Protocol I6T-MC-AMAK (a)

A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Withdrawal Maintenance Dosing Period to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis OASIS-1

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OASIS-1

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Confidential Information

Mirikizumab (LY3074828)

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Protocol Electronically Signed and Approved by Lilly: 25 January 2018.
Amendment (a) Electronically Signed and Approved by Lilly
on approval date provided below.

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1. Synopsis

Title of Study:
A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Withdrawal Maintenance Dosing Period to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis.

Rationale:
Mirikizumab (LY3074828) is a monoclonal, anti-interleukin-23 (anti-IL-23) antibody being developed for the treatment of immune-mediated diseases where the IL-23 pathway is thought to have a significant pathogenic role. The neutralizing activity of mirikizumab is directed against the p19 subunit of the IL-23 molecule and does not bind to IL-12. Study I6T-MC-AMAK (AMAK) is a confirmatory study testing mirikizumab as a treatment for plaque psoriasis and is intended to support registration of this indication. This Phase 3 study is designed to evaluate the superiority of mirikizumab versus placebo, as measured by improvement in disease severity and key patient-reported outcomes, and will contribute to the evaluation of the safety of mirikizumab.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary[a,b] To assess whether mirikizumab induction dosing is superior to placebo in the treatment of patients with respect to high levels of clinical response	At Week 16: • Proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline • Proportion of patients achieving a ≥90% improvement in PASI from baseline (PASI 90)
Major Secondary[a,b] To assess whether mirikizumab induction dosing is superior to placebo with respect to an early, clinically meaningful response	At Week 4: • Proportion of patients achieving a 75% improvement in PASI (PASI 75)
To assess whether the mirikizumab induction dosing is superior to placebo with respect to clinically meaningful response and the highest levels of clinical response	At Week 16: • Proportion of patients achieving PASI 75 • Proportion of patients achieving a 100% improvement in PASI (PASI 100)
To assess whether mirikizumab induction dosing is superior to placebo with respect to body surface area (BSA) affected by psoriasis	At Week 16: • Proportion of patients with ≤1% of BSA with psoriasis involvement

Objectives	Endpoints
To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline. • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5
To assess whether 250 mg mirikizumab Q8W and 125 mg mirikizumab Q8W maintenance dosing is superior to placebo with respect to maintenance of a high level of clinical response	At Week 52: • Proportion of patients maintaining clinical response (PASI 90) after re-randomization at the start of the randomized withdrawal period
Other Secondary[b] To compare mirikizumab to placebo with respect to clinical response and time to clinical response during the induction dosing period, and with respect to patient-reported outcomes during the induction dosing period	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90. • Change in PPASI total score in patients with palmoplantar involvement at baseline • Change in PSSI total score in patients with scalp involvement at baseline • Change in NAPSI total score in patients with fingernail involvement at baseline • Change from baseline on the SF-36 physical component summary (PCS) and mental component summary (MCS) • Change from baseline on PatGA of disease severity • Change from baseline for the WPAI-PSO scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) • Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1

Objectives	Endpoints
To assess whether 250 mg mirikizumab Q8W and 125 mg mirikizumab Q8W dosing is superior to placebo with respect to maintenance of high and highest levels of clinical response among patients who have an PASI 90 at Week 16 and are re-randomized	At Week 52 and at various time points during the Maintenance Dosing Period: • Time to relapse (the loss, at any visit, of ≥50% of the Week 16 PASI improvement from baseline). • Proportion of patients who have relapsed. • Proportion of patients maintaining clinical response (PASI 90) after re-randomization at the start of the randomized withdrawal period • Incidence of disease rebound within 12 weeks (worsening of psoriasis severity over baseline sPGA score, or worsening of psoriasis severity over baseline PASI score by 125%, or change in psoriasis phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 16.
To assess the efficacy of 250 mg mirikizumab Q8W following relapse after re-randomization to placebo treatment in the Maintenance Dosing Period	During the Maintenance Dosing Period: • Proportion of patients who regained PASI 90 within 16 weeks after mirikizumab retreatment.
To evaluate the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy (sPGA and PASI)

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = Patient's Global Assessment of Psoriasis; PCS = physical component summary; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; WPAI-PSO = Work Productivity Activity Impairment Questionnaire–psoriasis.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control technique called "graphical multiple testing procedure" to control the overall family-wise Type I error rate.

[b] Note: A "clinically meaningful" response is a PASI 75 response, which represents at least a 75% decrease (improvement) from the baseline PASI score. A "high level" of clinical response is a PASI 90 response, which represents at least a 90% decrease (improvement) from baseline in PASI score, or sPGA (0,1) response, which represents an "almost clear" response. The "highest level" of clinical response is a PASI 100 or sPGA (0) response, which represents complete resolution of psoriasis.

Summary of Study Design:

Study AMAK is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-period study. The study design includes 2 treatment periods (Induction and Maintenance with Randomized Withdrawal), which together last for up to 52 weeks, followed by a 12-week Post-Treatment Follow-Up period. The study population consists of patients aged 18 years or older at the time of screening who have chronic plaque psoriasis based on a

confirmed diagnosis of chronic plaque psoriasis for at least 6 months, are candidates for systemic and/or phototherapy, and have ≥10% body surface area (BSA) involvement, a static Physician's Global Assessment (sPGA) score of ≥3, and a Psoriasis Area and Severity Index (PASI) score ≥12 at screening and at baseline.

Treatment Arms and Duration:

Patients will be randomized 4:1 to receive double-blind ("blinded") subcutaneous (SC) administration of 250 mg mirikizumab or matching placebo at Weeks 0, 4, 8, and 12. Randomization will be stratified based on previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other). Patients who were responders (≥PASI 90) in the Induction Period and who continue in the blinded Maintenance Period will be monitored for maintenance of response or remission, as well as relapse and disease rebound following treatment withdrawal, and response to retreatment following relapse. Responders to mirikizumab treatment in the blinded Induction Period will be re-randomized 1:1:1 to 250 mg mirikizumab every 8 weeks (Q8W), 125 mg mirikizumab Q8W, or placebo Q8W, with treatments beginning at Week 16. Stratification in the Maintenance Period will be by body weight at baseline (<100 kg or ≥100 kg). The duration of treatment is 52 weeks. The total duration of participation in this study may be up to 68 weeks as detailed below.

Screening Period: Up to 4 weeks.

Treatment Period: Approximately 52 weeks.

Post-Treatment Follow-up Period: Approximately 12 weeks after the last visit for patients who discontinue treatment prior to the Week 52 assessment, or who are unable or not willing to participate in the long-term extension study (I6T-MC-AMAH [AMAH]).

Approximate Number of Planned Patients:

Screened: 650

Randomized: 500

Completed: 400

Statistical Analysis:

Approximately 500 patients will be randomized at a 4:1 ratio in the blinded Induction Period to receive 250 mg mirikizumab or placebo SC at Weeks 0, 4, 8, and 12. Stratified block randomization will be performed with the following stratification factors: previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other). Assuming that PASI 90 responses at Week 16 are 70% for the mirikizumab arm and 3% for the placebo arm, the planned samples size (mirikizumab, 400 patients; placebo, 100 patients) has a power of >95% for a test of superiority of mirikizumab compared to placebo with respect to PASI 90 at Week 16. Similarly, assuming the sPGA (0,1) responses at Week 16 are 70% for the mirikizumab arm and 5% for the placebo arm, the planned samples size has a

power of >95% for a test of superiority of mirikizumab compared to placebo with respect to the sPGA (0,1) endpoint. Eli Lilly and Company (Lilly) predicts that 70% of the mirikizumab-treated patients will be re-randomized in the Maintenance Period at Week 16 (Visit 7) at a 1:1:1 ratio to 250 mg mirikizumab Q8W, 125 mg mirikizumab Q8W, or placebo using body weight at baseline (<100 kg or ≥100 kg) as a stratification factor. Thus, approximately 93 patients will be included in each Maintenance Period treatment group. The estimated sample size will provide a power of >95% to test superiority of 250 mg mirikizumab Q8W against placebo, and also power of >95% to test superiority of 125 mg mirikizumab Q8W against placebo with respect to PASI 90 at Week 52.

For assessments of the primary endpoints and other categorical efficacy and health outcomes endpoints, the Cochran–Mantel–Haenszel (CMH) chi-square test along with Non-Responder Imputation (NRI) will be used to compare the treatment groups. The CMH stratification factors will be the same as those used in the stratified randomization scheme. The CMH chi-square p-value will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 95% 2-sided confidence interval estimate.

Treatment comparisons of continuous efficacy and health outcome variables with multiple post-baseline measurements will be made using mixed-effects model for repeated measures (MMRM). When MMRM is used, the model will include treatment, baseline value, visit, and the interaction of treatment-by-visit, and the variables used for stratified randomization in induction/maintenance will be used as covariates. Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance (ANCOVA) with the following covariates in the model: treatment group, baseline value, and variables used for stratified randomization in induction/maintenance.

Fisher's exact test will be used for categorical safety data, including adverse events, unless otherwise specified. Continuous safety data including vital sign and laboratory values will be analyzed using ANCOVA with treatment and baseline value in the model, unless otherwise specified. Also, laboratory analytes will be presented as mean changes from baseline and as incidence of shift between normal and abnormal states.

The prespecified graphical multiple testing approach (Bretz et al. 2011) will be implemented to control the overall Type I error rate at 2-sided alpha of 0.05, for the hypotheses for the primary and major secondary endpoints.

A Data Monitoring Committee (DMC) consisting of members external to Lilly will be established for interim safety monitoring across all Phase 3 trials in patients with psoriasis. A DMC charter will govern the role and responsibilities of DMC-related activities.

2. Schedule of Activities

Table AMAK.1. Schedule of Activities

Procedure[a]	Screening Period	Baseline	Induction Period				Maintenance Period										ETV[s]	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	85 ± 5
Informed Consent	X																		
Demographics	X																		
Height	X																		
Physical Examination[c]	X	X					X									X	X	X	X
Weight	X	X					X									X	X		
Inclusion/ Exclusion Criteria	X	X																	
Complete Medical/ Surgical History and Habits	X																		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting Conditions	X																		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, temp, and pulse)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure[a]	Screening Period	Baseline	Induction Period				Maintenance Period										ETVs	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	85 ± 5
Chest Radiography for TB Screening	X[e]																		
PPD/ QuantiFERON -TB Gold/ T-SPOT.TB (per local guidelines)	X[f]																		
ECG	X																X[g]		X[g]
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Suppl. Form[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QIDS-SR16 (patient completed)		X					X			X			X			X	X		X
IP Dosed		X		X	X	X	X	X	X	X	X	X	X	X	X				
Investigator-Completed Clinical Efficacy Scales																			
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure[a]	Screening Period	Baseline	Induction Period					Maintenance Period									ETV[s]	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	85 ± 5
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Facial Psoriasis		X					X									X	X		
PSSI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPASI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Completed Health Outcomes Scales[j]																			
PSS	|----------Daily Electronic Diary[k]----------|									X			X			X	X		
DLQI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SF-36		X					X									X	X		
PatGA		X	X	X	X	X	X			X			X			X	X		
WPAI-PSO		X					X			X			X			X	X		
EQ-5D-5L-PSO		X			X		X			X			X			X	X		
TSQM		X					X			X			X			X	X		
Laboratory Tests																			
Hematology[l]	X	X	X	X	X		X		X		X		X		X	X	X		X
Clinical Serum Chemistry[l]	X	X	X	X	X		X		X		X		X		X	X	X		X

Procedure[a]	Screening Period	Baseline	Induction Period				Maintenance Period										ETVs	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	85 ± 5
Lipid Panel (fasting)[m]		X					X									X			
Urinalysis	X	X					X										X[u]		
hsCRP		X		X	X		X		X		X		X			X			
HBsAg, HBcAb, HBsAb	X[n]																		
HBV DNA testing[n]	X					X			X			X			X		X	X	X
Hepatitis C Antibody	X																		
HCV RNA testing	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]		X[o]
HIV	X																		
Immuno-genicity for miri [p]		X	X	X	X		X	X	X		X		X			X	X		X
Serum for miri conc (PK)[q]		X	X	X	X		X	X	X		X		X			X	X		X
Serum Pregnancy Test (WCBP only)	X																		

Procedure[a]	Screening Period	Baseline	Induction Period					Maintenance Period									ETV[s]	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	85 ± 5
Urine Pregnancy Test (local; WCBP only)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH	X[r]																		
Serum/ Plasma for Storage/ CCI		X			X		X									X	X		X
Serum/ Plasma for Storage/ CCI		X	X	X	X		X		X		X		X		X	X	X		X
CCI		X			X		X									X	X		X
Blood for DNA Pharmaco-genetics		X																	

Abbreviations: BP = blood pressure; BSA = body surface area; conc = concentration; C-SSRS = Columbia–Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L-PSO = European Quality of Life–5 Dimensions–5 Levels–Psoriasis; ETV = early termination visit; FSH = follicle stimulating hormone; HBcAb = anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IL-19 = interleukin-19; IP = investigational product; LV = last study visit; miri = mirikizumab; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PatGA = Patient's Global Assessment of Psoriasis; PK = pharmacokinetic; PPASI = Palmoplantar Psoriasis Severity Index; PPD = purified protein derivative (skin test); PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; RNA = ribonucleic acid; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; Suppl. = supplement; TB = tuberculosis; temp = temperature; TSQM = Treatment Satisfaction Questionnaire for Medication; V = visit; W = weeks; WCBP = women of childbearing potential; WPAI-PSO = Work Productivity and Activity Impairment Questionnaire: Psoriasis.

[a] All activities should be completed prior to any study dose administration, unless otherwise stated.

[b] Visit 1 procedures may be conducted over more than 1 day, as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).

[c] One complete physical examination (excluding pelvic or rectal examinations) to include heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas) will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas).

[d] Sitting blood pressure, temperature, and pulse will be obtained within approximately the same time frame as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the preferred order of completion should be as follows: ECG (if applicable), vital signs, and then blood sampling.

[e] Chest radiography will be performed locally at screening unless it has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review). For additional details, see Section 9.4.5.3.

[f] TB testing will be performed at screening unless it has been performed within 3 months before initial screening (provided the formal report is available for the investigator's review). It may also be performed after screening if clinically indicated. TB testing will be performed locally using an interferon-γ release assay (IGRA; QuantiFERON®-TB Gold or T-SPOT.TB®) or a purified protein derivative (PPD) tuberculin skin test. If PPD test is performed, patients will return 2 to 3 days afterwards to have their PPD test read. For additional details on TB testing, see Exclusion Criterion [19] and Section 9.4.5.2.

[g] The preferred order of completion is supine ECG prior to vital signs, blood sampling, or any other study procedures. For additional details on ECG collection, see Section 9.4.1. ECG should be performed at the ETV and Visit 802 only if there is early termination due to a cardiovascular event.

[h] A Self-Harm Follow-Up Form is to be completed only during visits for which there is at least 1 discrete self-harm event identified on the Self-Harm Supplement Form (see Section 9.2.2).

[i] PSSI, NAPSI, and PPASI assessments are applicable only if symptoms are present at baseline.

[j] These assessments should be completed before administration of investigational product, before the patient's clinical examination, before the patient receives any tests or results, and before the patient's health, health data, or emotions are discussed.

[k] Electronic diaries will be distributed at the screening visit and collected at the Week 16 visit.

[l] Unscheduled hematology or blood chemistry panels may be performed at the discretion of the investigator.

[m] Patients should not eat or drink anything except water for 12 hours prior to sample collection.

[n] Any enrolled patient who is HBcAb+ will undergo monitoring of HBV DNA with HBV DNA testing (see Section 9.4.5.4). Any patient with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[o] Following screening, patients will not undergo monitoring for HCV RNA unless liver enzymes are elevated (see Section 9.4.5.5). Any patient with a positive HCV RNA test must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[p] Immunogenicity samples should be collected prior to dosing on visits when mirikizumab is administered. A sample will be obtained at unscheduled visits if a patient develops an acute hypersensitivity event after administration of IP (see Section 7.8.2.1).

[q] Scheduled PK samples are taken as an aliquot from the immunogenicity sample. Unscheduled PK samples, obtained if a patient develops an acute hypersensitivity event after administration of IP (see Section 7.8.2.1), will be collected in a separate tube.

[r] FSH test is to be performed at screening for women who have had spontaneous amenorrhea for 6 to 12 months to confirm lack of childbearing potential.

[s] If a patient discontinues IP early, the patient will complete the ETV and then enter the Post-Treatment Follow-up Period (V801 + V802).

[t] All patients who receive IP but do not participate in Study AMAH must enter the Follow-up Period and complete V801 + V802.

[u] Urinalysis assessed only for early termination due to an adverse event for which urinalysis is clinically indicated.

3. Introduction

3.1. Study Rationale

Mirikizumab (LY3074828) is a monoclonal, anti-interleukin-23 (anti-IL-23) antibody being developed for the treatment of immune-mediated diseases where the IL-23 pathway is thought to have a significant pathogenic role. The neutralizing activity of mirikizumab is directed against the p19 subunit of the IL-23 molecule and does not bind to IL-12. Study I6T-MC-AMAK (AMAK) is a confirmatory study testing mirikizumab as a treatment for plaque psoriasis and is intended to support registration of this indication. This Phase 3 study is designed to evaluate the superiority of mirikizumab versus placebo during the Induction Period (16 weeks), as measured by improvement in disease severity and key patient-reported outcomes. This study period is followed by a randomized Maintenance Dosing Period to Week 52 to evaluate the maintenance of response or remission as well as relapse and rebound following treatment withdrawal, and response to retreatment following relapse. The data will contribute to the evaluation of the safety of mirikizumab.

3.2. Background

The worldwide prevalence of psoriasis is nearly 3% (IFPA 2017), with rates varying across ethnic groups, ages, gender, and geographic regions (Parisi et al. 2013). Histologically, psoriasis is characterized by inflammatory infiltrate and hyperproliferative keratinocytes, which retain intact nuclei (parakeratosis), elongation of rete ridges, and hyperconvoluted vasculature in the papillary dermis. The infiltrate consists of prominent T cells, dendritic cells, and neutrophils in the dermis. The dysregulation of the immune system, especially the activation of pathogenic T cells, has been well demonstrated to play an important role in psoriasis development.

A typical organ-specific, T-cell-driven inflammatory disease, psoriasis had been considered a T helper (Th) 1-type skin disease for decades, until a new Th population, Th17, was identified (Lew et al. 2004; Steinman 2007; Weaver et al. 2007). Substantial clinical and basic research observations now suggest that the IL-23/Th17 axis is essential in the pathogenesis of psoriasis (Di Cesare et al. 2009). IL-23, a member of the IL-12 family of cytokines, is a heterodimeric protein comprised of 2 subunits; the p40 subunit, which it shares with IL-12, and the p19 subunit, believed to be specific to IL-23. IL-23 is produced by antigen-presenting cells, such as dendritic cells and macrophages, and plays an important role in maintenance and amplification of Th17 cells (Lee et al. 2004; Piskin et al. 2004). In addition, Th17 cells and their downstream effector molecules, including IL-17A, IL-17F, IL-21, IL-22, and tumor necrosis factor (TNF)-alpha, are found at increased levels in human psoriatic skin lesions and circulation (Boniface et al. 2007; Lowes et al. 2008; Caruso et al. 2009; Kagami et al. 2010).

A number of IL-23 targeting molecules are being investigated for the treatment of immune-mediated diseases. The first biologic to demonstrate clinical benefit through IL-23 inhibition in such diseases was ustekinumab, which is a monoclonal antibody approved by the United States Food and Drug Administration (FDA; Stelara® package insert 2017) and the European Medicines Agency (EMA; Stelara Summary of Product Characteristics 2017) for the treatment of psoriasis, psoriatic arthritis, and Crohn's disease, and is being evaluated in a Phase 3

trial for the treatment of ulcerative colitis (NCT02407236). Ustekinumab binds the p40 subunit common to IL-12 and IL-23; therefore, it targets both cytokines rather than IL-23 specifically. Blockade of the IL-12 pathway may prevent Th1 cell-induced interferon blockade of Th17 cell development, thus potentially limiting the clinical activity of p40-targeting antibodies. Experimental studies suggest that blocking the IL-23/Th17/IL-17 immune axis alone is sufficient to treat autoimmune inflammation (Monteleone et al. 2009). One such therapy that specifically targets the p19 subunit of IL-23, guselkumab, has been approved for the treatment of moderate-to-severe plaque psoriasis by the United States FDA (Tremfya™ package insert 2017) and the EMA (Tremfya Summary of Product Characteristics 2017). Other similar agents, including mirikizumab in Studies I6T-MC-AMAA (AMAA) and I6T-MC-AMAF (AMAF), have demonstrated clinical activity in plaque psoriasis (Krueger et al. 2015; Papp et al. 2015, 2017; Reich et al. 2017b).

3.3. Benefit/Risk Assessment

Psoriasis remains an important public health challenge. Therefore, there is a continuing need to develop treatment options with mechanisms of action that differ from existing therapies. Clinical data with mirikizumab (Studies AMAA and AMAF), as well as clinical data with ustekinumab, risankizumab, tildrakizumab, and guselkumab, support the hypothesis that IL-23 plays a significant role in the pathogenesis of psoriasis, and these compounds appear to have a favorable benefit/risk profile in patients with psoriasis.

To assess the nonclinical toxicity of mirikizumab and establish a margin of safety (MOS) for clinical studies, 4-week and 6-month general toxicity studies in 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 (subcutaneous [SC]), or 100 mg/kg (intravenous [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. Plasma exposure in monkeys at the no-observed-adverse-effect-level (NOAEL) in the 4-week and 6-month studies provided 52- and 22-fold MOS, respectively, relative to the predicted human exposure at the highest proposed clinical dose and frequency of 250 mg administered SC every 4 weeks.

After 16 weeks of treatment in Study AMAF, Psoriasis Area and Severity Index (PASI) 90 responses in all mirikizumab treatment arms were significantly higher than placebo, with the highest responses in the 100-mg and 300-mg dosing groups. Overall frequencies of adverse events (AEs) were similar for mirikizumab- and placebo-treated patients (Reich et al. 2017b).

The doses and regimens planned for Study AMAK were selected based on analyses of pharmacokinetic (PK), safety, and efficacy data from Phase 1 and Phase 2 studies, literature information for other anti-IL-23 antibodies, and nonclinical safety data. In addition, blinded trial-level safety reviews will be conducted at periodic intervals throughout the study. Interim safety analyses will be conducted by an external Data Monitoring Committee (DMC) to review unblinded safety data. These monitoring and risk-mitigation actions, along with regular review

of AEs and laboratory data, will assist in the evaluation and management of potential risks associated with mirikizumab administration.

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 AMAK are expected to outweigh the potential risks.

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

4. Objectives and Endpoints

Table AMAK.2 shows the objectives and endpoints of the study.

Table AMAK.2. Objectives and Endpoints

Objectives	Endpoints
Primary[a,b] To assess whether mirikizumab induction dosing is superior to placebo in the treatment of patients with respect to high levels of clinical response	At Week 16: • Proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline • Proportion of patients achieving a ≥90% improvement in PASI from baseline (PASI 90)
Major Secondary[a,b] To assess whether mirikizumab induction dosing is superior to placebo with respect to an early, clinically meaningful response	At Week 4: • Proportion of patients achieving a 75% improvement in PASI (PASI 75)
To assess whether the mirikizumab induction dosing is superior to placebo with respect to clinically meaningful response and the highest levels of clinical response	At Week 16: • Proportion of patients achieving PASI 75 • Proportion of patients achieving a 100% improvement in PASI (PASI 100)
To assess whether mirikizumab induction dosing is superior to placebo with respect to body surface area (BSA) affected by psoriasis	At Week 16: • Proportion of patients with ≤1% of BSA with psoriasis involvement
To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline. • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5
To assess whether 250 mg mirikizumab Q8W and 125 mg mirikizumab Q8W maintenance dosing is superior to placebo with respect to maintenance of a high level of clinical response	At Week 52: • Proportion of patients maintaining clinical response (PASI 90) after re-randomization at the start of the randomized withdrawal period
Other Secondary[b] To compare mirikizumab to placebo with respect to clinical response and time to clinical response during the induction dosing period, and with respect to patient-reported outcomes during the induction dosing period	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90. • Change in PPASI total score in patients with palmoplantar involvement at baseline • Change in PSSI total score in patients with scalp involvement at baseline • Change in NAPSI total score in patients with fingernail involvement at baseline

Objectives	Endpoints
	• Change from baseline on the SF-36 physical component summary (PCS) and mental component summary (MCS) • Change from baseline on PatGA of disease severity • Change from baseline for the WPAI-PSO scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) • Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1
To assess whether 250 mg mirikizumab Q8W and 125 mg mirikizumab Q8W dosing is superior to placebo with respect to maintenance of high and highest levels of clinical response among patients who have an PASI 90 at Week 16 and are re-randomized	At Week 52 and at various time points during the Maintenance Dosing Period: • Time to relapse (the loss, at any visit, of ≥50% of the Week 16 PASI improvement from baseline). • Proportion of patients who have relapsed. • Proportion of patients maintaining clinical response (PASI 90) after re-randomization at the start of the randomized withdrawal period • Incidence of disease rebound within 12 weeks (worsening of psoriasis severity over baseline sPGA score, or worsening of psoriasis severity over baseline PASI score by 125%, or change in psoriasis phenotype [for example, from plaque to pustular]) after re-randomization to placebo at Week 16.
To assess the efficacy of 250 mg mirikizumab Q8W following relapse after re-randomization to placebo treatment in the Maintenance Dosing Period	During the Maintenance Dosing Period: • Proportion of patients who regained PASI 90 within 16 weeks after mirikizumab retreatment.
To evaluate the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy (sPGA and PASI)
Exploratory To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, TEAEs, and mirikizumab exposure	At Week 16 and Week 52: • Relationship between TE-ADA and efficacy (sPGA and PASI) • Relationship between TE-ADA and TEAEs • Relationship between TE-ADA and mirikizumab pharmacokinetics.

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = Patient's Global Assessment of Psoriasis; PCS = physical component summary; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; TE-ADA = treatment-emergent anti-drug antibody; TEAEs = treatment-emergent adverse events; WPAI-PSO = Work Productivity Activity Impairment Questionnaire–psoriasis.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control technique called "graphical multiple testing procedure" to control the overall family-wise Type I error rate.

[b] Note: A "clinically meaningful" response is a PASI 75 response, which represents at least a 75% decrease (improvement) from the baseline PASI score. A "high level" of clinical response is a PASI 90 response, which represents at least a 90% decrease (improvement) from baseline in PASI score, or sPGA (0,1) response, which represents an "almost clear" response. The "highest level" of clinical response is a PASI 100 or sPGA (0) response, which represents complete resolution of psoriasis.

5. Study Design

5.1. Overall Design

Study AMAK is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-period study in which approximately 500 patients will be randomized to treatment groups involving different mirikizumab doses and regimens or placebo. The study is comprised of 2 treatment periods (Induction and Maintenance with Randomized Withdrawal), which together last for up to 52 weeks, followed by a 12-week Post-Treatment Follow-Up period.

Study governance considerations are described in detail in Appendix 3.

5.1.1. Screening Period

Patients will be evaluated for study eligibility ≤28 days before the baseline visit (Visit 2). The patient will sign the informed consent form (ICF) prior to any study assessments, examinations, or procedures being performed. Screening procedures will be performed according to the Schedule of Activities (Section 2). Electronic diary collection will begin at screening, approximately ≤28 days prior to Visit 2 (baseline). All inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively.

5.1.2. Baseline and Double-Blind Induction Period (Week 0 to Week 16):

At Visit 2 (Week 0; baseline), patients who meet the study eligibility criteria will be randomized 4:1 to receive 250 mg mirikizumab or matching placebo (SC), respectively, at Weeks 0, 4, 8, and 12. Randomization will be stratified, based on previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other).

Patients who discontinue the study for any reason during this period will stop treatment and continue to the early termination visit (ETV) and then complete the 12-week Post-Treatment Follow-up Period.

5.1.3. Double-Blind Maintenance Period (Week 16 to Week 52 [36 Weeks]):

All patients who complete the Induction Period may continue in the Maintenance Period.

The Maintenance Dosing Period will be a double-blind treatment period with randomized withdrawal. The first injection of study drug for this period will be at Week 16, with the last injection at Week 48.

At Week 16 (Visit 7), patients who enter the Maintenance Period will be classified as a responder (≥PASI 90) or non-responder (<PASI 90). Patients who are responders at Week 16 will be monitored for maintenance of response or remission, as well as relapse and disease rebound following treatment withdrawal, and response to retreatment following relapse. **Remission** is defined as the achievement of PASI 100. **Relapse** is defined as the loss, at any

visit, of ≥50% of the Week 16 PASI improvement from baseline. That is, a patient will have relapsed during the Maintenance Period if their PASI score increases to at or above the midpoint between their baseline and Week 16 PASI score. **Rebound** is defined as having *one or more* of the following: worsening of psoriasis severity over baseline static Physician's Global Assessment (sPGA) score, worsening of psoriasis severity over baseline PASI score by 125%, or change in psoriasis phenotype (for example, from plaque to pustular) after randomization to placebo at Week 16.

Patients will be treated as follows:

- Patients who were responders to mirikizumab in the blinded Induction Period (responder definition is PASI 90 at Week 16) will be re-randomized 1:1:1 to 250 mg mirikizumab every 8 weeks (Q8W), 125 mg mirikizumab Q8W, or placebo Q8W, according to their randomized treatment assignment at Week 16 (see Figure AMAK.1). Stratification for the re-randomization will be based on body weight at baseline (<100 kg or ≥100 kg).
    - Patients who relapse during the blinded Maintenance Period (see relapse criterion defined above) will remain on, or will be switched to, 250 mg mirikizumab for the remainder of the study and will be monitored for recapture of efficacy response. These patients will begin retreatment with mirikizumab at the visit at which relapse is identified and will receive another mirikizumab treatment at the next visit 4 weeks later. Subsequent mirikizumab treatments will be given at Q8W intervals.
- Patients who received placebo in the blinded Induction Period who are responders at Week 16 (Visit 7) will continue to receive placebo during the Maintenance Period until relapse; these patients will begin treatment with 250 mg mirikizumab at the visit at which relapse is identified and will receive another mirikizumab treatment at the next visit 4 weeks later. Subsequent mirikizumab treatments will be given at Q8W intervals.
- Patients who were not responders to mirikizumab in the blinded Induction Period will receive 250 mg mirikizumab Q8W.
    - Continued blinded treatment for nonresponders is provided so that partial or slow responders may remain in the study beyond Week 16, thus maintaining the study blind while patients continue to receive potentially beneficial longer-term treatment with mirikizumab.
- Patients who received placebo in the blinded Induction Period who are non-responders at Week 16 (Visit 7) will receive 250 mg mirikizumab every 4 weeks (Q4W) for Weeks 16 through 32 and mirikizumab treatments Q8W thereafter.

All patients will receive injections (mirikizumab or placebo, as appropriate) Q4W at Weeks 16 through 48 (Visits 7 through 15) in order to maintain study blind across the study treatment groups.

A discontinuation criterion has been included for patients in any treatment group who remain at or above their baseline sPGA score at Week 16 (Visit 7) and Week 24 (Visit 9), or who remain at or above their baseline PASI score at Week 16 (Visit 7) and Week 24 (Visit 9), to ensure that patients who have not shown any benefit from study treatment are offered alternative therapies (see Section 8.2).

At Week 52, patients will have one of the following two options:

1. Enter Study I6T-MC-AMAH (AMAH), a long-term extension study in which patients will receive 250 mg mirikizumab Q8W (SC) or 125 mg mirikizumab Q8W (SC),

   OR

2. Discontinue study treatment and complete Study AMAK's 12-week Post-Treatment Follow-Up Period.

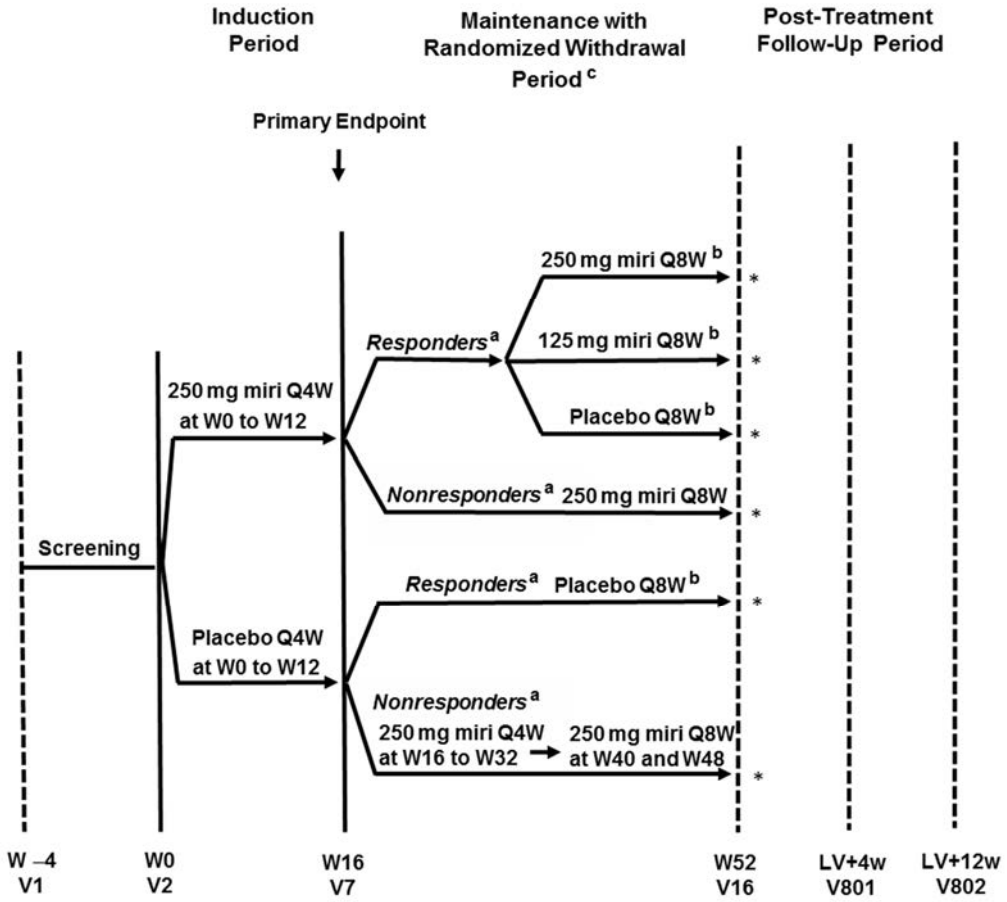
Patients who discontinue the study for any reason during this period will stop treatment and continue to the ETV and then complete the 12-week Post-Treatment Follow-up Period.

5.1.4. Post-Treatment Follow-up Period (12 Weeks)

Patients who do not enroll into Study AMAH or who discontinue early from study treatment in Study AMAK will complete the Post-Treatment Follow-Up Period (V801 and V802) of Study AMAK.

For patients who have entered the Post-Treatment Follow-Up Period, psoriasis therapy with another agent(s), as determined appropriate by the investigator, is allowed.

Figure AMAK.1 illustrates the study design.



Abbreviations: LV = last study visit; miri = mirikizumab; Q4W = every 4 weeks; Q8W = every 8 weeks; V = visit; w = weeks; W = week.

Note: Randomizations occur at Week 0 and Week 16.

* Option to enter Study AMAH or to enter the Post-Treatment Follow-Up Period.

a Patients may receive placebo injections during the Maintenance Period to maintain the study blind across treatment groups, as described in Section 5.1.3.

b Patients who relapse during the Maintenance Period will be treated with 250 mg mirikizumab for the remainder of the study and will be monitored for recapture of efficacy response, as described in Section 5.1.3.

c First Maintenance Period dosing at Week 16.

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

5.2. Number of Participants

Approximately 650 participants will be screened to achieve 500 randomized participants: 400 randomized to mirikizumab and 100 randomized to placebo.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4. Scientific Rationale for Study Design

This study will examine the effects of 16 weeks of double-blind dosing (1 dose regimen of mirikizumab versus placebo) during the Induction Period. The selection of placebo as a comparator is justified on the basis that the most robust evaluation of efficacy can be made versus placebo treatment, and the duration of the 16-week primary evaluation is sufficiently short for patients to receive placebo without lasting adverse effects.

In the Maintenance with Randomized Withdrawal Period, double-blind dosing with 250 mg mirikizumab Q8W, 125 mg mirikizumab Q8W, or placebo will be evaluated. Patients who were not responders to LY3074828 in the Induction Period will be switched to 250 mg mirikizumab Q8W in the Maintenance Period so that partial or slow responders may remain in the study beyond Week 16, thus maintaining the study blind while patients continue to receive longer-term treatment with mirikizumab. The purpose of this study period is to determine the optimal dosing level for the maintenance of response or remission, to evaluate relapse or rebound following treatment withdrawal, and to measure response to retreatment following relapse.

The Post-Treatment Follow-up Period is included for safety monitoring following the last study visit for patients who do not enroll in Study AMAH or who discontinue early from Study AMAK.

The dose justification for mirikizumab is outlined in Section 5.5, and the study blind will be maintained as described in Section 7.3.

5.5. Justification for Dose

The dose levels and regimens selected for this study were 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.

Safety Considerations

Single doses of up to 600 mg IV were evaluated in Study AMAA (healthy subjects and psoriasis patients) and up to 1200 mg IV in Study I6T-JE-AMAD (healthy subjects); no dose-related safety or tolerability issues were observed in either study. Evaluation of the safety data available to date in the ongoing Phase 2 studies in patients with ulcerative colitis (Study I6T-MC-AMAC) and in patients with Crohn's disease (Study I6T-MC-AMAG) that are evaluating higher and more frequent dose regimens of up to 1000 mg IV Q4W for up to 52 weeks has not revealed any difference in the safety profile resulting from these higher exposures.

CCI [redacted]

No dose-related safety or tolerability issues have been observed in Study AMAF, including in patients who were non-responders and received a third dose of 300 mg SC at Week 16. Although the proposed 250 mg Q4W induction dose regimen for this study is expected to produce modestly higher average concentrations than the highest dose regimen evaluated in

Study AMAF, the safety data collected from completed and ongoing clinical studies and from nonclinical toxicology studies supports the proposed dose regimens.

Efficacy Considerations

In Study AMAF, doses of 30, 100, and 300 mg mirikizumab administered Q8W SC provided significant efficacy relative to placebo, with 100 and 300 mg achieving greater efficacy than 30 mg at Week 16. The 300-mg dose provided the highest efficacy for the primary endpoint at Week 16 (PASI 90) and demonstrated a trend towards providing higher PASI 90 and PASI 100 rates at earlier time points; the 300-mg dose also provided a more durable response following Week 16. Thus, results from Study AMAF indicate that the highest dose (300 mg) provided the greatest efficacy.

Results from Study AMAF also suggest that additional dosing, if given during the Induction Period, might have further improved efficacy at Week 16. This suggestion is based on incremental benefits observed following a third dose administered to Week 16 nonresponders, when assessed within 4 week to 8 weeks of that dose. Model-based analyses and simulations indicate that 250-mg doses administered at Weeks 0, 4, 8, and 12 (1000 mg total) will maximize efficacy at the end of the 16-week Induction Period.

A dosing regimen of 250 mg SC Q8W during the Maintenance Period is expected to maintain or further enhance the efficacy achieved at the end of the Induction Period. The 250-mg dose is expected to achieve exposures and efficacy that are not distinguishable from that observed with 300-mg dosing. A second maintenance dosing regimen of 125 mg Q8W SC was chosen to determine whether efficacy could be maintained with a lower dosing regimen. This second dosing regimen is expected to result in mirikizumab concentrations that have, in individual subjects, minimal overlap with the concentrations produced with the 250 mg mirikizumab Q8W SC regimen.

CCI

[redacted]

6. Study Population

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 to be included in the study only if they meet all of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment unless otherwise defined:

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 baseline, and meet the following criteria:

A. Plaque psoriasis involving ≥10% body surface area (BSA) and absolute PASI score ≥12 in affected skin at screening (Visit 1) and baseline (Visit 2), and

B. sPGA score of ≥3 at screening (Visit 1) and baseline (Visit 2).

[2] Candidate for systemic therapy and/or phototherapy.

Patient Characteristics

[3a] Male patients:

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

[3b] Female patients:

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

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

OR

B. Postmenopausal, defined as:

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

a. Cessation of menses for at least 1 year,

OR

b. At least 6 months of spontaneous amenorrhea with a follicle stimulating hormone >40 mIU/mL,

OR

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

OR

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

Women of childbearing potential:

A. Must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

B. 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 (for example, 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.

   i. 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.

   ii. Of note, one of the two 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).

When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

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

[5] Have adequate organ function, including:

A. Hematology:

i. Absolute neutrophil count ≥1.5 x 10^9/L (≥1.5 x 10^3/µL or ≥1.5 GI/L),

ii. Platelet count ≥100 x 10^9/L (≥100 x 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 x 10^3/µL or >0.50 GI/L),

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

B. Chemistry:

i. Serum creatinine ≤2x the upper limit of normal (ULN),

ii. Alanine aminotransferase (ALT) ≤2x ULN,

iii. Aspartate aminotransferase (AST) levels ≤2x ULN,

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

v. Alkaline phosphatase (ALP) <1.5x 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 Eli Lilly and Company [Lilly]-designated medical monitor.)

[6] Are reliable and willing to make themselves available for the duration of the study and are able and willing to follow study procedures, including use of electronic device for recording of data.

Informed Consent

[7] Have given written informed consent as a legal adult according to local regulations.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening, unless otherwise specified:

Medical Conditions

[8] Have an abnormality in the 12-lead electrocardiogram (ECG) that, in the opinion of the investigator, increases the risks associated with participating in the study.

[9] 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.

[10] Presence of significant uncontrolled neuropsychiatric disorder or judged at-risk of suicide in the opinion of the investigator;

OR

marked "yes" to Columbia-Suicidality Severity Rating Scale (C-SSRS) question 4 or 5 on ideation at Visit 1, or prior to dosing at Visit 2;

OR

"yes" to C-SSRS suicide behaviors question 1 month prior to Visit 1, or prior to dosing at Visit 2;

OR

Has a history of suicide attempt within 1 month prior to screening.

[11] Have human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) or test positive human HIV antibodies at screening.

[12] 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 ribonucleic acid (RNA) test (see Section 9.4.5.5). Patients in sustained virologic response after HCV therapy, and patients who have spontaneously cleared HCV infection (see Section 9.4.5.5), can be included in this study.

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

A. Positive for hepatitis B surface antigen (HBsAg+),

OR

B. Positive for hepatitis B core antibody (HBcAb+) in conjunction with positive confirmatory HBV deoxyribonucleic acid (DNA) test

OR

C. Positive HBV DNA test, regardless of anti-hepatitis B surface antibody (HBsAb) status.

[14] Are women who are breastfeeding or plan to breastfeed during study.

[15] Have donated blood of >500 mL within 14 days prior to baseline.

[16] Have had serious, opportunistic (see Section 9.2.3 and Appendix 4), 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.

[17] Have received a systemic (including oral) anti-infective agent for an infection within 28 days of baseline (see Section 6.4 for information on rescreening).

[18] Have had, according to the investigator, clinically significant herpes zoster within 3 months of screening.

[19] Have evidence of active or latent tuberculosis (TB) (refer to Section 9.4.5.2 for details on full TB exclusion criteria and Section 6.4 for information on rescreening).

[20] Have received a Bacillus Calmette-Guerin (BCG) vaccination within 12 months or received live vaccine(s) (including attenuated live vaccines) within 12 weeks of baseline or intend to receive either during the study.

[21] Have history of hypersensitivity events to any components of the mirikizumab product formulation.

[22] Have active or history of lymphoma, leukemia, or any malignancy. *Exceptions:* 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 baseline.

[23] 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).

Prior/Concomitant Therapy

[24] Have received systemic nonbiologic 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; leflunomide; fumaric acid derivatives; or 1,25-dihydroxyvitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self-treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline.

[25] Have received topical treatment (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-hydroxyl acids, or medicated shampoos [for example, those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues]) within 14 days prior to baseline.

[26] Have received anti-TNF targeting biologics within 8 weeks prior to baseline, or anti-IL-17 targeting biologics within 12 weeks prior to baseline.

[27] Have previous exposure to any biologic therapy targeting IL-12/23 (p40 subunit), or IL-23 (p19 subunit), either marketed or investigational.

[28] Are unable or unwilling to avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline and during the study.

Prior/Concurrent Clinical Trial Experience

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

[30] 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.

[31] Have previously completed or withdrawn from this study or any other study investigating mirikizumab.

Other Exclusions

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

[33] Are Lilly employees or employees of third-party organization involved with the study who require exclusion of their employees.

[34] 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.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Patients less than 18 years of age are excluded from participation in this study. This is a confirmatory study designed to evaluate the efficacy and safety of mirikizumab as a treatment for plaque psoriasis and is intended to support registration of this indication in adult patients. Until efficacy and an adequate safety profile is developed in adult patients with psoriasis, adolescents and younger children with psoriasis will not be included in studies of this investigational product. Patients with particular medical conditions, including serious infections or other uncontrolled illnesses, are excluded for patient safety and to eliminate potential confounders to data interpretation. Patients taking particular concomitant medications are excluded to eliminate potential confounders to data interpretation. Exclusion of patients currently or recently enrolled in other clinical trials, or patients affiliated with the investigator or study Sponsor, are excluded to meet Good Clinical Practice (GCP) initiatives for unbiased selection of patients.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for 12 weeks following their last dose of investigational product.

6.4. Screen Failures

Individuals may be rescreened only 1 time for failure due to criteria [17] or [19]. Patients who do not qualify at screening under Exclusion Criteria [17] (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 [19]) at screening may be rescreened following appropriate treatment as described in Section 9.4.5.2.

Each time rescreening is performed, the individual must sign a new 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.

7. Treatments

7.1. Treatments Administered

This study involves evaluation of mirikizumab (250 mg or 125 mg) and placebo administered SC during 52 weeks of double-blind treatment. Table AMAK.3 shows the treatment regimens.

Table AMAK.3. Treatment Regimens

Regimen Group	Dosing	Description
250 mg miri Q4W	250 mg miri [redacted]	At W0, 4, 8, and 12 for patients randomized to mirikizumab during the Induction Period At W16, 20, 24, 28 and 32 of the Maintenance Period, for patients who were randomized to placebo during the Induction Period
250 mg miri Q8W	250 mg miri [redacted]	During the Maintenance Period only, starting at W16
125 mg miri Q8W	125 mg miri [redacted]	During the Maintenance Period only, starting at W16
Placebo	Placebo [redacted]	At W0, 4, 8, and 12 for patients randomized to placebo during the Induction Period At all visits during the Maintenance Period, as necessary, to maintain the study blind across treatment groups

Abbreviations: miri = mirikizumab; [redacted]; Q4W = every 4 weeks; Q8W = every 8 weeks; W = Week.

Detailed instructions for investigational product administration will be provided by the Sponsor, and the investigational product will be administered at the site by clinical staff.

The investigator or his/her designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the site personnel,
- Verifying that instructions are followed properly,
- Maintaining accurate records of investigational product dispensing and collection,
- At the end of the study returning all unused medication to Lilly, or its designee, unless the Sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

Mirikizumab and placebo will be supplied to the investigator by Lilly. Clinical trial materials 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. Clinical trial materials are manufactured in accordance with current Good Manufacturing Practices (GMP).

Investigational product will be supplied as single-use, solution pre-filled syringes containing mirikizumab or placebo. CCI [redacted]

Mirikizumab cannot be distinguished visually from placebo.

Investigational product will be provided with study-specific labels. Syringes will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the investigational product.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign prefilled syringes containing double-blind investigational product to each patient. Investigational product will be dispensed according to the Schedule of Activities (Section 2) for treatment of patients in the clinic. Site personnel will confirm that they have located the correct carton(s) of pre-filled syringes by entering a confirmation number found on the carton(s) into the IWRS.

7.2.1. Selection and Timing of Doses

Study visits at which investigational product is administered are preferred, if possible, to occur on the same day of the week. In any case, the study visits should occur within the visit window specified on the Schedule of Activities (see Section 2). The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

7.3. Blinding

This is a double-blind study. The blinding applies to patients, site personnel, and Sponsor personnel.

To preserve the blinding of the study, a minimum number of Lilly and site personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient

remain in the study, the investigator must obtain specific approval from a Lilly-designated medical monitor for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

Dose adjustments are not permitted in this study except for patients who relapse during the Maintenance Period; these patients may be switched to 250 mg mirikizumab through the IWRS, as described in Section 5.1.3.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- Confirming that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions with access limited to 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).

Detailed instructions regarding supplies and preparation and handling of investigational products will be provided by the Sponsor.

Investigational products will be supplied by Lilly or its representative, in accordance with current GMP and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable. All investigational products will be stored, inventoried, reconciled, and returned or destroyed according to applicable regulations.

Mirikizumab and placebo should be transported and stored in refrigerated conditions 2°C to 8°C (36°F to 46°F).

7.6. Treatment Compliance

All doses of study medication will be administered at the study site by site personnel. Deviations from the prescribed dosage regimen should be recorded in the eCRF.

Every attempt will be made to select patients who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

If a patient is noncompliant with study procedures and/or investigational product administration, the investigator should assess the patient to determine the reason for noncompliance and educate and/or manage the patient, as appropriate, to improve compliance. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses within the protocol-defined dosing interval and not missing 2 consecutive doses. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the patient may be discontinued from the study.

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.

Subjects 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), the investigator should base decisions on the patient and clinical factors. 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 AMAK.4 below (also see the Exclusion Criteria [Section 6.2]).

Table AMAK.4. Excluded Classes of Concomitant Medications or Classes with Restricted Use

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
Topical treatment for psoriasis or any other skin condition *(for example, corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)*	N	N	

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
Topical treatment for psoriasis limited to face, axilla, or genitalia	N	Y	Mild or least potent topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits.
Photochemotherapy *(for example, PUVA)*	N	N	
Phototherapy *(for example, UVA, UVB, excimer laser)*	N	N	
Biological immunomodulating agents *(for example, alefacept, briakinumab, efalizumab, ixekizumab, secukinumab, etanercept, adalimumab, infliximab, certolizumab)*	N	N	
Other systemic immunomodulating treatments *(for example, MTX, cyclosporine A, corticosteroids, cyclophosphamide)*	N	N	
Systemic immunomodulating treatments *(corticosteroids only)*	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 *(for example, retinoids, fumarates, apremilast)*	N	N	
Bacillus Calmette-Guerin (BCG) vaccinations or live virus vaccinations *(BCG prohibited for 12 months before baseline, live vaccinations prohibited for 12 weeks before baseline. Both are prohibited throughout the study and for 12 weeks after discontinuation of study drug).*	N	N	
Any investigational treatment	N	N	

Abbreviations: MTX = methotrexate; N = No; PUVA = psoralen and ultraviolet A; TEAE = treatment-emergent adverse event; UVA = ultraviolet A; UVB = ultraviolet B; Y = Yes.

Topical therapies allowed during the study include shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers/emollients and other non-prescription topical products that do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues; and bath oils and oatmeal bath preparations. These topical therapies are not to be used within 12 hours prior to a study visit.

For patients who have entered the Post-Treatment Follow-Up Period, psoriasis therapy with another agent(s), as determined appropriate by the investigator, is allowed.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

Mirikizumab will not be made available to patients who either discontinue early from Study AMAK, or complete Study AMAK but do not enroll in Study AMAH.

7.8.2. Special Treatment Considerations

7.8.2.1. Management of Hypersensitivity Events, Including Injection Site Events

All biological agents carry the risk of systemic allergic/hypersensitivity events. Clinical manifestations of these events may include, but are not limited to the following:

- Skin rash
- Pruritus (itching)
- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic events.

Sometimes, these events can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all patients should be closely monitored for signs or symptoms that could result from such events, educated on the signs or symptoms of these types of events, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute hypersensitivity event after an injection of investigational product, he or she should be managed appropriately and given instructions to receive relevant supportive care.

Additionally, for an event judged by the investigator to be a potential systemic hypersensitivity event, blood samples will be collected for PK, immunogenicity, and exploratory hypersensitivity analyses at, or as close as possible to:

1. the onset of the event
2. the resolution of the event, and
3. 30 (±3) days following the event.

Exploratory hypersensitivity samples may, as appropriate for the clinical presentation,

- be analyzed for tryptase (a marker of basophil/mast cell activation),
- have a complement panel performed (asses immune complex formation), and
- have a cytokine panel performed.

See also Section 9.4.4.

Patients who develop clinically significant systemic hypersensitivity events following administration of investigational product should be discontinued from the study and not receive further doses of investigational product, with or without premedication (see Section 8.2).

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Patients for whom investigational product should be permanently discontinued, irrespective of the reason, should complete the Post-Treatment Follow-Up and then be permanently discontinued from the study. Section 8.2 provides the list of criteria for permanent discontinuation of patients from study treatment and the study.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 5.1.4 (Post-Treatment Follow-up Period), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Interruption (Withholding) of Study Treatment

Some possible reasons for temporarily withholding investigational product include, but are not limited to:

- Development of:
    - Serious or opportunistic infections, as described in Section 9.2.3).
    - Hypertension (see Section 9.4.2.1).
    - Latent TB infection (LTBI) (see Section 9.4.5.2).
    - Positive HBV DNA results that are below the level of quantification (see Section 9.4.5.4).
    - Hepatic event or liver test abnormality: Investigational product should be withheld and additional testing performed following consultation with the Lilly-designated medical monitor, if the results of repeat tests following elevated ALT, ALP or total bilirubin level (TBL) include one of the following (Section 9.4.6.1):
        - ALT ≥3x ULN and TBL <2x ULN
        - ALP ≥2x ULN and TBL <2x ULN
        - TBL ≥2x ULN without increase from baseline in ALT/AST/ALP.
- Surgery: Patients requiring surgery at any time during the study should interrupt administration of the investigational product, beginning 8 weeks before the surgery or as early as possible within 8 weeks of surgery, and resume administration of the investigational product only after complete wound healing.

Cases that may merit temporary withholding of the study treatment should be discussed with the medical monitor. The medical monitor, in consultation with the investigator, will determine when it is appropriate to recommence study treatment.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the Sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with the investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients should permanently discontinue the investigational product, complete the Post-Treatment Follow-up, and then permanently discontinue from the study for any of the following reasons:

- **Subject Decision**
    - The patient requests to be either discontinued from the investigational product or withdrawn from the study.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

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

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and TBL >2x ULN or international normalized ratio (INR) >1.5
- ALT or AST >3x ULN, with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3x ULN
- ALP >2.5x ULN and TBL >2x ULN

- ALP >2.5x ULN, with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- In addition, patients who meet any one of the following criteria should be discontinued from the investigational product, enter the Post-Treatment Follow-Up Period, and discontinue from the study:
  - Total white blood cell (WBC) count <2000 cells/µL (<2.00 x 10^3/µL or <2.00 GI/L).
  - Lymphocyte count <500 cells/µL (<0.50 x 10^3/µL or <0.50 GI/L).
  - Platelet count <50,000 cells/µL (<50 x 10^3/µL or <50 GI/L).
  - Changes in blood pressure (BP) (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 2]; 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 experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the investigator, merits the discontinuation of the investigational product.
  - Clinically significant systemic hypersensitivity event following administration of investigational product.
  - The patient becomes pregnant.
  - The patient develops a malignancy (Note: patients may be allowed to continue if they develop no more than 2 non-melanoma skin cancers during the study).
  - Any patient who has a change in disease phenotype at any time (for example, a change to pustular psoriasis).
  - If the patient remains at or above their baseline sPGA score at Week 16 (Visit 7) and Week 24 (Visit 9), or remains at or above their baseline PASI score at Week 16 (Visit 7) and Week 24 (Visit 9).
  - 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:
    i. The patient, at any time during the study, scores a 3 for Item 12 (Thoughts of Death or Suicide) on the 16-item Quick Inventory of Depressive Symptomatology (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.

- The patient develops active TB or HIV/AIDS during the study.
- The patient becomes HBV DNA or HCV RNA positive. The patient should be referred to a specialist physician (see Sections 8.1.2 and 9.4.5.4 for HBV, and Section 9.4.5.5 for HCV).

- Patients will also be permanently discontinued from study drug, complete Post-Treatment Follow-up, and then permanently discontinued from the study 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 GCP
  - Investigator decision
    - The investigator decides that the patient should be discontinued from the study
    - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Patients permanently discontinuing from investigational product, completing the Post-Treatment Follow-Up, and permanently discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 5.1.4 (Post-Treatment Follow-up Period), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. 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, with the study procedures and their timing (including tolerance limits for timing).

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

Unless otherwise stated in the 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

9.1.1. Primary Efficacy Assessments

The primary efficacy endpoints are the proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline at Week 16 and the proportion of patients achieving a ≥90% improvement in PASI from baseline (PASI 90) at Week 16.

9.1.1.1. Static Physician's Global Assessment

The sPGA is the physician's global assessment of the patient's psoriasis lesions 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).

9.1.1.2. Psoriasis Area and Severity Index

The PASI is an accepted primary efficacy measurement for this phase of development of psoriasis treatments (EMA 2004). The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of scaling, redness, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials (EMA 2004; Menter et al. 2008). 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 (HRQoL) (Puig 2015).

9.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments will include the following:

9.1.2.1. Static Physician's Global Assessment

Both sPGA (0) and sPGA (0,1) will be assessed at various time points up to Week 52. For assessment description, see Section 9.1.1.1.

9.1.2.2. Psoriasis Area and Severity Index

PASI 75, PASI 90, and PASI 100 will be assessed at various time points up to Week 52. PASI 75, 90, and 100 are the percentage improvements in PASI (75%, 90%, and 100%, respectively). For assessment description, see Section 9.1.1.2.

9.1.2.3. Body Surface Area

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 2016).

9.1.2.4. Nail Psoriasis Severity Index

The Nail Psoriasis Severity Index (NAPSI) is used to evaluate the severity of fingernail bed psoriasis and fingernail matrix psoriasis by area of involvement in the fingernail unit. In this study, only fingernail involvement will be assessed. The fingernail is divided with imaginary horizontal and longitudinal lines into quadrants. Each fingernail is given a score for fingernail bed psoriasis (0 to 4) and fingernail matrix psoriasis (0 to 4) depending on the presence (score of 1) or absence (score of 0) of any of the features of fingernail bed and fingernail matrix psoriasis in each quadrant. The NAPSI score of a fingernail is the sum of scores in fingernail bed and fingernail matrix from each quadrant (maximum of 8). Each fingernail is evaluated, and the sum of all the fingernails is the total NAPSI score (range, 0 to 80).

9.1.2.5. Psoriasis Scalp Severity Index

The Psoriasis Scalp Severity Index (PSSI) measures the affected scalp area and the severity of clinical symptoms. The PSSI is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range, 0 to 72). Higher scores indicate worse severity (Thaçi et al. 2015).

9.1.2.6. Palmoplantar Psoriasis Severity Index

The Palmoplantar Psoriasis Severity Index (PPASI) is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement (range, 0 to 72).

9.1.2.7. Health Outcomes Assessments

The following patient-reported questionnaires will be administered according to the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. These assessments should be completed before administration of investigational product; before the patient's clinical examination; before the patient receives any tests or results; and before the patient's health, health data, or emotions are discussed.

9.1.2.7.1. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated, dermatology-specific, patient-reported measure that evaluates a patient's HRQoL. This questionnaire has 10 items that are grouped into 6 domains, namely symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last

week" Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as "0." The total score ranges from 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008). A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL, and a 5-point change from baseline is considered as the minimal clinically important difference (MCID) threshold (Khilji et al. 2002; Hongbo et al. 2005).

9.1.2.7.2. European Quality of Life–5 Dimensions–5 Levels–Psoriasis

The European Quality of Life–5 dimensions–5 levels (EQ–5D–5L) questionnaire is a widely used, generic questionnaire that assesses health status (EuroQol Group 1990; Herdman et al. 2011). The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems. This part of the EQ–5D–5L can be used to generate a health state index. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility. The second part of the questionnaire consists of a visual analog scale on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The study will use the EQ–5D–5L–Psoriasis (EQ–5D–5L–PSO), which is a version of the EQ–5D–5L with two additional items related to psoriasis: skin irritation and self-confidence (Swinburn et al. 2013).

9.1.2.7.3. Work Productivity and Activity Impairment Questionnaire: Psoriasis

The Work Productivity and Activity Impairment-Psoriasis (WPAI-PSO) Questionnaire is a patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (psoriasis). It contains 6 items that measure: 1) employment status, 2) hours missed from work due to the psoriasis, 3) hours missed from work for other reasons, 4) hours actually worked, 5) degree of health affected-productivity while working, and 6) degree of health affected-productivity in regular unpaid activities. Four scores are calculated from the responses to these 6 items: absenteeism, presenteeism, work productivity loss, and activity impairment. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher numbers indicating greater impairment and less productivity, that is, worse outcomes.

9.1.2.7.4. Psoriasis Symptoms Scale

The Psoriasis Symptoms Scale (PSS) is a patient-administered assessment of 4 symptoms (itch, pain, stinging, and burning); 3 signs (redness, scaling, and cracking); and 1 item on discomfort related to symptoms/signs. Respondents are asked to answer the questions based on their psoriasis symptoms.

The overall severity for each individual symptom/sign from the patient's psoriasis is indicated by selecting the number from a numeric rating scale (NRS) of 0 to 10 that best describes the worst level of each symptom/sign in the past 24 hours, where 0=no symptom/sign and 10=worst imaginable symptom/sign.

The symptom severity scores, ranging from 0 to 10, are the values of the selected numbers indicated by the patient on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, stinging, burning, redness, scaling, cracking, and discomfort. In addition, a symptoms score ranging from 0 (no symptoms) to 40 (worst imaginable symptoms), and a signs score of 0 (no signs) to 30 (worst imaginable signs) will be reported.

9.1.2.7.5. Medical Outcomes Study 36-Item Short-Form Health Survey

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF 36) is a patient-reported, generic, HRQoL instrument originally published in 1992, with some item wordings and response options revised in 2000 (Ware and Sherbourne 1992; Ware 2000). It consists of 36 questions measuring 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. The patient's responses are solicited using Likert scales that vary in length, with 3–6 response options per item. The SF-36 can be scored into the 8 health domains named above and two overall summary scores: physical component summary (PCS) and mental component summary (MCS) scores. The domain and summary scores range from 0 to 100; higher scores indicate better levels of function and/or better health. The SF-36 version 2 (acute version) will be used, which utilizes the recall period of "the past week" (Ware 2000).

9.1.2.7.6. 16-Item Quick Inventory of Depressive Symptomatology-Self Report

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 (DSM-V) (American Psychiatric Association 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.

This instrument will also be used for AE monitoring (see Section 9.2.2).

9.1.2.7.7. Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a self-administered 9-item measure to evaluate patient treatment satisfaction with medication in the domains of effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). The recall period is the last 2-3 weeks or since the medication was last taken. Item formats include both a 1- to 7-point and a 1- to 5-point Likert scale. Higher scores indicate greater satisfaction (Bharmal et al. 2009).

9.1.2.7.8. Patient's Global Assessment of Psoriasis

The Patient's Global Assessment of Psoriasis (PatGA) is a patient-reported, single-item scale on which patients are asked to rank, by selecting a number on a 0 to 5 NRS, the severity of their psoriasis "today," from 0 (clear/no psoriasis) to 5 (severe).

9.1.3. Appropriateness of Assessments

The clinical safety parameters in this study are standard elements of clinical health assessment and Phase 3 drug development. The disease activity and health outcome measurements are used both in clinical practice and psoriasis clinical trials. Psoriasis is associated with numerous skin-based symptoms and HRQoL impairment, which justifies the use of the psoriasis symptom severity, as well as dermatologic and generic HRQoL assessments used in this study (EMA 2004; Kimball et al. 2005).

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.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

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. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

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

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

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions 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, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- When a condition related to the prefilled syringes 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.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the Sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF but prior to receiving investigational product, the SAE should be reported to the Sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient disposition CRF 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.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Event Monitoring with a Systematic Questionnaire

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 C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. 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.

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 at every visit with the administration of the C-SSRS and the Self-Harm Supplement Form. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events 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 QIDS-SR16 instrument (for description, see Section 9.1.2.7.6) will be used to collect patient-reported data on signs and symptoms related to depression.

9.2.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs which the Sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. The AESIs for this study are defined in the statistical analysis plan (SAP), and may include, but not be limited to the following:

- Infections, including opportunistic infections
- Hypersensitivity events, including anaphylaxis
- Injection site events
- Cerebro-cardiovascular events
- Malignancies
- Depression, or suicidal ideation or behaviors
- Hepatic AEs.

For some AESIs, sites should provide additional information regarding the event, as instructed on the eCRF.

Infections, Including Opportunistic Infections

Drugs that modulate the immune system may increase the risk of infection, including serious or opportunistic infections.

Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015). Examples are listed in Appendix 4.

Hypersensitivity Events

Site personnel should educate patients and/or caregivers about the symptoms and signs of hypersensitivity events and provide instructions on dealing with these events. A blood sample will be collected when possible for any patient who experiences an AE of hypersensitivity during the study.

Cerebro-Cardiovascular Adjudication

Data collected regarding a potential or actual cerebro-cardiovascular AE will be provided to, and adjudicated by, an independent, external adjudication committee. The role of the committee is to adjudicate the reported cardiovascular AEs in a blinded, consistent, and unbiased manner throughout the course of the study, thereby ensuring that all such reported events are evaluated uniformly.

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

- Complaints must be reported by site staff within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Investigational product should be retained under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly or its designee.
- Product complaints for non-Lilly products (including concomitant drugs) that do not have a Lilly Product Batch or Control number are reported directly to the manufacturer per product label.
- Instructions outlined in the Product Complaint Form should be followed for other reporting requirements.

9.3. Treatment of Overdose

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

9.4. Safety

9.4.1. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations and read locally for evaluation of study eligibility and safety monitoring.

Patients should be supine for approximately 5 to 10 minutes before ECG collection, and remain supine but awake during ECG collection. Sitting BP, temperature, and pulse (see Section 9.4.2) should be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the preferred order of completion should be as follows: ECG, vital signs, and then blood sampling.

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

9.4.2. Vital Signs

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

Sitting vital signs (BP, temperature, and pulse) will be measured after resting for a minimum of 10 minutes at times indicated in the Schedule of Activities (Section 2), and prior to blood sampling or administration of the investigational product.

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

9.4.2.1. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 2]; 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 8.1.2) and/or the introduction of antihypertensive agent(s) as medically appropriate.

9.4.3. Laboratory Tests

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

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

9.4.3.1. Pregnancy Testing

Pregnancy testing is to be performed only on women of childbearing potential.

Serum pregnancy test will be done at screening only and will be performed centrally. Patients determined to be pregnant will be excluded from the study.

Patients will undergo urine pregnancy testing at the clinic during designated scheduled visits (see Section 2), which will be performed locally. Result will be read prior to administration of the investigational product. The urine pregnancy test at Week 0 must be performed within 24 hours prior to exposure to the investigational product.

Urine pregnancy testing may be performed at additional time points during the treatment period and/or follow-up period, at the discretion of the investigator or if this is required by local regulations. Patients determined to be pregnant will be discontinued from the study.

If a urine pregnancy test is not available, a serum pregnancy test is an acceptable alternative.

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 blood sample for PK analysis will be collected at the same time points. All samples for immunogenicity should be taken predose when applicable. With reports of hypersensitivity events (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 resolution of the event. Samples will be evaluated for PK, anti-drug antibodies (ADAs), CCI [redacted] Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of mirikizumab at a laboratory approved by the Sponsor. Patient samples will be analyzed using a 4-tiered approach. All samples will be assessed in Tier 1 (screening). Samples above the disease state screening assay cut point factor (Tier 1) will be assessed in Tier 2 (confirmation). Any samples confirmed as positive for anti-mirikizumab antibodies in Tier 2 will be reported as "detected." All samples below the screening assay cut point factor in Tier 1 or not confirmed in Tier 2 will be reported as "not detected." Any "detected" sample in Tier 2 will be assessed in Tier 3 (titer assessment; values reported) and Tier 4 (neutralizing ADA assay). Any samples above the disease state Tier 4 cut point will be reported as "detected" for neutralizing antibodies; samples below the disease state Tier 4 cut point will be reported as "not detected" for neutralizing antibodies.

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

9.4.5. Other Tests

9.4.5.1. Physical Examination

Physical examination will be performed as specified in the Schedule of Activities (Section 2). One complete physical examination (excluding pelvic or rectal examinations), which includes heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas), will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation, as well as examination of heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas).

9.4.5.2. Tuberculosis Screening

Screening:

Screening for active or latent TB (LTBI) will include a history, physical examination (Section 9.4.5.1), chest x-ray (Section 9.4.5.3), and, except as noted below under "Prior

Treatment for LTBI or TB," testing by an interferon-γ release assay (IGRA; QuantiFERON®-TB Gold or T-SPOT.TB®) or a purified protein derivative (PPD) tuberculin skin test.

In people aged 5 years and over, IGRA is the preferred screening test for LTBI. In countries where the PPD is available and is preferred (in the judgment of the investigator) as an alternative screening test for LTBI, that test may be used instead of an IGRA.

Patients with documentation of a negative IGRA or PPD within 3 months before initial screening may not need to repeat TB testing at screening, based on the judgment of the investigator. Source documentation must include the original laboratory report (for IGRA) or a record of the size in millimeters of the induration response (for PPD). A PPD recorded as negative without documenting the size of induration in millimeters, will not be acceptable and will require a retest.

Monitoring:

After initial screening, tuberculosis testing will only be required based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and according to local regulations and/or local standard of care. Such clinical assessments should be conducted periodically, at least every 4 months.

Interpretation of Screening Tests for LTBI

The QuantiFERON-TB Gold assay will be reported as negative, indeterminate, or positive. The T-SPOT.TB assay will be reported as negative, borderline, or positive.

A positive PPD is indicated with a skin test response ≥5 mm of induration, documented between approximately 48 and 72 hours after test application (regardless of BCG vaccination history). Patients who do not return within 48 to 72 hours of test administration will be required to have the test repeated and then interpreted within this time frame.

Patients with a diagnosis of LTBI, based on a positive IGRA test result or a positive PPD response ≥5 mm of induration and no evidence of active TB, may be rescreened once after they meet the following requirements:

- Have received at least 4 weeks of appropriate ongoing prophylactic therapy for LTBI as per local standard of care, and
- Have no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2x ULN) upon retesting of serum ALT and AST levels before randomization.

Such patients must continue and complete appropriate LTBI therapy during the course of the study to remain eligible and must continue to meet all other inclusion and exclusion criteria for participation.

Re-Testing and Confirmatory Testing

One retest is allowed for patients with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT.TB assay. Patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT.TB assays will be excluded.

Confirmatory testing with an IGRA is allowed for selected patients who have a positive QuantiFERON-TB Gold assay, positive T-SPOT.TB assay, or positive PPD, who meet all of the following criteria and are assessed and documented by the investigator as likely to have a false-positive test result: no risk factors for LTBI, no risk factors for increased likelihood of progressing from LTBI to active TB, and have never resided in a high-burden country (detailed in Appendix 5). If the confirmatory test is positive, the patient will be excluded from the study unless they complete at least 4 weeks of appropriate therapy for LTBI, based on national or international guidelines (as defined above), have no evidence of hepatotoxicity (ALT and AST levels must remain ≤2x ULN) upon retesting of serum ALT and AST levels after at least 4 weeks of LTBI treatment. Such patients must continue and complete appropriate full course of LTBI therapy during the course of the study to remain eligible to participate. If the confirmatory test is negative, these results will be discussed with the medical monitor in order to determine eligibility for the study.

Diagnosis of LTBI During Study

Patients diagnosed with LTBI during the study will temporarily discontinue the investigational product and will be offered treatment by the referring physician. These patients can be considered for resumption of investigational product after completing the first 4 weeks of appropriate treatment and no evidence of treatment hepatotoxicity, as described above. These patients must continue and complete a full course of treatment for LTBI in order to continue on investigational product.

Prior Treatment for LTBI or TB

Patients who have a documented history of completing an appropriate TB prophylaxis or treatment regimen (consistent with World Health Organization and/or United States Centers for Disease Control at the time of treatment), with no history of re-exposure since their treatments were completed and no evidence of active TB, are eligible to participate in the study; these patients should not undergo TB testing unless advised to do so based on local guidelines.

Active TB

Patients diagnosed with active TB at screening will be excluded.

Patients diagnosed with active TB during the study will be discontinued and should be referred for appropriate treatment.

9.4.5.3. Chest Radiography

Posterior-anterior (PA) chest x-ray (CXR) will be obtained at screening (Visit 1) unless, in the opinion of the investigator or based on local standard of care, both PA and lateral views are indicated.

A CXR does not have to be performed if the patient has had a CXR that is sufficient for TB evaluation according to local standard of care within 3 months of screening, and the CXR film(s) or a radiology report is available to the investigator for review.

9.4.5.4. Hepatitis B Screening

Patients who test HBsAg+, test HBcAb+ in conjunction with positive confirmatory HBV DNA test, or have positive HBV DNA test, regardless of HBsAb status, at screening will be excluded.

Any enrolled patient who is HBcAb+ will undergo periodic monitoring of HBV DNA as per the Schedule of Activities (Section 2).

In addition to the above, any enrolled patient who is HBcAb+ and who experiences an elevated ALT or AST level >3x ULN must undergo HBV DNA testing. If the HBV DNA test is negative, the investigator should consult with the Lilly-designated medical monitor regarding further management of the patient.

If the result of the HBV DNA test is positive but below quantification, study drug should be withheld and a repeat test done immediately. The Lilly-designated medical monitor should be contacted regarding study status of the patient. If the result of the HBV DNA test is positive and quantifiable, the patient must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted, and the patient should potentially be started on antiviral therapy prior to discontinuation of any immunosuppressant therapy (including study drug). Timing of discontinuation from the study treatment, the study, and of any immunosuppressant therapy (including study drug) needs to be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

9.4.5.5. Hepatitis C Screening

Patients who test positive for HCV antibody and have a positive confirmatory HCV RNA test at screening will be excluded.

Patients with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virologic response may be eligible for inclusion in the study, provided they have no detectable RNA on the screening HCV RNA test for this protocol. A sustained virologic response is defined as an undetectable HCV RNA level, 12 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as (i) a positive HCV antibody test and (ii) a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study.

Any patient with a history of HCV infection who develops elevated ALT >3xULN will be tested for HCV RNA.

Anyone diagnosed with hepatitis C during the study will be discontinued from the study and should receive appropriate follow-up medical care.

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, members of the DMC, consisting of members external to Lilly (see Section 10.3.8), and/or the Lilly Global Patient Safety (GPS) Safety Internal Review Committee (SIRC), consisting of GPS reviewers outside the study team, when appropriate, can view unblinded data and conduct additional analyses of the unblinded safety data. The SIRC and the GPS expedited reporting team can also unblind at the individual SAE case level, when appropriate.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3x ULN, ALP ≥2x ULN, or elevated TBL ≥2x ULN, liver testing (Appendix 6) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine 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 and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

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

- Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests
- Elevated serum TBL to ≥2x ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE

9.5. Pharmacokinetics

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

Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

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

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole 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 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 investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits. 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 becomes 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, and candidate gene studies. Regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

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9.9. Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 500 patients will be randomized at a 4:1 ratio in the blinded Induction Period to receive 250 mg mirikizumab or placebo SC at Weeks 0, 4, 8, and 12. Stratified block randomization will be performed with the following stratification factors: previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other).

There are multiple primary endpoints in this study: sPGA (0,1) and PASI 90 at Week 16. The assumed sPGA (0,1) responses are 70% for the mirikizumab arm and 5% for the placebo arm. The assumed PASI 90 responses are 70% for the mirikizumab arm and 3% for the placebo arm. These assumptions are based upon the results of the mirikizumab Phase 2 Study AMAF (Reich et al. 2017b) and review of historical clinical studies in psoriasis (Langley et al. 2014; Gordon et al. 2016; Blauvelt et al. 2017; Papp et al. 2017; Reich et al. 2017a).

With a total sample size of 500 patients, randomizing 400 patients to the mirikizumab arm and 100 patients to the placebo arm, this study has power of >95% for testing superiority of mirikizumab to placebo based on a 2-sided chi-square test with alpha of 5% on sPGA(0,1). It also provides a power of >95% for testing superiority of mirikizumab to placebo on PASI 90 based on a 2-sided chi-square test with alpha of 5%.

In order to account for multiple testing for the comparisons of 2 mirikizumab groups against the placebo group in the Maintenance Period, a 2-sided chi-square test at the 0.025 level is assumed. Assuming 70% of the mirikizumab patients are re-randomized in the Maintenance Period at Week 16 (Visit 7) at a 1:1:1 ratio to 250 mg mirikizumab Q8W, 125 mg mirikizumab Q8W or placebo, approximately 93 patients will be included in each treatment group. Stratified block randomization will be performed with the stratification factor of body weight at baseline (<100 kg or ≥100 kg). This sample size will provide >95% power to test the difference in the proportion of patients maintaining PASI 90 from Week 16 (Visit 7) after re-randomization at the start of the Maintenance Dosing Period to Week 52 (Visit 16) between each mirikizumab dosing interval and placebo, assuming the proportions of patients maintaining PASI 90 are 80% for 250 mg mirikizumab Q8W, 70% for 125 mg mirikizumab Q8W, and 10% for placebo.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Induction ITT	All randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned. Unless otherwise noted, efficacy and health outcomes analyses for the Induction Period will be conducted on this population.
Induction Safety	All randomized patients who received at least 1 dose of the study treatment. Patients will be analyzed according to the treatment to which they were assigned. Safety analyses for the Induction Period will be conducted on this population.
Re-randomized Maintenance ITT	All ITT patients who received at least 1 induction dose of the study treatment and have been re-randomized at Week 16. Efficacy and health outcomes analyses for the Maintenance Period will be conducted on this population.
Re-randomized Maintenance Safety	All ITT patients who received at least 1 induction dose of the study treatment, have been re-randomized at Week 16, and have received at least 1 maintenance dose. Safety analyses for the Maintenance Period will be conducted on this population.

Abbreviation: ITT = intent-to-treat.

Additional analysis populations will be described in the SAP as deemed appropriate.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Efficacy analysis for induction outcomes will be conducted on the Induction intent-to-treat (ITT) population, while efficacy analysis for the maintenance outcomes will be conduction on the re-randomized maintenance population as defined in Section 10.2. The induction and maintenance safety analysis will be performed on the induction safety and re-randomized maintenance safety populations, respectively. Additional safety and efficacy analysis of the patients who are not re-randomized for the maintenance portion of the study will be defined in the SAP.

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages. Unless otherwise specified, all hypothesis tests will be 2-sided with alpha of 0.05. Multiple testing will be controlled as described in Section 10.3.1.2.

Unless otherwise specified, baseline for efficacy and health outcomes endpoints during both the Induction and Maintenance Periods will be defined as the last available value before the initial randomization during the Induction Period, which in most cases will be the measure recorded at Week 0 (Visit 2). Detailed definitions of baseline for safety-related analyses will be described in the SAP.

Unless otherwise specified, the statistical analysis models for the Induction Period will adjust for the covariates: previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other). Similarly, unless otherwise specified, the statistical analysis models for the Maintenance Period will adjust for the covariate body weight (<100 kg or ≥100 kg).

For assessments of the primary endpoints and other categorical efficacy and health outcomes endpoints, the Cochran–Mantel–Haenszel (CMH) chi-square test will be used to compare the treatment groups with the stratification factors mentioned above. The CMH chi-square p-value will be provided. In addition, the absolute treatment difference in proportions will be provided along with the 95% 2-sided confidence interval estimate.

Treatment comparisons of continuous efficacy and health outcome variables with multiple post-baseline measurements will be made using mixed-effects model for repeated measures (MMRM). When MMRM is used, the model includes treatment, baseline value, visit, the interaction of treatment-by-visit as fixed factors, and the induction/maintenance covariates mentioned above. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least squares means will be used for the statistical comparison; the 95% confidence interval will also be reported.

Treatment comparisons of continuous efficacy and health outcome variables with a single post-baseline time point will be made using analysis of covariance (ANCOVA) with the following in the model: treatment group, baseline value, and Induction Period/Maintenance Period covariates mentioned above. Type III tests for least-square (LS) means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% confidence interval, unless otherwise specified, will also be reported. Missing data imputation method for ANCOVA model will be specified in the SAP.

Fisher's exact test will be used for categorical safety data including AEs, unless otherwise specified. Continuous safety data including vital sign and laboratory values will be analyzed using ANCOVA with treatment and baseline value in the model, unless otherwise specified. Also, laboratory analytes will be presented as mean changes from baseline and as incidence of shift between normal and abnormal states.

10.3.1.1. Missing Data Imputation

The following methods for imputation of missing data will be used:

- *Non-Responder Imputation (NRI) for Binary Clinical Response:* Patients will be considered non-responders for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized subjects without at least 1 postbaseline observation will also be defined as non-responders for the NRI analysis.
- *Mixed-Effects Model for Repeated Measures (MMRM):* It will be the primary analysis method for longitudinal continuous measurements. It assumes missing at random and the bias caused by missing data can be attenuated by modelling random effects using the within-patient error correlation structure.

Additional missing data imputation methodologies, for example, modified baseline observation carried forward (mBOCF), may be considered as sensitivity analyses and will be detailed in the SAP. By using mBOCF, for patients discontinuing study treatment due to an AE, the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation.

10.3.1.2. Multiple Comparisons/Multiplicity

The prespecified graphical multiple testing approach (Bretz et al. 2011) will be implemented to control the overall Type I error rate at 2-sided alpha of 0.05, for the hypotheses for the primary and major secondary endpoints. The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Alosh et al. 2014).

The Week 16 endpoints of sPGA (0,1) and PASI 90 represent a primary endpoint family. The graphical testing scheme will sequentially test sPGA (0,1) first, followed by PASI 90 before proceeding to test the major secondary endpoints. Details of the specific graphical testing scheme (including testing order, interrelationships, Type I error allocation for the major secondary endpoints, and the associated propagation) will be pre-specified in the SAPs prior to the first unblinded analysis.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

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

Patient disposition will be summarized for each treatment period. Reasons for discontinuation from the study will be summarized.

10.3.2.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include gender, age, age category, weight, race, geographic region, baseline disease severity, duration of disease, prior exposure to biologic therapy, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical measurements will include sPGA score, PASI score, BSA, PSSI, PSS symptom and sign scores, PatGA, DLQI total score, SF-36 (PCS), and SF-36 (MCS).

10.3.2.3. Concomitant Therapy

Previous and concomitant medications will be summarized for patients who enter each treatment period and will be presented using the latest version of the World Health Organization (WHO) drug dictionary.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who enter the Induction and Maintenance Periods. A patient will be considered as having missed the visit if he or she fails to attend for administration of the investigational product within the required treatment window as defined in the Schedule of Activities (Section 2). Overall compliance with therapy is defined to be missing no more than 20% of the expected doses within the protocol-defined dosing interval and not missing 2 consecutive doses. The proportion of patients who demonstrate overall compliance during the Induction Period will be compared between treatment groups using Fisher's exact test.

10.3.3. Efficacy Analyses

Primary and secondary analyses will be based on the Induction ITT population and Maintenance ITT population as defined in Section 10.2.

10.3.3.1. Primary Analyses

Treatment comparisons between mirikizumab and placebo in the proportion of patients achieving sPGA (0,1) with at least a 2-point improvement from baseline at Week 16 will be analyzed using the CMH method with NRI as described in Section 10.3.1. Also, treatment comparisons between mirikizumab and placebo in the proportion of patients achieving PASI 90 at Week 16 will be analyzed using the CMH method with NRI as described in Section 10.3.1.

10.3.3.2. Secondary Analyses

Protocol-defined secondary efficacy and health outcome endpoints of the trial are presented in Table AMAK.2. Details of the analysis methods that will be utilized are provided in Section 10.3.1. As noted in Section 10.3.1.2, our graphical testing approach to multiplicity control will require both primary endpoints to be successful before proceeding to the major secondary endpoints.

Additional analyses of secondary efficacy and health outcome endpoints may be considered and will be fully detailed in the SAP. Additional endpoints may be pre-specified in the SAP.

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10.3.4. Safety Analyses

Safety assessments will include AEs, SAEs, AESIs, laboratory analytes, vital signs, QIDS-SR16, and C-SSRS.

The Induction Period safety analyses will compare mirikizumab to placebo using the methods described in Section 10.3.1. The Maintenance Period safety analyses will summarize safety measures by treatment.

Adverse events will be coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarized by system organ class, preferred term, severity, and relationship to investigational product. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. For each event classification term, the number of patients experiencing a TEAE with that classification term will be tabulated.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. If a patient reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the most related of those events will be included in the summary tables of treatment-related events. For events that are gender specific, the denominator and computation of the percentage will only include patients from the given gender.

Adverse events of special interest are defined in Section 9.2.3 and the analysis plan will be described in the Program Safety Analysis Plan and SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

The PK of mirikizumab will be characterized using visualization/graphical evaluations and mixed-effect (population PK) modeling approaches. Various structural and error models will be evaluated. Intrinsic factors (such as age, body weight, gender, immunogenicity) and extrinsic factors (such as co-medications) will be investigated to assess their influence on model parameters. Model evaluation will include a visual predictive check. Estimates of PK model parameters and covariate effects and corresponding 90% confidence intervals will be reported.

Analyses of exposure-response relationships will be conducted using both exploratory visualization/graphical approaches and model-based approaches. Exploratory visualization/graphical analysis approaches for categorical clinical endpoints (for example, PASI 90, sPGA [0,1]) may consist of graphs showing the percentage of patients who achieve the clinical endpoint at different percentiles (for example, quartiles) of exposure of mirikizumab at Weeks 16 and 52. Measures of exposure may include population PK estimated average concentrations (C_{avg}), or estimated or observed trough concentrations at the time of the clinical endpoint. Model-based analyses of the binary clinical endpoints will utilize population exposure-response logistic regression models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to the probability of achieving the endpoint. These models may be used to evaluate patient factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure-response models

for PASI scores or response rates may be developed, which relate the time course and magnitude of mirikizumab exposure to the time course and magnitude of the PASI response.

Additional analyses may be conducted, if they are deemed appropriate. Data from this study may be combined with other study data, if appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of patients with pre-existing (baseline) ADA, ADA at any time post baseline, and with treatment-emergent ADA (TE-ADA) to mirikizumab will be tabulated. The frequency of neutralizing antibodies will also be tabulated.

The relationship between the presence of antibodies and the PK parameters and PD response, including safety and efficacy to mirikizumab, will be assessed.

10.3.7. Other Analyses

10.3.7.2. Psoriasis Symptoms Scale Psychometric Analysis

Psychometric analysis of PSS will be defined in a separate health outcomes SAP. The analyses will evaluate the validity, responsiveness, and interpretability of the PSS.

10.3.8. Interim Analyses

One DMC consisting of members external to Lilly will be established for interim safety monitoring across all Phase 3 trials in patients with psoriasis. This committee will consist of a minimum of 3 members, including a physician with expertise in dermatology and a statistician. No member of the DMC may have contact with study sites. A Statistical Analysis Center (SAC) will prepare and provide unblinded safety data to the DMC. The SAC members may be Lilly employees or from third-party organizations designated by Lilly. However, they will be external to the study team and will have no contact with sites and no privileges to influence change in the ongoing study. Access to the unblinded safety data will be limited to the DMC and the SAC or their designees. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded data. The purpose of the DMC is to advise Lilly regarding continuing patient safety; however, the DMC may request key efficacy data to put safety observations into context and to confirm a reasonable benefit/risk profile for ongoing patients in the study. Hence, there will be no alpha adjustment for these interim assessments. Study sites will receive information about interim assessments ONLY if they need to know for the safety of their patients. This committee will make recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue a treatment group, or discontinue the study. Details outlining the roles and responsibilities of the DMC will be finalized in the DMC charter and an associated DMC analysis plan prior to the first unblinded assessment.

In addition to the DMC interim assessments for safety, a limited number of Lilly employees or their designees *not in direct contact with the clinical sites* will be provided access to the data from this study once all randomized patients either complete the assessments for primary endpoints at Week 16 (Visit 7) or discontinue from the study. The purpose of providing this access to a small group is to initiate work related to regulatory submission upon completion of the study. The study will not be terminated prematurely on the basis of either efficacy or futility following the Week 16 interim analysis. Although this is an interim analysis with respect to the entire study, it is the only and final analysis for the primary endpoint. Therefore, no alpha adjustment for this interim analysis is planned.

In addition, a limited number of pre-identified internal Lilly personnel that are not in contact with clinical sites may gain access to unblinded PK data, as specified in the unblinding plan, prior to final database lock, in order to initiate the final population PK model development processes. Unblinding details will be provided in the unblinding plan.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AIDS	acquired immune deficiency syndrome
ADA	anti-drug 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 adverse event 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.
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the Sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BCG	Bacillus Calmette-Guerin
BP	blood pressure
BSA	body surface area
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form

CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CXR	chest x-ray
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
eCRF	electronic case report form
EMA	European Medicines Agency
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the 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.
EQ-5D-5L-PSO	European Quality of Life–5 Dimensions–5 Levels–Psoriasis
ERB	Ethical Review Board
ETV	early termination visit
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPS	Global Patient Safety
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGRA	interferon-γ release assay
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IL-23	interleukin-23
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
INR	international normalized ratio
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
LTBI	latent tuberculosis infection
LS	least-squares
mBOCF	modified baseline observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary of the SF-36
medical monitor	Individual responsible for the medical conduct of the study. Responsibilities of the medical monitor may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures

MOS	margin of safety
NAPSI	Nail Psoriasis Severity Index
NOAEL	no-observed-adverse-effect-level
NRI	non-responder imputation
NRS	numeric rating scale
PA	posterior-anterior (chest x-ray)
PASI	Psoriasis Area and Severity Index
PatGA	Patient's Global Assessment of Psoriasis
PCS	physical component summary of the SF-36
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PK/PD	pharmacokinetics/pharmacodynamics
PPASI	Palmoplantar Psoriasis Severity Index
PPD	purified protein derivative (skin test)
PSS	Psoriasis Symptoms Scale
PSSI	Psoriasis Scalp Severity Index
PUVA	psoralen and ultraviolet A
Q4W	every 4 weeks
Q8W	every 8 weeks
QIDS-SR16	16-item Quick Inventory of Depressive Symptomatology
RNA	ribonucleic acid
SAC	Statistical Analysis Center
SAP	statistical analysis plan
SC	subcutaneous
SAE	serious adverse event
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.
SF-36	Medical Outcomes Study 36-item Short-Form Health Survey

SIRC	Safety Internal Review Committee
sPGA	static Physician's Global Assessment
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TE-ADA	treatment-emergent anti-drug antibody
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
Th	T helper
TNF	tumor necrosis factor
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WPAI-PSO	Work Productivity and Activity Impairment Questionnaire: Psoriasis

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical (Serum) Chemistry**[a]	**Other**
Hemoglobin	**Serum Concentrations of:**	Human immunodeficiency virus (HIV)[b]
Hematocrit	Sodium	Hepatitis B surface antigen (HBsAg)[b]
Erythrocyte count (RBC)	Potassium	Hepatitis B core antibody (HBcAb)[b]
Mean cell volume	Total bilirubin	Hepatitis B surface antibody (HBsAb)[b]
Mean cell hemoglobin	Total protein	HBV DNA test[c]
Mean cell hemoglobin concentration	Direct bilirubin	Hepatitis C antibody[b]
Leukocytes (WBC)	Alkaline phosphatase (ALP)	HCV RNA test[c]
Cell morphology	Alanine aminotransferase (ALT)	Pregnancy Test (females only)
Absolute Counts and Percentage of:	Aspartate aminotransferase (AST)	Serum[b]
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)	Urine (assayed locally by clinical study site)
Lymphocytes	Blood urea nitrogen (BUN)	Follicle-stimulating hormone (FSH)[b]
Monocytes	Creatinine	PPD or QuantiFERON-TB Gold test or T-SPOT.TB test[d]
Eosinophils	Uric acid	Exploratory storage samples (DNA)
Basophils	Calcium	Exploratory storage samples (serum, plasma, whole blood, RNA)
Absolute Counts of:	Glucose	Anti-mirikizumab antibodies (immunogenicity)[a]
Platelets	Albumin	Serum mirikizumab concentration (PK)[a]
	Cholesterol (total)	Tryptase[a]
	Triglycerides	Complement panel (C3 and C4)[a]

Urinalysis	Creatine kinase (CK)	Cytokine panel[a]
Specific gravity		High-sensitivity C-reactive protein (hsCRP)
pH	Lipid Panel (fasting)	
Protein	Low-density lipoprotein (LDL)	
Glucose	High-density lipoprotein (HDL)	
Ketones	Very-low-density lipoprotein (VLDL)	
Bilirubin		
Urobilinogen		
Blood		
Nitrite		
Urine leukocyte esterase		
Microscopic examination of sediment		

Abbreviations: DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic(s); PPD = purified protein derivative (skin test); RBC = red blood cells; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cells.

[a] Unscheduled hematology or blood chemistry panels may be performed at the discretion of the investigator. If a patient develops an acute hypersensitivity event after administration of IP, blood samples will be collected for pharmacokinetic, immunogenicity, and exploratory hypersensitivity analyses.

[b] Performed at screening only.

[c] Following screening, patients will not undergo monitoring for Hepatitis C unless liver enzymes are elevated. Hepatitis B monitoring will be performed at protocol-specified intervals in patients who test positive for anti-hepatitis B core antibody.

[d] TB testing will be performed locally using an interferon-γ release assay (IGRA, for example QuantiFERON®-TB Gold or T-SPOT.TB) or a PPD tuberculin skin test. If PPD test is performed, patients will return 2 to 3 days afterwards to have their PPD test read.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. 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.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an 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, including any changes made by the ERBs, 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 protocol and related amendments and addenda, current IB and updates during the course of the study
- Informed consent form
- Other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in dermatology or other relevant specialties with appropriate experience in diagnosis and treatment of patients with psoriasis will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The Sponsor's responsible medical officer and statistician 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.

Appendix 3.1.7. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR 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 CSR coordinating investigator will be selected by the Sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Appendix 3.2. 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
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.

- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate CRF data and 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 or its representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

An electronic case report form (eCRF) system will be used in this study. The site maintains a separate source for the data entered by the site into the Sponsor-provided eCRF system. Case report form data will be encoded and stored in a clinical trial database.

Electronic clinical outcome assessments (eCOA) measures (questionnaires, scales, self-reported diary data, etc.) will be collected by the patients and site personnel at the time that the information is obtained. In these instances, where there is no prior written or electronic source data at the site, the eCOA data record will serve as the source. The eCOA data will be stored at a third party site. Investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention. Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. 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.

Appendix 3.3.2. 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 3.4. Publication Policy

The publication policy for Study I6T-MC-AMAK is described in the letters of agreement between the Sponsor and the investigators and institutions.

Appendix 4. Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeria monocytogenes (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy (PML), John Cunningham (JC) virus [excluded from the study]
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or pharyngeal)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicillium marneffei
	Pneumocystis jirovecii (formerly *Pneumocystis carinii*)
	Sporothrix schenckii
	Other invasive fungi: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Protozoan	
	Leishmaniasis (visceral only)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only)

Source: Adapted from Winthrop et al. (2015).

This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy, for the purposes of Exclusion Criterion [16]. This list is not exhaustive. Investigators should use their clinical judgement, as well as discussion with the Lilly-designated medical monitor, in determining if other infections may be considered opportunistic, for the purposes of Exclusion Criterion [16].

Winthrop et al. (2015) consider tuberculosis (TB) and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy. See Section 9.4.5.2 for the approach to screening for latent TB infection within the study.

Appendix 5. Risk Factors for Latent Tuberculosis Infection

Risk Factors for Latent Tuberculosis Infection
Household contact or recent exposure to an active case
Mycobacterial laboratory personnel
Birth or residency in a high burden country (>20/100,000)
Residents and employees of high risk congregate settings, for example, prisons, homelessness, intravenous drug use

Source: Adapted from Horsburgh and Rubin (2011) and Lewinsohn et al. (2017).

Risk Factors for Increased Likelihood of Progression from LTBI to Active TB
Household contact or close contact with an active case
HIV
Radiographic evidence of old, healed TB that was not treated
Silicosis
Treatment with ≥15 mg prednisone (or equivalent) per day
Children <5 years of age
Chronic renal failure
Treatment with an anti-TNF antibody
Poorly controlled diabetes
Intravenous drug use
Weight ≥10% below normal
Smoking

Abbreviations: HIV = human immunodeficiency virus; LTBI = latent tuberculosis infection; TB = tuberculosis; TNF = tumor necrosis factor.

Source: Adapted from Horsburgh and Rubin (2011) and Lewinsohn et al. (2017).

World Health Organization List of High Burden Countries		
Angola	India	Peru
Azerbaijan	Indonesia	Philippines
Bangladesh	Kenya	Russian Federation
Belarus	Kazakhstan	Sierra Leone
Botswana	Democratic People's Republic of Korea	Somalia
Brazil	Kyrgyzstan	South Africa
Cambodia	Lesotho	Swaziland
Cameroon	Liberia	Tajikistan
Central African Republic	Malawi	United Republic of Tanzania
Chad	Moldova	Thailand
China	Mozambique	Uganda
Congo	Myanmar	Ukraine
Democratic Republic of the Congo	Namibia	Uzbekistan
Ethiopia	Nigeria	Vietnam
Ghana	Pakistan	Zambia
Guinea-Bissau	Papua New Guinea	Zimbabwe

Source: WHO (2015).

Appendix 6. 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 the Lilly-designated medical monitor.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Red blood cells (RBC)	Prothrombin time
White blood cells (WBC)	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	**Anti-Nuclear Antibody[a]**
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	**Alkaline Phosphatase Isoenzymes[a]**
Creatine phosphokinase (CPK)	
	Anti-Smooth Muscle Antibody (or Anti-Actin Antibody)[a]

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

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

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

Appendix 7. Protocol Amendment I6T-MC-AMAK(a) Summary A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Withdrawal Maintenance Dosing Period to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis OASIS-1

Overview

Protocol I6T-MC-AMAK (A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Withdrawal Maintenance Dosing Period to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis [OASIS-1]) 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 primary changes in this amendment are:

- The major secondary endpoint of DLQI (0,1) response at Week 16 has been revised per FDA feedback. Previously, DLQI (0,1) response was to be assessed in patients with baseline DLQI >1. Now, DLQI (0,1) response will include a 5-point reduction and be assessed in patients with baseline DLQI ≥5.
- Stricter discontinuation language for clinically significant systemic hypersensitivity events has been applied throughout the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I6T-MC-AMAK Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Global		
Global	Various typos fixed and clarifications made	
Section 1		
Section 1. Synopsis	Revised to align with changes in protocol body	
Section 2		
Section 2. Schedule of Activities	1. In header, moved line separating Induction and Maintenance to the center of Visit 7 2. Added "temp" to Vital Signs 3. Added peripheral lymph nodes examination to the physical examination 4. Added that TB testing may be performed after screening if clinically indicated 5. *If PPD test is performed, patients will return 2 to 3 days afterwards ~~Visit 1~~ to have their PPD test read.* (also amended in Appendix 2)	1. Alignment with other studies in program 2. Regulatory request from US FDA 3. New safety guideline and alignment with other studies in program 4. New patient safety guidelines 5. Allows PPD to be performed at visits other than Visit 1
Section 4		
Section 4. Objectives and Endpoints	1. Revised major secondary endpoint so that DLQI (0,1) response will include a 5-point reduction and be assessed in patients with baseline DLQI ≥5 (also included this endpoint at other times as Other Secondary endpoint) 2. Moved DLQI (0,1) response assessed in patients with baseline DLQI >1 to Other Secondary objectives 3. Changed PPASI, PSSI, and NAPSI endpoints from "percent change" to "change."	1. FDA feedback 2. As it is no longer a major secondary objective, but Lilly would still like to perform indirect and direct comparisons 3. To give flexibility to report both absolute and percentage change

Section # and Name	Description of Change	Brief Rationale
Section 5		
Section 5.1.4. Post-Treatment Follow-Up Period (12 Weeks)	Added ability for patients to receive psoriasis therapy with another agent(s)	Allow patients not receiving benefit from study drug to access other treatments more quickly
Section 6		
Section 6.1. Inclusion Criteria	Added that local contraception guidelines must be followed	Allow sites to meet local regulatory requirements
Section 7		
Section 7.7. Concomitant Therapy	1. *BCG prohibited for 12 months before baseline, live vaccinations prohibited for 12 weeks before baseline. Both are prohibited throughout the study and for ~~12 months or~~ 12 week~~s, respectively,~~ after discontinuation of study drug* 2. Added paragraph on allowed topical therapies	1. Error in original protocol 2. Clarification and alignment with other studies in program
Section 7.8.2.1. Management of Hypersensitivity Events, Including Injection Site Events	1. Added that if a patient experiences an acute hypersensitivity event after an injection of the investigational product, blood samples will be collected for PK, immunogenicity, and exploratory hypersensitivity analyses. (also amended in Appendix 2) 2. *Patients who develop clinically significant systemic hypersensitivity events following administration of investigational product~~, who do not respond to symptomatic medication, or whose event results in clinical sequelae (for example, hospitalization),~~ should be discontinued from the study.*	1. To align this section with the rest of the protocol 2. Commitment to FDA

Section # and Name	Description of Change	Brief Rationale
Section 8		
Section 8.2. Discontinuation from the Study (sixth subbullet of third bullet point)	*Clinically significant systemic hypersensitivity event following administration of investigational product ~~that does not respond to symptomatic medication or results in clinical sequelae~~.*	Commitment to FDA
Section 9		
Section 9.4.1. Electrocardiograms and Section 9.4.2. Vital Signs	Added temperature to list of vital signs	Alignment with Schedule of Activities
Section 9.4.4. Immunogenicity Assessments	Added that immunogenicity samples will be evaluated for PK, ADA, CCI [redacted]	To provide information in the event of a hypersensitivity event
Section 9.4.5.1. Physical Examination	Added peripheral lymph nodes to list for symptom-directed evaluation	New safety guideline
Section 9.4.5.2. Tuberculosis Screening	1. Added Monitoring subsection beneath the Screening subsection 2. Removed sentence "*Follow-up TB testing with IGRA or PPD, tailored in accordance with a person's risk (for example, hospital care worker, residence in a high risk location), may be performed according to local guidelines.*" 3. Added prior treatment for TB to subsection on prior treatment for LTBI	1. New safety guideline 2. Redundant with new monitoring language 3. Clarification and alignment with other studies in program
Appendices		
Appendix 2. Clinical Laboratory Tests	1. Added "Gamma-glutamyl transferase (GGT)" to list of clinical chemistry CCI [redacted]	1. Regulatory request from FDA CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Appendix 4. Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy	Removed statement that patients with any history of active TB are excluded from the study	Error in original protocol

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Section 1. Synopsis

Objective(s)/Endpoints:

Objectives	Endpoints
Major Secondary[a,b] To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline. • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in ~~those~~ patients with a baseline DLQI ~~baseline~~ total score ≥5~~>1~~
Other Secondary[b] To compare mirikizumab to placebo with respect to clinical response and time to clinical response during the induction dosing period, and with respect to patient-reported outcomes during the induction dosing period	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90. • ~~Percent c~~Change in PPASI total score in patients with palmoplantar involvement at baseline • ~~Percent c~~Change in PSSI total score in patients with scalp involvement at baseline • ~~Percent c~~Change in NAPSI total score in patients with fingernail involvement at baseline • Change from baseline on the SF-36 physical component summary (PCS) and mental component summary (MCS) • Change from baseline on PatGA of disease severity • Change from baseline for the WPAI-PSO scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) • Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = Patient's Global Assessment of Psoriasis; PCS = physical component summary; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; QIDS-SR16 =

16-item Quick Inventory of Depressive Symptomatology; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; WPAI-PSO = Work Productivity Activity Impairment Questionnaire–psoriasis.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control technique called "graphical multiple testing procedure" to control the overall family-wise Type I error rate.

[b] Note: A "clinically meaningful" response is a PASI 75 response, which represents at least a 75% decrease (improvement) from the baseline PASI score. A "high level" of clinical response is a PASI 90 response, which represents at least a 90% decrease (improvement) from baseline in PASI score, or sPGA (0,1) response, which represents an "almost clear" response. The "highest level" of clinical response is a PASI 100 or sPGA (0) response, which represents complete resolution of psoriasis.

Section 2. Schedule of Activities (overleaf)

Table AMAK.1. Schedule of Activities

Procedure[a]	Screening Period	Baseline	Induction Period				Maintenance Period										ETVs	Follow-up Period[t]	
Visit Number	V 1[b]	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16		V 801	V 802
Week	-4	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		LV +4W	LV +12W
Day with Visit Tolerance Interval	≤28 days from V2	1	15 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5		29 ± 5	~~112~~85 ± 5
Vital Signs (BP, temp, and ~~P~~pulse)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP = blood pressure; BSA = body surface area; conc = concentration; C-SSRS = Columbia–Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L-PSO = European Quality of Life–5 Dimensions–5 Levels–Psoriasis; ETV = early termination visit; FSH = follicle stimulating hormone; HBcAb = anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IL-19 = interleukin-19; IP = investigational product; LV = last study visit; miri = mirikizumab; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PatGA = Patient's Global Assessment of Psoriasis; PK = pharmacokinetic; PPASI = Palmoplantar Psoriasis Severity Index; PPD = purified protein derivative (skin test); PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; RNA = ribonucleic acid; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; Suppl. = supplement; TB = tuberculosis; temp = temperature; TSQM = Treatment Satisfaction Questionnaire for Medication; V = visit; W = weeks; WCBP = women of childbearing potential; WPAI-PSO = Work Productivity and Activity Impairment Questionnaire: Psoriasis.

a All activities should be completed prior to any study dose administration, unless otherwise stated.

b Visit 1 procedures may be conducted over more than 1 day, as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).

c One complete physical examination (excluding pelvic or rectal examinations) to include heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas) will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas).

d Sitting blood pressure, temperature, and pulse will be obtained within approximately the same time frame as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the preferred order of completion should be as follows: ECG (if applicable), vital signs, and then blood sampling.

e Chest radiography will be performed locally at screening unless it has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review). For additional details, see Section 9.4.5.3.

[f] TB testing will be performed at screening unless it has been performed within 3 months before initial screening (provided the formal report is available for the investigator's review). It may also be performed after screening if clinically indicated. TB testing will be performed locally using an interferon-γ release assay (IGRA; QuantiFERON®-TB Gold or T-SPOT.TB®) or a purified protein derivative (PPD) tuberculin skin test. If PPD test is performed, patients will return 2 to 3 days afterwards ~~Visit 1~~ to have their PPD test read. For additional details on TB testing, see Exclusion Criterion [19] and Section 9.4.5.2.

[g] The preferred order of completion is s~~S~~upine ECG~~s should preferably be completed~~ prior to vital signs, blood sampling, or any other study procedures. For additional details on ECG collection, see Section 9.4.1. ECG should be performed at the ETV and Visit 802 only if there is early termination due to a cardiovascular event.

[h] A Self-Harm Follow-Up Form is to be completed only during visits for which there is at least 1 discrete self-harm event identified on the Self-Harm Supplement Form (see Section 9.2.2).

[i] PSSI, NAPSI, and PPASI assessments are applicable only if symptoms are present at baseline.

[j] These assessments should be completed before administration of investigational product, before the patient's clinical examination, before the patient receives any tests or results, and before the patient's health, health data, or emotions are discussed.

[k] Electronic diaries will be distributed at the screening visit and collected at the Week 16 visit.

[l] Unscheduled hematology or blood chemistry panels may be performed at the discretion of the investigator.

[m] Patients should not eat or drink anything except water for 12 hours prior to sample collection.

[n] Any enrolled patient who is HBcAb+ will undergo monitoring of HBV DNA with HBV DNA testing (see Section 9.4.5.4). Any patient with a positive HBV DNA test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[o] Following screening, patients will not undergo monitoring for HCV RNA unless liver enzymes are elevated (see Section 9.4.5.5). Any patient with a positive HCV RNA test must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.

[p] Immunogenicity samples should be collected prior to dosing on visits when mirikizumab is administered. A sample will be obtained at unscheduled visits if a patient develops an acute hypersensitivity event after administration of IP (see Section 7.8.2.1).

[q] Scheduled PK samples are taken as an aliquot from the immunogenicity sample. Unscheduled PK samples, obtained if a patient develops an acute hypersensitivity event after administration of IP (see Section 7.8.2.1), will be collected in a separate tube.

[r] FSH test is to be performed at screening for women who have had spontaneous amenorrhea for 6 to 12 months to confirm lack of childbearing potential.

[s] If a patient discontinues IP early, the patient will complete the ETV and then enter the Post-Treatment Follow-up Period (V801 + V802).

[t] All patients who receive IP but do not participate in Study AMAH must enter the Follow-up Period and complete V801 + V802.

[u] Urinalysis assessed only for early termination due to an adverse event for which urinalysis is clinically indicated.

Section 4. Objectives and Endpoints

Table AMAK.2. Objectives and Endpoints

Objectives	Endpoints
Major Secondary[a,b] To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline. • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in ~~those~~ patients with a baseline DLQI ~~baseline~~ total score ≥5~~>1~~
Other Secondary[b] To compare mirikizumab to placebo with respect to clinical response and time to clinical response during the induction dosing period, and with respect to patient-reported outcomes during the induction dosing period	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90. • ~~Percent c~~Change in PPASI total score in patients with palmoplantar involvement at baseline • ~~Percent c~~Change in PSSI total score in patients with scalp involvement at baseline • ~~Percent c~~Change in NAPSI total score in patients with fingernail involvement at baseline • Change from baseline on the SF-36 physical component summary (PCS) and mental component summary (MCS) • Change from baseline on PatGA of disease severity • Change from baseline for the WPAI-PSO scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) • Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = Patient's Global Assessment of Psoriasis; PCS = physical component summary; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; TE-ADA = treatment-emergent anti-drug antibody; TEAEs = treatment-emergent adverse events; WPAI-PSO = Work Productivity Activity Impairment Questionnaire–psoriasis.

[a] All primary and major secondary endpoint analyses will utilize the multiplicity control technique called "graphical multiple testing procedure" to control the overall family-wise Type I error rate.

[b] Note: A "clinically meaningful" response is a PASI 75 response, which represents at least a 75% decrease (improvement) from the baseline PASI score. A "high level" of clinical response is a PASI 90 response, which represents at least a 90% decrease (improvement) from baseline in PASI score, or sPGA (0,1) response, which represents an "almost clear" response. The "highest level" of clinical response is a PASI 100 or sPGA (0) response, which represents complete resolution of psoriasis.

Section 5.1.4. Post-Treatment Follow-up Period (12 Weeks)

Patients who do not enroll into Study AMAH or who discontinue early from study treatment in Study AMAK will complete the Post-Treatment Follow-Up Period (V801 and V802) of Study AMAK.

For patients who have entered the Post-Treatment Follow-Up Period, psoriasis therapy with another agent(s), as determined appropriate by the investigator, is allowed.

Section 6.1. Inclusion Criteria

Patient Characteristics

[3b] Female patients:

Women of childbearing potential:

A. Must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

B. 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 (for example, 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.

i. 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.

ii. Of note, one of the two 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).

When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

[5] Have adequate organ function, including:

A. Hematology~~ic~~:

Section 6.2. Exclusion Criteria

Prior/Concomitant Therapy

[24] Have received systemic nonbiologic 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; leflunomide~~lefludimide~~; fumaric acid derivatives; or 1,25-dihydroxyvitamin D3 and analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self-treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline.

Section 7.7. Concomitant Therapy

Table AMAK.4. Excluded Classes of Concomitant Medications or Classes with Restricted Use

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
Biological immunomodulating agents *(for example, alefacept, briakinumab, efalizumab, ixekizumab, secukinumab, etanercept, adalimumab, infliximab, certolizumab~~amb~~)*	N	N	
Systemic immunomodulating treatments *(corticosteroids only)*	N	Y	Limited use of system~~i~~tic 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.
Bacillus Calmette-Guerin (BCG) vaccinations or live virus vaccinations *(BCG prohibited for 12 months before baseline, live vaccinations prohibited for 12 weeks before baseline. Both are prohibited throughout the study and for ~~12 months or~~ 12 weeks~~, respectively,~~ after discontinuation of study drug).*	N	N	
Any investigational treatment	N	N	

Abbreviations: MTX = methotrexate; N = No; PUVA = psoralen and ultraviolet A; TEAE = treatment-emergent adverse event; UVA = ultraviolet A; UVB = ultraviolet B; Y = Yes.

Topical therapies allowed during the study include shampoos that do not contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues; topical moisturizers/emollients and other non-prescription topical products that do not contain urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, corticosteroids, or vitamin D3 analogues; and bath oils and oatmeal bath preparations. These topical therapies are not to be used within 12 hours prior to a study visit.

For patients who have entered the Post-Treatment Follow-Up Period, psoriasis therapy with another agent(s), as determined appropriate by the investigator, is allowed.

Section 7.8.2.1. Management of Hypersensitivity Events, Including Injection Site Events

All biological agents carry the risk of systemic allergic/hypersensitivity events. Clinical manifestations of these events may include, but are not limited to the following:

- Skin rash
- Pruritus (itching)

- Urticaria (hives)
- Angioedema (for example, swelling of the lips and/or tongue)
- Anaphylactic events.

Sometimes, these events can be life threatening. Proteins may also cause redness, itching, swelling, or pain locally at the injection site. Therefore, all patients should be closely monitored for signs or symptoms that could result from such events, educated on the signs or symptoms of these types of events, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute hypersensitivity event after an injection of investigational product, he or she should be managed appropriately and given instructions to receive relevant supportive care.

Additionally, for an event judged by the investigator to be a potential systemic hypersensitivity event, blood samples will be collected for PK, immunogenicity, and exploratory hypersensitivity analyses at, or as close as possible to:

1. the onset of the event
2. the resolution of the event, and
3. 30 (±3) days following the event.

Exploratory hypersensitivity samples may, as appropriate for the clinical presentation,

- be analyzed for tryptase (a marker of basophil/mast cell activation),
- have a complement panel performed (asses immune complex formation), and
- have a cytokine panel performed.

~~a blood sample should be drawn to test for anti-drug antibodies (ADAs; s~~See also Section 9.4.4~~)~~.

Patients who develop clinically significant systemic hypersensitivity events following administration of investigational product~~, who do not respond to symptomatic medication or whose event results in clinical sequelae (for example, hospitalization),~~ should be discontinued from the study and not receive further doses of investigational product, with or without premedication (see Section 8.2).

Section 8.2. Discontinuation from the Study

- In addition, patients who meet any one of the following criteria should be discontinued from the investigational product, enter the Post-Treatment Follow-Up Period, and discontinue from the study:
    - Clinically significant systemic hypersensitivity event following administration of investigational product~~ that does not respond to symptomatic medication or results in clinical sequelae~~.

Section 9.2.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs which the Sponsor specifies as being of special interest based on standard drug registration topics, safety findings from previous studies in development program, potential risks associated with biologic immunomodulators as noted in product labels and published literature, and comorbidities and risk factors prevalent in the studied populations. The AESIs for this study are defined in the statistical analysis plan (SAP), and may include, but not be limited to the following:

- Infections, including ~~O~~opportunistic infections
- Hypersensitivity events, including anaphylaxis
- Injection site events
- Cerebro-cardiovascular events
- Malignancies
- Depression, or suicidal ideation ~~and~~ or behaviors
- Hepatic AEs.

For some AESIs, sites should provide additional information regarding the event, as instructed on the eCRF.

Infections, Including Opportunistic Infections

Drugs that modulate the immune system may increase the risk of infection, including serious or opportunistic infections.

Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al. (2015). Examples are listed in Appendix 4.

Hypersensitivity Events

Site personnel should educate patients and/or caregivers about the symptoms and signs of hypersensitivity events and provide instructions on dealing with these events. A blood sample will be collected when possible for any patient who experiences an AE of hypersensitivity ~~events~~ during the study.

Section 9.4.1. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations and read locally for evaluation of study eligibility and safety monitoring.

Patients should be supine for approximately 5 to 10 minutes before ECG collection, and remain supine but awake during ECG collection. Sitting BP, temperature, and pulse (see Section 9.4.2) should be obtained at approximately the same time as ECG measurements or blood sampling.

When multiple assessments are scheduled for the same time point, the preferred order of completion should be as follows: ECG, vital signs, and then blood sampling.

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

Section 9.4.2. Vital Signs

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

Sitting vital signs (BP, temperature, and pulse) will be measured after resting for a minimum of 10 minutes at times indicated in the Schedule of Activities (Section 2), and prior to blood sampling or administration of the investigational product.

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

Section 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 blood sample for PK analysis will be collected at the same time points. All samples for immunogenicity should be taken predose when applicable. With reports of hypersensitivity events (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 resolution of the event. Samples will be evaluated for PK, anti-drug antibodies (ADAs), CCI [redacted] Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of mirikizumab at a laboratory approved by the Sponsor. Patient samples will be analyzed using a 4-tiered approach. All samples will be assessed in Tier 1 (screening). Samples above the disease state screening assay cut point factor (Tier 1) will be assessed in Tier 2 (confirmation). Any samples confirmed as positive for anti-mirikizumab antibodies in Tier 2 will be reported as "detected." All samples below the screening assay cut point factor in Tier 1 or not confirmed in Tier 2 will be reported as "not detected." Any "detected" sample in Tier 2 will be assessed in Tier 3 (titer assessment; values reported) and Tier 4 (neutralizing ADA assay). Any samples above the disease state Tier 4 cut point will be reported as "detected" for neutralizing antibodies; samples below the disease state Tier 4 cut point will be reported as "not detected" for neutralizing antibodies.

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

Section 9.4.5.1. Physical Examination

Physical examination will be performed as specified in the Schedule of Activities (Section 2). One complete physical examination (excluding pelvic or rectal examinations), which includes heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas), will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation, as well as examination of heart, lungs, peripheral lymph nodes, and abdomen, and visual examination of all skin areas (including genitalia and breast areas).

Section 9.4.5.2. Tuberculosis Screening

Initial Screening:

Screening for active or latent TB (LTBI) will include a history, physical examination (Section 9.4.5.1), chest x-ray (Section 9.4.5.3), and, except as noted below under "Prior Treatment for LTBI or TB," testing by an interferon-γ release assay (IGRA; QuantiFERON®-TB Gold or T-SPOT.TB®) or a purified protein derivative (PPD) tuberculin skin test.

In people aged 5 years and over, IGRA is the preferred screening test for LTBI. In countries where the PPD is available and is preferred (in the judgment of the investigator) as an alternative screening test for LTBI, that test may be used instead of an IGRA.

Patients with documentation of a negative IGRA or PPD within 3 months before initial screening may not need to repeat TB testing at screening, based on the judgment of the investigator. Source documentation must include the original laboratory report (for IGRA) or a record of the size in millimeters of the induration response (for PPD). A PPD recorded as negative without documenting the size of induration in millimeters, will not be acceptable and will require a retest.

Monitoring:

After initial screening, tuberculosis testing will only be required based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and according to local regulations and/or local standard of care. Such clinical assessments should be conducted periodically, at least every 4 months.

Interpretation of Screening Tests for LTBI

The QuantiFERON-TB Gold assay will be reported as negative, indeterminate, or positive. The T-SPOT.TB assay will be reported as negative, borderline, or positive.

A positive PPD is indicated with a skin test response ≥5 mm of induration, documented between approximately 48 and 72 hours after test application (regardless of BCG vaccination history). Patients who do not return within 48 to 72 hours of test administration will be required to have the test repeated and then interpreted within this time frame.

Patients with a diagnosis of LTBI, based on a positive IGRA test result or a positive PPD response ≥5 mm of induration and no evidence of active TB, may be rescreened once ~~if~~ after they meet the following requirements:

- Have received at least 4 weeks of appropriate ongoing prophylactic therapy for LTBI as per local standard of care, and
- Have no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2x ULN) upon retesting of serum ALT and AST levels before randomization.~~)~~

Such patients must continue and complete appropriate LTBI therapy during the course of the study to remain eligible and must continue to meet all other inclusion and exclusion criteria for participation. ~~Follow-up TB testing with IGRA or PPD, tailored in accordance with a person's risk (for example, hospital care worker, residence in a high risk location), may be performed according to local guidelines.~~

Prior Treatment for LTBI or TB

Patients who have a documented history of completing an appropriate TB prophylaxis or treatment regimen (consistent with World Health Organization and/or United States Centers for Disease Control at the time of treatment), with no history of re-exposure since their treatments were completed and no evidence of active TB, are eligible to participate in the study; these patients should not undergo TB testing unless advised to do so based on local guidelines.

Section 9.4.5.5. Hepatitis C Screening

Patients who test positive for HCV antibody and have a positive confirmatory HCV RNA test at screening will be excluded.

Patients with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained ~~anti-~~virologic response may be eligible for inclusion in the study, provided they have no detectable RNA on the screening HCV RNA test for this protocol. A sustained virologic response is defined as an undetectable HCV RNA level, 12 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as (i) a positive HCV antibody test and (ii) a negative HCV RNA test, with no history of anti-HCV treatment, may be eligible

for inclusion in the study, provided they have no detectable HCV RNA on screening for this study ~~*and* no detectable HCV RNA on the screening HCV RNA test for this protocol~~.

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Clinical (Serum) Chemistry[a]	**Other**
Serum Concentrations of:	
Gamma-glutamyl transferase (GGT)	
	PPD or QuantiFERON-TB Gold test or T-SPOT.TB test~~[b,d]~~
	Tryptase[a]
	Complement panel (C3 and C4)[a]
	Cytokine panel[a]

Abbreviations: DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic(s); PPD = purified protein derivative (skin test); RBC = red blood cells; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cells.

a Unscheduled hematology or blood chemistry panels may be performed at the discretion of the investigator. ~~An immunogenicity sample may be obtained at unscheduled visits i~~If a patient develops an acute hypersensitivity event after administration of IP, blood samples will be collected for pharmacokinetic, immunogenicity, and exploratory hypersensitivity analyses.

b Performed at screening only.

c Following screening, patients will not undergo monitoring for Hepatitis C unless liver enzymes are elevated. Hepatitis B monitoring will be performed at protocol-specified intervals in patients who test positive for anti-hepatitis B core antibody.

d TB testing ~~may~~ will be performed locally using an interferon-γ release assay (IGRA, for example QuantiFERON®-TB Gold or T-SPOT.TB) or a PPD tuberculin skin test. If PPD test is performed, patients will return 2 to 3 days afterwards ~~Visit 1~~ to have their PPD test read.

Appendix 4. Examples of Infections That May Be Considered Opportunistic in the Setting of Biologic Therapy

Winthrop et al. (2015) consider tuberculosis (TB) and non-TB mycobacterial disease to be opportunistic infections in the context of biologic therapy. See Section 9.4.5.2 for the approach to screening for latent TB infection within the study. ~~Patients with any history of **active** TB are excluded from the study, regardless of previous or current TB treatments.~~

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