nonresponders.
• To evaluate the effects of mirikizumab treatment over time on inflammatory biomarker concentrations in patients with moderate-to-severe psoriasis.	• Change from baseline in inflammatory biomarker concentrations over time during 16 weeks of mirikizumab treatment.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CYP = cytochrome P450; MR = metabolic ratio; PK = pharmacokinetics; TEAE = treatment-emergent adverse event.

5. Study Design

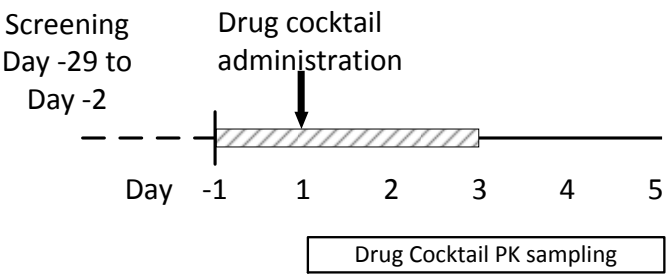
5.1. Overall Design

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

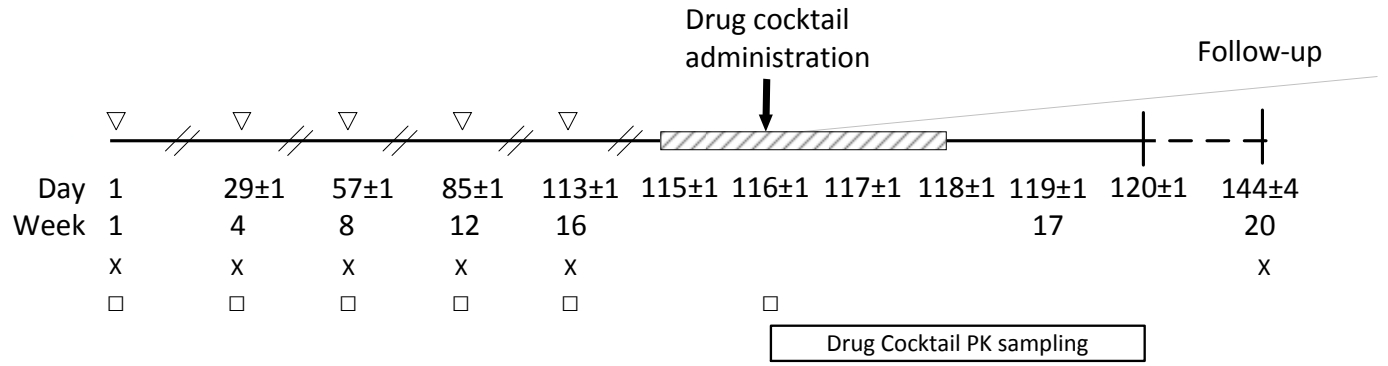
Blood sampling for assessment of PK of the CYP substrates (and metabolites, as appropriate), inflammatory biomarkers, and mirikizumab PK and immunogenicity will be collected at prespecified visits. Efficacy will be evaluated using static Physicians Global Assessment (sPGA), PASI, and percentage of body surface area (BSA) assessments at prespecified visits. 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), Lilly Self-Harm Supplement, and electrocardiograms (ECGs).

Study governance considerations are described in detail in Appendix 3.

Period 1



Period 2



Inpatient period

▽ 250 mg mirikizumab administration

X Mirikizumab immunogenicity and PK samples

□ PASI, sPGA, and % BSA assessment and Inflammatory biomarker samples

Abbreviations: BSA = body surface area; PASI = Psoriasis Area Severity Index; PK = pharmacokinetic; sPGA = static Physicians Global Assessment.
Note: In Period 2, drug cocktail will be administered 48 to 96 hours after the final mirikizumab dose.

Figure AMBP.1. Illustration of study design for Protocol I6T-MC-AMBP.

5.2. Number of Participants

Approximately 30 patients will be enrolled with the assumption that 21 evaluable patients complete the study. For purposes of this study, a patient completes the study when all scheduled blood samples for drug cocktail PK analyses shown in the Schedule of Activities (Section 2) have been collected in Period 2.

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, which is an appropriate approach for the primary PK objectives of the study. The fixed-sequence design is used due to the long half-life of mirikizumab.

This study will be conducted in patients with moderate-to-severe plaque psoriasis as this is one of the patient populations for whom mirikizumab treatment is indicated; conducting the study in this population allows the assessment of the effect of mirikizumab on CYP enzymes expressed in the disease state before and after treatment.

Regulatory agencies recommend conducting a clinical drug interaction study using a drug cocktail approach when interactions with multiple CYPs are investigated (EMA 2012; FDA 2017; PMDA 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 in Period 1, prior to initiation of mirikizumab dosing, and again on Day 116 (3 days post the last mirikizumab dose) of Period 2, when steady-state concentrations of mirikizumab should be achieved.

The total required blood volume of 590 mL is considered acceptable given that blood samples are taken during the course of the study which has a minimum duration of approximately 20 weeks.

5.5. Justification for Dose

Drug cocktail containing 1 mg midazolam, 10 mg warfarin (+ 10 mg vitamin K to counteract the anticoagulation effect of warfarin), 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 mirikizumab dose level and regimen selected for this study are consistent with that planned for the treatment induction period in the Phase 3 Study AMAK and are based primarily on analyses of interim PK, safety, and efficacy data from the Phase 2 Study AMAF, safety data from other clinical studies evaluating mirikizumab, and nonclinical safety data.

In Period 2, the drug cocktail will be administered on Day 116 (3 days post the last mirikizumab dose), which is approximately at C_{max} of mirikizumab concentration at steady state.

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, QIDS-SR16, C-SSRS, Lilly Self-Harm Supplement, 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:

Type of Patient and Disease Characteristics

[1] present with chronic plaque psoriasis based on the investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to screening, and meet the following criteria at screening and first admission to the clinical research unit (CRU):

A. plaque psoriasis involving ≥10% BSA,

B. absolute PASI score ≥12 in affected skin, and

C. sPGA score of ≥3

[2] candidate for systemic therapy and/or phototherapy

Patient Characteristics

[3] males or females

A. male patients: no male contraception required except in compliance with specific local government study requirement

B. female patients:
women not of childbearing potential may participate and include those who are:

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

OR

ii. postmenopausal, defined as:

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

1. cessation of menses for at least 1 year

OR

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

OR

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

OR

c. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

women of childbearing potential:

i. must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative pregnancy test within 24 hours prior to exposure in both periods

ii. must agree to either remain abstinent, if complete abstinence is their preferred and usual lifestyle, or remain in same-sex relationships, if part of their preferred and usual lifestyle, without sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

OR

must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue for 12 weeks following completion of investigational product administration.

a. Two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The patient may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

b. Of note, one of the 2 methods of contraception may be a highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices).

[4] are at least 18 years of age at the time of screening

[5] have adequate organ function, including:

A. hematologic:

i. absolute neutrophil count ≥1.5 × 10^9/L (≥1.5 × 10^3/μL or ≥1.5 GI/L)

ii. platelet count ≥100 × 10^9/L (≥100 × 10^3/μL or ≥100 GI/L)

iii. hemoglobin level ≥10.0 g/dL (≥100 g/L)

iv. lymphocyte count >500 cells/μL (>0.50 × 10^3/μL or >0.50 GI/L)

v. total white blood cell count ≥3.0 × 10^9/L (≥3.0 × 10^3/μL or ≥3.0 GI/L)

B. chemistry:

i. serum creatinine ≤2× the upper limit of normal (ULN)

ii. ALT ≤2× ULN

iii. AST ≤2× ULN

iv. total bilirubin level (TBL) <1.5× ULN (patients with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL or <25.7 μmol/L)

v. alkaline phosphatase (ALP) <1.5× ULN

(Note: The tests for AST and ALT may be repeated once within a week if the initial response exceeds this limit, and the repeat value may be accepted if it meets this criterion. Other laboratory tests should not be repeated unless there is a technical error or clinical reasons to believe a result may be erroneous, and requires approval by the Lilly-designated medical monitor.)

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

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

[8] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

Medical Conditions

[9] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[10] have an unstable or uncontrolled illness, including, but not limited to, a cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disease or abnormal laboratory values at screening that, in the opinion of the investigator, would potentially affect patient safety within the study or of interfering with the interpretation of data

[11] presence of significant uncontrolled neuropsychiatric disorder or judged at-risk of suicide in the opinion of the investigator

OR

scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16 at screening

OR

a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS at screening or at first admission to the CRU

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 and the ideation or behavior occurred within 1 month prior to screening or at first admission to the CRU

[12] have human immunodeficiency virus (HIV)/acquired immune deficiency syndrome or test positive for HIV antibodies at screening

[13] have hepatitis C or test positive for hepatitis C virus (HCV) at screening, defined as: positive result for hepatitis C antibody and positive confirmatory HCV RNA test. Patients in sustained virologic response after HCV therapy, and patients who have spontaneously cleared HCV infection can be included in this study.

[14] have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as:

A. positive for hepatitis B surface antigen

OR

B. positive for hepatitis B core antibody in conjunction with positive confirmatory HBV DNA test

OR

C. positive HBV DNA test, regardless of anti-hepatitis B surface antibody status

[15] have had serious, opportunistic, or chronic/recurring infection within 3 months prior to screening. Examples include, but are not limited to, infections requiring IV antibiotics, hospitalization, or prolonged treatment.

[16] have received a systemic (including oral) anti-infective agent for an infection within 28 days of first admission to the CRU

[17] have had, according to the investigator, clinically significant herpes zoster within 3 months prior to screening

[18] have evidence of active or latent tuberculosis (TB), as documented by medical history and physical examination, chest x-rays (posterior anterior), 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 Bacillus Calmette-Guerin [BCG] or other vaccination history) or a negative (not indeterminate) QuantiFERON-TB Gold test or T-SPOT. If the QuantiFERON-TB Gold test or T-SPOT is indeterminate, one repeat test is permitted. 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).

[19] have received a BCG vaccination within 12 months or received live vaccine(s) (including attenuated live vaccines) within 12 weeks of first admission to the CRU or intend to receive either during the study

[20] have active or history of lymphoma, leukemia, or any malignancy. The following conditions are not exclusionary: successfully treated basal cell skin carcinoma, squamous cell skin carcinoma, or cervical carcinoma in situ, with no evidence of recurrence or metastatic disease within the 5 years prior to first admission to the CRU.

[21] have any other skin conditions (excluding plaque psoriasis) that would affect interpretation of the results (including, but not limited to, scleroderma, eczema, drug-induced psoriasis, guttate psoriasis, pustular psoriasis, parapsoriasis, or cutaneous manifestations of other autoimmune diseases such as systemic lupus erythematosus)

[22] have a known allergy or hypersensitivity to any component of the mirikizumab product formulation or the drug cocktail that would pose an unacceptable risk to the patient if participating in this study

[23] are women who are breastfeeding or plan to breastfeed during study

[24] have donated blood of >500 mL within 14 days prior to first admission to the CRU, or intend to donate blood during the course of the study

[25] 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

[26] have a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new-onset ischemic heart disease or other serious cardiac disease, within 12 weeks prior to first admission to the CRU

[27] 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.)

[28] have any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator

[29] clinically significant increased prothrombin time at screening

Prior/Concomitant Therapy

[30] have received systemic nonbiologic psoriasis therapy (including, but not limited to, oral psoralen and ultraviolet A [PUVA] light therapy; cyclosporine; corticosteroids; methotrexate; oral retinoids; apremilast; tofacitinib; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; tacrolimus; azathioprine; lefludimide; fumaric acid derivatives; or 1,25-dihydroxy vitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self-treatment with tanning booths or therapeutic sunbathing) within 4 weeks prior to the first administration of the drug cocktail

[31] have received topical treatment for psoriasis or any other skin condition (including, but not limited to, corticosteroids [mild or least potent topical steroids will be permitted for use limited to the face, axilla, or genitalia], crisaborole, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, emollients and other nonprescription topical products containing urea, >3% salicylic acid, alpha- or beta-hydroxy acids, or medicated shampoos [eg, those that contain >3% salicylic acid,

corticosteroids, coal tar, or vitamin D3 analogues]) within 14 days prior to the first administration of the drug cocktail

[32] have received anti-Tumor Necrosis Factor targeting biologics within 8 weeks prior to baseline, or anti-IL-17 targeting biologics within 12 weeks prior to the first administration of the drug cocktail

[33] have previous exposure to any biologic therapy targeting IL-12/23 (p40 subunit) or IL-23 (p19 subunit), either marketed or investigational, or exposure to other biological immunomodulating treatments

[34] are unable or unwilling to 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

[35] 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 until Period 2 Day 120 assessments are complete

[36] 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 until Period 2 Day 120 assessments are complete, at the discretion of the investigator and by agreement with the Lilly clinical research physician (CRP), or clinical pharmacologist (CP), or designee

[37] 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 until Period 2 Day 120 assessments are complete

Prior/Concurrent Clinical Study Experience

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

[39] have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening.

[40] have previously completed or withdrawn from this study or any other study investigating mirikizumab

Study Restrictions

[41] are unwilling to comply with the dietary requirements/restrictions during the study which include:

A. Consume, during the inpatient visits, only the meals provided, and

B. 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 until Period 2 Day 120 assessments are complete

[42] 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

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

[44] intend to consume caffeine- or xanthine-containing food or beverages (eg, tea, coffee, colas, and chocolate) 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

[45] 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)

Other Exclusions

[46] have CYP2D6 genotype, if known, indicative of a poor metabolizer

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

[48] are Lilly employees or employees of third-party organization involved with the study who require exclusion of their employees

[49] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the patient's safety or confound data interpretation

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 (Day 1 of Period 1) until the last drug cocktail PK sample is collected in Period 2.

6.3.2. Caffeine, Alcohol, and Tobacco

Patients are not allowed to consume caffeine- or xanthine-containing food or beverages from 5 days prior to each drug cocktail administration (Period 1 Day 1 and Period 2 Day 116) until collection of the 48-hour drug cocktail PK samples in each period.

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 may be rescreened only 1 time for failure due to Exclusion Criteria [16] or [18]. Patients who do not qualify at screening under Exclusion Criteria [16] (recent systemic anti-infective treatment) may be rescreened (1 time) 4 or more weeks after documented resolution of underlying condition being treated. Patients who test positive for latent TB (Exclusion Criteria [18]) at screening may be rescreened (1 time) if they meet the following requirements:

- Have received at least 4 weeks of appropriate ongoing prophylactic therapy for latent TB as per local standard of care, and
- Have no evidence of treatment hepatotoxicity (ALT and AST levels must remain $\leq 2\times$ ULN upon retesting of serum ALT and AST levels prior to first dose)

Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Patients who have had previous screening chest radiography and TB tests as per protocol within 3 months of their rescreening date of consent do not need to repeat these procedures but may do so at the discretion of the investigator.

Repeat testing to confirm laboratory test results will not be considered rescreening.

7. Treatment

7.1. Treatment Administered

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

Drug cocktail and mirikizumab will be administered at the site by clinical staff at the time points specified in the Schedule of Activities (Section 2). Detailed instructions for study treatment administration will be provided by the Sponsor.

Mirikizumab

Mirikizumab will be administered by SC injection. Each 250-mg mirikizumab dose will be supplied as two 1-mL PFS.

Drug cocktail

The drug cocktail will contain midazolam, warfarin (plus vitamin K), dextromethorphan, omeprazole, and caffeine. The cocktail drugs will be coadministered orally with approximately 240 mL of room temperature water, in a sitting position. Administration of each cocktail drug will be according to the respective instructions for use.

Midazolam

The 1-mg oral dose will be administered as 0.5 mL of 2-mg/mL commercially available midazolam syrup.

Warfarin

The 10-mg oral doses will be administered as 2 × 5-mg tablets of commercially available warfarin plus 2 × 5-mg tablets of commercially available vitamin K.

Dextromethorphan

The 30-mg oral dose will be administered as 2 × 15-mg liquid gel capsules of commercially available dextromethorphan.

Omeprazole

The 20-mg oral dose will be administered as 1 × 20-mg tablet of commercially available omeprazole.

Caffeine

The 100-mg (caffeine base) oral dose will be administered as 10 mL of 20-mg/mL commercially available caffeine citrate solution (with 10 mg caffeine base per 1 mL 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 materials.

7.1.1. Packaging and Labeling

Mirikizumab will be supplied by the sponsor as single-use, solution PFS. The 1-mL syringe of mirikizumab is manufactured to contain 125 mg. Syringes will be supplied in cartons, with the appropriate quantity 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. 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.

The investigational product will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and returned or 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

All patients will receive the dose regimen as specified in the Schedule of Activities (Section 2).

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

Mirikizumab should be transported and stored in refrigerated conditions of 2°C to 8°C (36°F to 46°F). Detailed instructions regarding supplies and preparation and handling of investigational products will be provided by the sponsor.

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

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

The investigator, 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

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

7.7. Concomitant Therapy

All concomitant medications taken during the study must be recorded on the Concomitant Medication eCRF. All patients should maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically excluded in the protocol.

Patients taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study unless changes need to be made because of AEs. Additional systemic drugs are to be avoided during the study, unless required to treat AEs. If the need for concomitant medication arises for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered psoriasis therapies), inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Other medications may be allowed if they are approved by the sponsor or its designee.

Use of nonlive (killed, inactivated, or subunit) vaccinations are allowed for all patients; however, their efficacy with concomitant mirikizumab is unknown. Use of live, attenuated vaccines is prohibited.

Classes of therapies not permitted during the course of the study, or permitted with use restrictions, are specified in Table AMBP.3 (also see the Exclusion Criteria [Section 6.2]).

Table AMBP.3. Excluded Classes of Concomitant Medications or Classes with Restricted Use

Drug Class	Allowed Prior to First Dose	Allowed During Study	Allowed with Restrictions	Conditions for Allowed Use
Treatment with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine	N within 14 days	N until final PK assessments are complete	N	
Drugs contraindicated with midazolam, warfarin, dextromethorphan, omeprazole, or caffeine (per the prescribing label and Package Insert for each drug)	N within 14 days	N until final PK assessments are complete	N	
Known inhibitors of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2; inducers of CYP3A or CYP1A2; or rifampin (inducer of multiple CYPs)	N within 14 days	N until final PK assessments are complete	N	
Known substrates of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 with narrow therapeutic indices	N within 14 days	N until final PK assessments are complete	Y	At the discretion of the investigator and by agreement with the Lilly CRP or designee.
Topical treatment for psoriasis or any other skin condition *(eg, corticosteroids, crisaborole, anthralin, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy acids, or fruit acids)*	N within 14 days	N until final PK assessments are complete	N	
Topical treatment for psoriasis limited to face, axilla, or genitalia	N within 2 days	N within 24 hours prior to study visits	Y	Mild or least potent topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed.
Photochemotherapy *(eg, PUVA)*	N within 4 weeks	N	N	
Phototherapy *(eg, UVA, UVB, excimer laser)*	N within 4 weeks	N	N	
Anti-TNF biological agents *(eg, etanercept, adalimumab, infliximab, certolizumab)*	N within 8 weeks	N	N	

Drug Class	Allowed Prior to First Dose	Allowed During Study	Allowed with Restrictions	Conditions for Allowed Use
Anti-IL-17 biological agents (eg, *secukinumab, ixekizumab*)	N within 12 weeks	N	N	
Biological therapy targeting IL-12/23 or IL-23 *(eg, briakinumab, ustekinumab)*	N	N	N	
Biological immunomodulating agents *(eg, alefacept, efalizumab)*	N	N	N	
Other systemic immunomodulating treatments *(eg, MTX, cyclosporine A, corticosteroids, cyclophosphamide)*	N within 4 weeks	N	N	
Systemic immunomodulating treatments *(corticosteroids only)*	N	N	Y	Limited use of systemic corticosteroids ONLY as needed for limited, short-term medical management of TEAE may be considered. Such drug class might be considered psoriasis therapy if used under other regimens. Limited use during TEAE management is considered to not be consistent with psoriasis therapy.
Systemic psoriasis therapies *(eg, retinoids, fumarates, apremilast)*	N within 4 weeks	N	N	
BCG or live virus vaccinations	N	N	N	
Any investigational treatment	N	N	N	

Abbreviations: BCG = Bacillus Calmette-Guerin; CRP = clinical research physician; CYP = cytochrome P450; MTX = methotrexate; N = No; PK = pharmacokinetics; PUVA = psoralen and ultraviolet A; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; UVA = ultraviolet A; UVB = ultraviolet B; Y = Yes.

7.8. Treatment after the End of the Study

This section is not applicable to this study.

8. Discontinuation Criteria

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

Patients discontinuing from the study prematurely for any reason must complete AE and other follow-up procedures per Section 2 of this protocol.

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 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST >5× ULN.
- ALT or AST >3×ULN sustained for more than 2 weeks.
- ALT or AST >3× ULN and TBL >2× ULN or international normalized ratio >1.5.
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- 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:

- Total white blood cell count <2000 cells/µL (<2.00 × 103/µL or <2.00 GI/L).
- Lymphocyte count <500 cells/µL (<0.50 × 103/µL or <0.50 GI/L).
- Platelet count <50,000 cells/µL (<50 × 103/µL or <50 GI/L).
- Changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) that do not respond following maximal allowed intervention (further explanation in Section 9.4.2.1).
- The patient becomes pregnant.
- It is recommended that the patient be assessed by an appropriately trained professional to assist in deciding whether the patient is to be discontinued from study treatment and the study if the patient:

  i. Scores a 3 for Item 12 (Thoughts of Death or Suicide) on the QIDS-SR16;

  OR

ii. Develops active suicidal ideation with some intent to act with or without a specific plan ("yes" to Question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS);

OR

iii. Develops suicide-related behaviors as recorded on the C-SSRS;

OR

iv. Develops self-injurious behaviors that would be classified as non-suicidal self-injurious behavior.

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 study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- Investigator Decision
    - the investigator decides that the 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.

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 (including tolerance limits for timing).

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

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

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

9.1. Efficacy Assessments

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

The PASI is an accepted and commonly used primary endpoint to measure psoriasis severity in clinical studies (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 (scaling), erythema (redness), and plaque induration/infiltration (thickness) in each anatomical region, yielding an overall score of 0 for no psoriasis to 72 for severe disease (Fredriksson and Pettersson 1978). A clinically meaningful response is a PASI 75, which represents at least a 75% decrease (improvement) from the baseline PASI score. Higher levels of clearance (PASI 90), as well as complete resolution of psoriasis (PASI 100), have become additional endpoints because of the increasing recognition of the association of higher clearance with greater health-related quality of life (Puig 2015).

The sPGA is the physician's global assessment of the patient's psoriasis lesions evaluated at a given time point (EMA 2004). 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).

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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the 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 potential cause and effect relationship between the study treatment (ie, drug cocktail, mirikizumab, or drug cocktail + mirikizumab), study device, and/or study procedure and the AE.

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

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.

If an AE of injection site reaction is reported, then the investigator will complete a supplemental injection site reaction form. The injection site reaction form documents the presence of erythema, induration, pain (mild, moderate, or severe), pruritus, and edema.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

- when a condition related to the PFS necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

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

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

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the 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 reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Adverse Event Monitoring with Systematic Questionnaires

Before administering the C-SSRS or QIDS-SR16, study site personnel will question the patient about any change in the preexisting condition(s) and the occurrence and nature of any AEs. Nonserious AEs obtained through the questionnaires are recorded and analyzed separately. Only *serious* AEs elicited through the C-SSRS or QIDS-SR16 are to be recorded as AEs via eCRF and reported to Lilly or its designee within 24 hours as SAEs.

9.2.1.2.1. Columbia-Suicide Severity Scale

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.

Suicide-related events (behavior and/or ideations) will be assessed and evaluated with the administration of the C-SSRS, Self-Harm Supplement Form, and Self-Harm Follow-up Form. The C-SSRS 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 Self-Harm Forms focus on behaviors (suicidal and non-suicidal self-harm). If the number of behavioral events identified on the Self-Harm Supplement Form is greater than zero, it will lead to the completion of the Self-Harm Follow-up Form. The Self-Harm Follow-up Form is a series of questions that provides a more detailed description of the behavior cases. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

9.2.1.2.2. 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, 5th Edition (APA 2013). 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.

9.2.2. Complaint Handling

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

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 or PFS so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of mirikizumab or the cocktail drugs is considered any dose higher than the assigned dose.

In case of suspected mirikizumab overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary. There is no known antidote for mirikizumab.

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, sitting vital signs (BP and pulse rate) should be measured after resting for at least 5 minutes at times indicated in the Schedule of Activities (Section 2), and prior to blood sampling or administration of study treatment.

Additional vital signs may be measured during each study period if warranted. 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 then stand for at least 2 minutes.

9.4.2.1. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) on 2 consecutive visits are to receive intervention for the management of hypertension. Intervention may begin with lifestyle changes and could lead to the maximal intervention of withholding the dose of investigational product (see Section 8.1) and/or the introduction of antihypertensive agent(s) as medically appropriate.

9.4.3. Electrocardiograms

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 samples. 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 (the investigator or qualified designee) 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/QTc 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 clinically relevant findings should be reported as an AE.

9.4.4. Immunogenicity Assessments

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

Treatment-emergent antidrug antibodies (TE ADAs) are defined in Section 10.3.3. If the immunogenicity titer at the last scheduled assessment or discontinuation visit is increasing (compared to previous measurements) or remains high (titer greater than 1:1000), additional samples may be taken until the titer reaches a plateau/decreases (if increasing) or remains the same/decreases (if high).

Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies (ADAs) in the presence of the mirikizumab at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the mirikizumab.

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

9.4.5. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs

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

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or

worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), separate venous blood samples will be collected to determine 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 will also be collected to determine serum concentrations of mirikizumab. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Plasma concentrations of each analyte in the drug cocktail will be assayed using a validated method. Serum concentrations of mirikizumab will be measured using a validated enzyme-linked immunosorbent assay method.

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

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to mirikizumab 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 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 mirikizumab or after mirikizumab is commercially available.

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 to measure IL-19. Samples are collected for C-reactive protein 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 mirikizumab, pathways associated with psoriasis, mechanism of action of mirikizumab, 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. 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 mirikizumab or after mirikizumab is commercially available.

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 evaluable patients complete the study.

Midazolam

For midazolam area under the concentration versus time curve (AUC) and C_{max}, the intrasubject variability (coefficient of variation [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% confidence interval (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 (HMA 2009). 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, body mass index, and other demographic characteristics will be recorded. Baseline disease severity (PASI, 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 and listed. 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 mirikizumab PK, the full analysis set includes all data from all patients receiving at least one dose of mirikizumab with evaluable PK data. For patients with serum mirikizumab concentrations that are less than the drug exposure range expected after multiple doses, the drug cocktail PK results for Period 2 may be excluded from the analysis and the rationale will be provided in the study report.

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

Biomarker analyses will be conducted for all patients receiving at least one dose of mirikizumab 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 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}, AUC from zero to infinity (AUC[0-∞]), and metabolic ratio (MR). Metabolic ratios will be calculated as AUC(0-∞) metabolite/AUC(0-∞) parent corrected for molecular weight. Other noncompartmental parameters such as time of maximum observed drug concentration (t_{max}), AUC from time zero to the last time point with a measurable concentration (AUC[0-t_{last}]), $t_{1/2}$, apparent clearance, and apparent volume of distribution will be reported.

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

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 mirikizumab will represent the reference treatments and will be analyzed separately. Each drug administered with mirikizumab will represent the test treatments and will be analyzed separately. 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 derive ratios of geometric least squares means and the corresponding 90% CIs. The MR and AUC(0-t_{last}) will also be analyzed using this method.

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.

10.3.1.3. Pharmacokinetic Exploratory Analyses

The same model used for the primary PK analysis will be applied to the subgroups of responders to mirikizumab and nonresponders. A responder to mirikizumab will be defined as a patient with an sPGA equal to 0 or 1 at Day 116 in Period 2. A nonresponder will be defined as a patient with sPGA >1 at Day 116 in Period 2. The treatment differences for each subgroup will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

10.3.2. Safety Analyses

10.3.2.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with study treatment 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 study treatment-related SAEs will be reported.

10.3.2.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical laboratory parameters, vital signs, C-SSRS scores, Lilly Self-Harm Supplement responses, and QIDS-SR16 scores. Clinical chemistry and hematology data, vital signs, C-SSRS scores, Lilly Self-Harm Supplement responses, and QIDS-SR16 scores will be listed and summarized using standard descriptive statistics. Urinalysis data will be listed. Electrocardiograms and physical examinations will be performed for safety monitoring purposes and will not be presented. Additional analysis will be performed if warranted upon review of the data.

10.3.3. Immunogenicity Analyses

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency and percentage of patients with preexisting ADAs and with TE ADA+ to mirikizumab will be listed and summarized. The frequency of neutralizing antibodies will also be tabulated for TE ADA+ patients.

The relationship between the presence of antibodies and the PK parameters and other responses, including safety and efficacy to mirikizumab, may be assessed.

10.3.4. Exploratory Analyses

10.3.4.1. Efficacy Assessments

The PASI scores, sPGA responses, and percent BSA evaluation results will be listed and summarized. The proportion of patients who achieved sPGA (0, 1) and sPGA (0), and PASI 75, PASI 90, and PASI 100 (at least a 75%, 90%, and 100% improvement from baseline in PASI score, respectively) will be summarized over time using descriptive statistics. The change from baseline in percent BSA will also be summarized over time using descriptive statistics.

10.3.4.2. Biomarker Analyses

Concentrations of IL-19 and changes from baseline will be listed and summarized by treatment.

10.3.5. Interim Analyses

An interim analysis may be performed after all enrolled subjects have completed the outpatient visit and PK sample collection on Day 120 in Period 2. The purpose of this interim analysis is to provide PK results to support a regulatory submission. No changes to the study design are planned.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
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-Guerin
BP	blood pressure
BSA	body surface area
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist

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
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
IL	interleukin
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.

IV	intravenous
MR	metabolic ratio
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
PFS	prefilled syringe
PK	pharmacokinetic(s)
PPD	purified protein derivative
PUVA	psoralen and ultraviolet A
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report (16 items)
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
sPGA	static Physicians Global Assessment
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
TB	tuberculosis
TBL	total bilirubin level
TE ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
Th	T helper
t_{max}	time of maximum observed drug concentration
UC	ulcerative colitis
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets
- Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Urine leukocyte esterase
- Microscopic examination of sediment[d]

Coagulation parameters[a]
- PT (INR)

Clinical chemistry[a]
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Phosphorus
- Glucose random
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Creatinine
- Gamma-glutamyl transferase (GGT)

Additional tests[a]
- Ethanol testing[b]
- Urine drug screen[b]
- PPD/QuantiFERON-TB Gold/T-SPOT[c]
- Hepatitis C antibody[c]
- Hepatitis B core antibody (HBcAb+)[c]
- Hepatitis B surface antigen[c]
- Hepatitis B virus DNA
- HIV[c]
- Pregnancy test (females, as appropriate)[e]
- FSH (females, as appropriate)[c]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PPD = purified protein derivative; PT = prothrombin time; RBC = red blood cells; TB = tuberculosis; 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] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 2).

[c] Performed at screening only.

[d] Test only if dipstick result is abnormal.

[e] Serum pregnancy test to be performed at screening for all females. Serum or urine pregnancy test will be performed locally at all other times for females of childbearing potential. Additional tests may be performed 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 nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the 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 study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for 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 good clinical practice (GCP).

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

- the current mirikizumab Investigator's Brochure, drug cocktail package inserts, and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

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

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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 electronic case report forms (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.

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I6T-MC-AMBP Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	36	1	36
Clinical laboratory tests[a]	16	10	160
Pharmacokinetics :			
Midazolam and 1'-hydroxymidazolam	2	20	40
S-warfarin	2	22	44
Dextromethorphan and dextrorphan	2	20	40
Omeprazole and 5-hydroxyomeprazole	2	22	44
Caffeine and paraxanthine	2	22	44
Mirikizumab	2	7	14
Blood discard for cannula patency	1	22	22
Immunogenicity	10	5	60
High sensitivity C-reactive protein	2.5	9	22.5
Interleukin-19	2.5	6	15
Exploratory inflammatory biomarkers	5	6	30
Pharmacogenetics	10	1	10
Total			581.5
Total for clinical purposes rounded up to nearest 10 mL			590

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

Appendix 6. Protocol Amendment I6T-MC-AMBP(a) Summary Evaluation of the Effect of Mirikizumab on the Pharmacokinetics of Cytochrome P450 Substrates in Patients with Moderate-to-Severe Plaque Psoriasis

Overview

Protocol I6T-MC-AMBP Evaluation of the Effect of Mirikizumab 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 7.1, a dosing volume error for midazolam has been corrected. The administered midazolam volume has been updated to 0.5 mL to achieve a 1-mg midazolam dose from 2 mg/mL midazolam syrup.
- In the Study Schedule for Period 2 (Section 2), an error in the footnote letter designations within the table has been corrected. The footnote for mirikizumab PK samples has been updated from “g” to “h”.

Revised Protocol Sections

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

2. Schedule of Activities

Study Schedule Protocol I6T-MC-AMBP – Period 2

PK Samples (hours)												
Mirikizumab~~n~~	Predose	Predose	Predose	Predose	Predose		Predose					X

7.1. Treatment Administered

The 1-mg oral dose will be administered as ~~0.1~~ 0.5 mL of 2-mg/mL commercially available midazolam syrup.

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