Protocol I6T-MC-AMAH(a)

A Multicenter, Long-Term Extension to Evaluate the Long-Term Safety and Maintenance of Treatment Effect of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis (OASIS-3)

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OASIS-3

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Confidential Information

Mirikizumab (LY3074828)

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1. Synopsis

Title of Study:
A Multicenter, Long-Term Extension to Evaluate the Long-Term Safety and Maintenance of Treatment Effect of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis

Rationale:
LY3074828 (mirikizumab) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of IL-23 and does not bind IL-12. Mirikizumab is being developed for the treatment of immune-mediated or inflammatory diseases in which the IL-23 pathway is thought to have a pathogenic role. Study I6T-MC-AMAH (AMAH) is a confirmatory study testing mirikizumab as a treatment for plaque psoriasis and is intended to support registration of this indication. This Phase 3 trial is designed to contribute to the evaluation of the safety, and to evaluate the long-term efficacy as measured by improvement in disease severity and key patient-reported outcomes following long-term treatment with mirikizumab.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the long-term maintenance of efficacy of mirikizumab in patients with moderate-to-severe plaque psoriasis	Over the duration of the study: • Proportion of patients with an sPGA (0,1) among those who entered Study AMAH with sPGA (0,1) • Proportion of patients who maintained a ≥90% improvement in PASI (PASI 90) among those who entered Study AMAH with a PASI 90 response

Abbreviations: PASI = Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in PASI from baseline; sPGA = static Physician's Global Assessment

Summary of Study Design:

Study AMAH is a long-term study in which patients completing one of four originator studies (16T-MC-AMAF [AMAF], 16T-MC-AMAJ [AMAJ], 16T-MC-AMAK [AMAK], or 16T-MC-AMBK [AMBK]) will receive mirikizumab for an extended period of time (approximately 4 years or until commercial availability of mirikizumab), and then enter a 12-week Post-Treatment Follow-Up period (Figure AMAH.1). Patients who qualify for Study AMAH may enter directly into the study upon the final visit of a qualifying study period of the originator study. The qualifying study periods of the originator studies are as follows:

- AMAJ, AMAK, AMAF: Blinded Maintenance Period
- AMBK: Treatment Period

Most patients will enter Study AMAH at the last visit of a qualifying study period of the originator studies. All patients must enter Study AMAH within 12 weeks of their final visit in these periods or they will become ineligible. Patients in the secukinumab treatment group of Study AMAJ will be eligible to enter Study AMAH; such patients will receive mirikizumab for the first time in Study AMAH.

Treatment Period:

All patients participating in Study AMAH will receive subcutaneous (SC) administration of mirikizumab every 8 weeks (Q8W). The dose used in Study AMAH will depend on the treatment that the patients were receiving during the qualifying period of the originator study. For all treatment groups in Study AMAH, dosing begins at Visit 1 and continues to Week 208.

- Patients entering from Study AMAJ or Study AMAK who received mirikizumab during the qualifying period will continue to receive the dose they were receiving (either 250 mg mirikizumab Q8W SC or 125 mg mirikizumab Q8W SC). Patients entering from Study AMAJ or Study AMAK who were receiving secukinumab or placebo, respectively, during the qualifying period will receive 250 mg mirikizumab Q8W SC.
- Patients entering from Study AMBK will receive 250 mg mirikizumab Q8W SC.
- Patients entering from Study AMAF whose last treatment was 300 mg mirikizumab, on either the fixed Q8W dosing regimen or on the as-needed (PRN) regimen, will start 250 mg mirikizumab Q8W SC in Study AMAH. Patients entering from Study AMAF whose last treatment was either 30 mg or 100 mg mirikizumab on a PRN regimen will start 125 mg mirikizumab Q8W SC in Study AMAH.
- After Study AMAH dosing is no longer blinded, patients who in the opinion of the investigator have experienced significant clinically meaningful loss of efficacy during study participation may be increased from 125 mg mirikizumab Q8W to 250 mg mirikizumab Q8W if it is determined by the patient and the investigator that the patient might benefit from additional study drug in order to maintain satisfactory disease

control. All patients who increase dosing to 250 mg mirikizumab Q8W will remain on this dose until completion of the study or early discontinuation.

Post-Treatment Follow-up Period (12 weeks):

All patients, whether they discontinue early for any reason or else complete study treatment, will enter the 12-week Post-Treatment Follow-Up Period.

Number of Patients:

Approximately 1600-2000 participants are expected to enroll in Study AMAH from the originator studies.

Statistical Analysis:

The sample size for Study AMAH will be determined by the number of patients who continue into Study AMAH from the originator studies.

The analysis will be focused on point estimates and confidence intervals. Thus, no hypothesis testing will be performed, and multiple testing will not need to be accounted for.

Efficacy and safety summaries will be reported by the following 3 cohorts:

(1) Patients assigned to 250 mg mirikizumab Q8W SC in Study AMAH, excluding patients who received secukinumab during the qualifying period of their originating study.
(2) Patients assigned to 125 mg mirikizumab Q8W SC in Study AMAH
(3) Patients who received secukinumab during the qualifying period of their originating study.

For assessment of the primary endpoints and other categorical efficacy endpoints, proportions and 95% confidence intervals will be reported using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution). For the primary endpoint, missing data will be handled in at least 2 different ways: (1) proportions, calculated using only observed data, and (2) non-responder imputation (NRI). For the NRI method, all patients who do not meet the clinical response criteria or have missing clinical response data at the analysis time point will be defined as nonresponders.

For continuous efficacy and health outcome variables with multiple post-baseline measurements, the mean response over time will be estimated using the mixed-effects model for repeated measures (MMRM). For continuous efficacy and health outcome variables with a single post-baseline time point, the mean response will be estimated using analysis of covariance (ANCOVA).

Continuous safety data, including vital sign and laboratory values, will be analyzed by 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.

A single Data Monitoring Committee consisting of members external to Eli Lilly and Company will be established for interim safety monitoring across all Phase 3 trials in patients with psoriasis.

2. Schedule of Activities

Table AMAH.1. Schedule of Activities

Procedure[a]	Treatment Period (Visits 1-14, every-8-week visits)													
Visit Number	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week Relative to Study Drug Initiation	**0**	**8**	**16**	**24**	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**1 ± 5**	**57 ± 5**	**113 ± 5**	**169 ± 5**	**225 ± 5**	**281 ± 5**	**337 ± 5**	**393 ± 5**	**449 ± 5**	**505 ± 5**	**561 ± 5**	**617 ± 5**	**673 ± 5**	**729 ± 5**
Informed consent	X													
Demographics	X													
Physical examination[c]	X													
Weight	X													
Review and confirm inclusion/exclusion criteria	X													
Complete medical/surgical history and habits	X													
Concomitant medications	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
Vital signs (BP, temperature, and heart rate)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD/QuantiFERON-TB Gold/ T-SPOT.TB® (per local guidelines)[e]	TB testing required only 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.													
ECG[f]														
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	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	X	X	X	X	X	X	X
IP dosed	X	X	X	X	X	X	X	X	X	X	X	X	X	
IP dispensed														X[h]

Procedure[a]	Treatment Period (Visits 1-14, every-8-week visits)													
Visit Number	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week Relative to Study Drug Initiation	**0**	**8**	**16**	**24**	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**1 ± 5**	**57 ± 5**	**113 ± 5**	**169 ± 5**	**225 ± 5**	**281 ± 5**	**337 ± 5**	**393 ± 5**	**449 ± 5**	**505 ± 5**	**561 ± 5**	**617 ± 5**	**673 ± 5**	**729 ± 5**
Investigator-Completed Clinical Efficacy Scales														
PASI	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
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PSSI[i]	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
PPASI[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Completed Health Outcomes Scales[j]														
PSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests														
Hematology[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical serum chemistry[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X													
hsCRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA testing[l]		X		X		X		X		X		X		X
HCV RNA testing	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Immunogenicity for mirikizumab[n]	X[o]	X	X	X			X			X			X	
Serum for mirikizumab concentrations (PK)[p]	X[o]	X	X	X			X			X			X	
Urine pregnancy test[q] (local; WCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure[a]	Treatment Period (Visits 15-21, every-16-week visits)							ETV[r]	Follow-up Period (Visits 801 and 802)	
Visit Number	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**		**V801**	**V802**
Week Relative to Study Drug Initiation	**120**	**136**	**152**	**168**	**184**	**200**	**208**		**LV +4W**	**LV +12W**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**841 ± 5**	**953 ± 5**	**1065 ± 5**	**1177 ± 5**	**1289 ± 5**	**1401 ± 5**	**1457 ± 5**		**29 ± 5**	**85 ± 5**
Physical examination[c]								X		X
Weight							X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, temperature, and heart rate)[d]	X	X	X	X	X	X	X	X	X	X
PPD/QuantiFERON-TB Gold/ T-SPOT.TB® (per local guidelines)[e]	TB testing required only 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.									
ECG[f]								X		X
C-SSRS	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[g]	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form	X	X	X	X	X	X	X	X	X	X
QIDS-SR16 (patient completed)	X	X	X	X	X	X	X	X		X
IP dispensed	X	X	X	X	X	X	X			
IP returned	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
BSA	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X
PSSI[i]	X	X	X	X	X	X	X	X	X	X
NAPSI[i]	X	X	X	X	X	X	X	X	X	X

Procedure[a]	Treatment Period (Visits 15-21, every-16-week visits)							ETV[r]	Follow-up Period (Visits 801 and 802)	
Visit Number	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**		**V801**	**V802**
Week Relative to Study Drug Initiation	**120**	**136**	**152**	**168**	**184**	**200**	**208**		**LV +4W**	**LV +12W**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**841 ± 5**	**953 ± 5**	**1065 ± 5**	**1177 ± 5**	**1289 ± 5**	**1401 ± 5**	**1457 ± 5**		**29 ± 5**	**85 ± 5**
PPASI[i]	X	X	X	X	X	X	X	X	X	X
Patient-Completed Health Outcomes Scales[j]										
PSS	X	X	X	X	X	X	X	X		X
DLQI	X	X	X	X	X	X	X	X		X
Laboratory Tests										
Hematology[k]	X	X	X	X	X	X	X	X	X	X
Clinical Serum chemistry[k]	X	X	X	X	X	X	X	X	X	X
Urinalysis									X[s]	X
HsCRP	X	X	X	X	X	X	X	X	X	X
HBV DNA testing[l]	X	X	X	X	X	X	X	X	X	X
HCV RNA testing	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Immunogenicity for mirikizumab[n]	X		X		X		X			X
Serum for mirikizumab concentrations (PK)[p]	X		X		X		X			X
Urine pregnancy test[q] (local; WCBP only)	X	X	X	X	X	X	X	X		X

Abbreviations: ALT = alanine aminotransferase; BP = blood pressure; BSA = body surface area; C-SSRS = Columbia–Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ETV = early termination visit; HBcAb+ = positive for hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; hsCRP = high-sensitivity C-reactive protein; IP = investigational product; LV = last study visit; LVTP = last visit of a qualifying study treatment period; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; 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; sPGA = static Physician's Global Assessment; TB = tuberculosis; ULN = upper limit of normal; V = visit; W = weeks; WCBP = women of child-bearing potential.

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

[b] For most patients, the final visit of the originating study will coincide with Visit 1 (Week 0) of Study AMAH. In these cases, any assessments/procedures (including laboratory tests) conducted during the patient's final visit in the originating study should not be repeated for Visit 1 (Week 0) of Study AMAH. In cases where entry into Study AMAH is delayed beyond the LVTP of the originating study, assessments/procedures (including laboratory tests) indicated for Visit 1 (Week 0) of Study AMAH that are not conducted during the patient's last visit of the originating study will be performed as indicated in the Schedule of Activities. 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 Visit 1. 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) (see Section 9.4.5.1.) Physical examination does not need to be performed again if Visit 1 occurs on the same date as the last visit of the originator study and if physical examination was performed at the last visit of the originator study.

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

[e] Tuberculosis testing will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure; risk factors detailed in Appendix 5), determined by the principal investigator, and according to local regulations and/or local standard of care (Section 9.4.6). Tuberculosis 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 the 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 Section 9.4.5.2.

[f] 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.

[g] 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).

[h] Patients will self administer injections starting at Visit 14. Sites will train patients on how to self inject the drug at Visit 14 and will provide a log for patients to track their at home dosing.

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

[j] These assessments should be completed before administration of IP; 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] Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator. See Appendix 2, for details.

l Any enrolled patient who is HBcAb+ in the originator trial will undergo monitoring of HBV DNA with HBV DNA testing (see Section 9.4.5.3). 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.

m Any enrolled patient with a history of HCV infection (tested positive for HCV antibody in the originator study) who develops elevated ALT >3xULN will be tested for HCV RNA (see Section 9.4.5.4). 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.

n 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).

o Sample from last vist of originator study should be used. If no sample <4 weeks old is available, then a baseline sample should be collected in this study.

p Scheduled pharmacokinetic samples are taken as an aliquot from the immunogenicity sample. Unscheduled pharmacokinetic 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.q To be performed only on women of child-bearing potential. Between visits, urine pregnancy tests are to be performed monthly at home.

r If a patient discontinues IP early, the patient will complete the ETV and then enter the Post-Treatment Follow-up Period (Visit 801 and Visit 802).

s 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 humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody being developed for the treatment of immune-mediated or inflammatory diseases in which the IL-23 pathway is thought to have a 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-AMAH (AMAH) is a long-term extension study of 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 long-term efficacy and safety of mirikizumab in patients with moderate-to-severe plaque psoriasis, who wish to continue treatment following completion of Studies 16T-MC-AMAF (AMAF), 16T-MC-AMBK (AMBK), 16T-MC-AMAK (AMAK), or 16T-MC-AMAJ (AMAJ).

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). Interleukin-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. Interleukin-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 Food and Drug Administration (FDA)-approved monoclonal antibody for the treatment of psoriasis, psoriatic arthritis, and Crohn's disease (Stelara® package insert 2017) 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 European Medicines Agency (EMA) (Tremfya Summary of Product Characteristics 2017). Other similar agents, including mirikizumab in Studies I6T-MC-AMAA (AMAA) and AMAF, have demonstrated clinical activity in plaque psoriasis (Krueger et al. 2015; Papp et al. 2015, 2017; Reich et al. 2017).

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. 2017).

The doses and regimens planned for Studies AMAJ, AMAK, and AMAH 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, 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 of 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 AMAH 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 AMAH.2 shows the objectives and endpoints of the study.

Table AMAH.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the long-term maintenance of efficacy of mirikizumab in patients with moderate-to-severe plaque psoriasis	Over the duration of the study: • Proportion of patients with an sPGA (0,1) among those who entered Study AMAH with sPGA (0,1) • Proportion of patients who maintained a ≥90% improvement in PASI (PASI 90) among those who entered Study AMAH with a PASI 90 response
Secondary • To evaluate the long-term efficacy and patient reported outcomes with mirikizumab treatment in patients with moderate-to-severe plaque psoriasis	Over the duration of the study: • Proportion of patients achieving sPGA (0,1) • Proportion of patients achieving PASI 90 • Proportion of patients achieving a 100% improvement in PASI (PASI 100) • Proportion of patients with a PSS symptom score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline. • Proportion of patients achieving Dermatology Life Quality Index (DLQI) score of 0,1 with baseline score >1 • Percent change in Palmoplantar Psoriasis Severity Index (PPASI) total score in patients with palmoplantar involvement at baseline • Percent change in Psoriasis Scalp Severity Index (PSSI) total score in patients with scalp involvement at baseline • Percent change in Nail Psoriasis Severity Index (NAPSI) total score in patients with fingernail involvement at baseline

Exploratory To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, TEAEs, and mirikizumab exposure	Over the course of the 208 week study, by treatment-emergent anti-drug antibody (TE-ADA) status and by neutralizing anti-drug antibody (NAb) status: • Relationship between ADA and efficacy (sPGA and PASI) • Relationship between ADA and TEAEs • Relationship between TE-ADA and mirikizumab pharmacokinetics

Abbreviations: ADA= antidrug antibodies; DLQI = Dermatology Life Quality Index; Nab = neutralizing anti-drug antibody; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; sPGA = static Physician's Global Assessment; TE-ADA = treatment-emergent anti-drug antibody; TEAEs = treatment-emergent adverse events.

5. Study Design

5.1. Overall Design

Study AMAH is a long-term study in which patients completing 1 of the 4 originator studies (AMAF, AMAJ, AMAK, or AMBK) will receive 250 mg or 125 mg mirikizumab Q8W, administered SC, for an extended period of time (approximately 4 years or until commercial availability of mirikizumab) and then enter a 12-week Post-Treatment Follow-Up period.

Study governance considerations are described in detail in Appendix 3.

5.1.1. Qualifying Period

Patients who qualify for Study AMAH may enter directly into the study upon the last visit of a qualifying study treatment period (LVTP) of the originator study. For most patients, Week 52 of the originating study (AMAJ and AMAK) will be the LVTP and will coincide with Week 0 (Visit 1) for Study AMAH. Similar alignment will occur for other originator studies, that is, Visit 1 of Study AMAH to coincide with the LVTP in AMAF or AMBK. The qualifying study treatment periods of the originator studies are as follows:

- AMAJ, AMAK, AMAF: Blinded Maintenance Period
- AMBK: Treatment Period

Study investigator(s) will review patient data from the LVTP in the respective originating study to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for participation in Study AMAH.

If, at LVTP of the originating study, a patient is not able to enter Study AMAH (for example, due to unresolved safety concerns), the patient will be evaluated in the originating study for up to 12 weeks beyond the LVTP (that is, in a post-treatment follow up period) to determine whether treatment with investigational product can resume in Study AMAH. If, in the opinion of the investigator, starting or restarting treatment with mirikizumab does not pose an unacceptable risk, the patient can begin participation in Study AMAH, that is, have Visit 1 in Study AMAH. Eligible patients must enter Study AMAH within 12 weeks of the LVTP of originating study or they will become ineligible.

5.1.2. Treatment Period

All patients participating in Study AMAH will receive mirikizumab every 8 weeks (Q8W) SC. The dose used in Study AMAH will depend on the treatment patients were receiving during the qualifying period of the originator study. For all treatment groups in Study AMAH, dosing begins at Visit 1 and continues to Week 208.

- Patients entering from Study AMAJ or Study AMAK who received mirikizumab during the qualifying period, will continue to receive the dose they were using (either 250 mg mirikizumab Q8W SC or 125 mg mirikizumab Q8W SC). Patients entering

from Study AMAJ or Study AMAK who were receiving secukinumab or placebo, respectively, during the qualifying period will receive 250 mg mirikizumab Q8W SC.

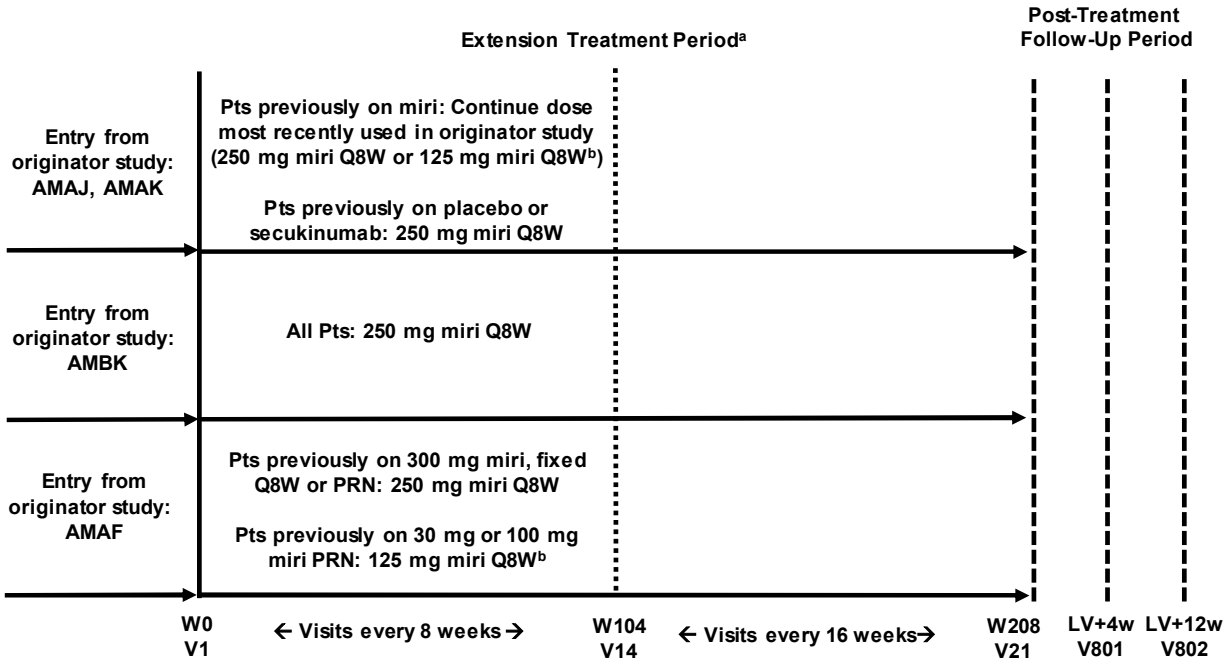
- Patients entering from Study AMBK will receive 250 mg mirikizumab Q8W SC.
- Patients entering from Study AMAF whose last treatment was 300 mg mirikizumab Q8W, on either the fixed dosing regimen or in the as needed (PRN) regimen, will start 250 mg mirikizumab Q8W SC in Study AMAH. Patients entering from Study AMAF whose last treatment was either 30 mg or 100 mg mirikizumab on a PRN regimen will start 125 mg mirikizumab Q8W SC in Study AMAH.
- After Study AMAH dosing is no longer blinded, patients who in the opinion of the investigator have experienced significant clinically meaningful loss of efficacy during study participation may be increased from 125 mg mirikizumab Q8W to 250 mg mirikizumab Q8W if it is determined by the patient and the investigator that the patient might benefit from additional study drug in order to maintain satisfactory disease control. All patients who increase dosing to 250 mg mirikizumab Q8W will remain on this dose until completion of the study or early discontinuation.

5.1.3. Post-Treatment Follow-Up Period (12 Weeks)

All patients, whether they discontinue early for any reason or complete study treatment, will enter the 12-week Post-Treatment Follow-Up Period (Visit 801 and Visit 802) of Study AMAH.

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 AMAH.1 illustrates the study design.



Abbreviations: LV = last study visit; miri = mirikizumab given as subcutaneous injection (SC); PRN=as needed; pts = patients; Q8W =every 8 weeks; V = visit; W or w = week.

[a]Patients will remain blinded to treatment until the last patient completes the last originator study.

[b]Patients receiving 125 mg Q8W may be eligible to escalate to 250 mg Q8W; see Section 7.4

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

5.2. Number of Participants

Approximately 1600-2000 participants are expected to enroll in Study AMAH from the originator studies.

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

Mirikizumab (LY3074828) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of IL-23 and does not bind IL-12. Mirikizumab is being developed for the treatment of immune-mediated or inflammatory diseases in which the IL-23 pathway is thought to have a pathogenic role. Study AMAH is a confirmatory study testing mirikizumab as a treatment for plaque psoriasis and is intended to support registration of this indication. This Phase 3 trial is designed to evaluate the safety and efficacy of mirikizumab

following long-term administration, as determined by the evaluation of safety laboratory results and analysis of AE parameters and by improvement in disease severity and key patient-reported outcomes.

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 patients and patients with psoriasis), and up to 1200 mg IV were evaluated in Study I6T-JE-AMAD (healthy patients); 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 dosing regimens of up to 1000 mg IV every 4 weeks for up to 52 weeks has not revealed any difference in the safety profile resulting from these higher exposures.

The MOS for the highest dosing regimen of 250 mg Q8W SC proposed for this study relative to the NOAEL level in the 6-month nonclinical toxicology study in cynomolgus monkeys is 44, based on area under the plasma concentration versus time curve.

Efficacy Considerations

A dosing regimen of 250 mg mirikizumab Q8W SC is the highest dosing regimen being evaluated during the maintenance periods of Studies AMAJ and AMAK. This dosing regimen is expected to maintain or further enhance the efficacy achieved at the end of the Induction Period in those studies. A second maintenance dosing regimen of 125 mg Q8W SC is also being evaluated during maintenance in those studies 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 patients, minimal overlap with the concentrations produced with the 250 mg mirikizumab Q8W SC regimen.

Formulation Considerations

A 125 mg/mL concentration was selected to provide the maximum amount of mirikizumab that could be delivered as a single SC injection (that is, 2 mL). Therefore, a 2 mL dose of mirikizumab (delivered either as two 1 mL injections or a single 2 mL injection) would deliver 250 mg of mirikizumab, which is comparable to the 300 mg dose that was evaluated in the Phase 2 Study, AMAF. The 125 mg dose will be delivered as a single 1 mL SC injection; this dose is comparable to the 100 mg dose evaluated in Study AMAF.

Therefore, based on all the available clinical and non-clinical data, the dosing regimens planned for this study are expected to provide an acceptable safety profile while providing maximum clinical response in patients with plaque psoriasis.

6. Study Population

The study population for Study AMAH will include patients who have completed participation in qualifying study periods of 1 of the originating studies (Study AMAF, AMAJ, AMAK, or AMBK) and meet eligibility criteria for Study AMAH, and will therefore include adult patients with moderate-to-severe plaque psoriasis at the time of entry into the originating study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Patients in the secukinumab treatment group of Study AMAJ will be eligible to enter Study AMAH; such patients will receive mirikizumab for the first time in Study AMAH.

Approximately 1600-2000 patients are planned to be enrolled in Study AMAH.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet the following criteria before the start of treatment in Study AMAH, unless otherwise specifically defined:

Type of Patient

[1] Have completed the last visit of an eligible study period of 1 of the originator studies (Study AMAF, AMAJ, AMAK, or AMBK).

Patient Characteristics

[2a] Male patients

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

[2b] Female Patients

<u>Women not of child-bearing potential may participate and include those who are</u>:

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

- Cessation of menses for at least 1 year,

OR

- At least 6 months (or longer if required by local regulatory requirements) of spontaneous amenorrhea with a follicle stimulating hormone level of >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 child-bearing potential:

A. Must test negative for pregnancy prior to first dose in Study AMAH as indicated 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, or 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, 1 of the 2 methods of contraception may be a highly effective (less than 1% failure rate) method of contraception (such as, combination oral contraceptives, implanted contraceptives or intrauterine devices).

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

[3] 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

[4] 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, unless otherwise specified:

[5] 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 that developed during the originating mirikizumab study (Studies AMAF, AMAJ, AMAK, or AMBK) that, in the opinion of the investigator, would potentially affect patient safety within the study or would interfere with the interpretation of data.

[6] Have a known hypersensitivity to mirikizumab or any component of this investigational product.

[7] Have had investigational product permanently discontinued during a previous mirikizumab study.

[8] Have had temporary investigational product interruption at any time during or at the final study visit of a previous mirikizumab study and, in the opinion of the investigator, restarting mirikizumab would pose an unacceptable risk for the patient's participation in the study.

[9] Have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol.

[10] 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.

Other Exclusions

[11] 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 who were not suitable candidates to receive mirikizumab treatments at the end of the originator study treatment period will be excluded from this study, which is intended to evaluate the safety and efficacy of long-term mirikizumab treatment.

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

Screen failures are not applicable as study participation is dependent on completion of the originator studies and not the screening process.

7. Treatments

7.1. Treatments Administered

This study involves an evaluation of long-term maintenance of response to mirikizumab 250 mg or 125 mg administered SC for up to 208 weeks of dosing. Table AMAH.3 shows the treatment regimens.

Table AMAH.3. Treatment Regimens

Originator Study	Treatment at End of Originating Study	Treatment in Study AMAH (Q8W)
AMBK	250 mg miri Q4W	250 mg miri (2 x 1-mL miri PFS)
AMAF	300 mg miri, Q8W fixed or PRN	250 mg miri (2 x 1-mL miri PFS)
	30 mg or 100 mg miri PRN	125 mg miri[a] (1 x 1-mL miri PFS plus 1 x 1-mL placebo PFS[b])
AMAJ	250 mg miri Q8W or secukinumab	250 mg miri (2 x 1-mL miri PFS)
	125 mg miri Q8W	125 mg miri[a] (1 x 1-mL miri PFS plus 1 x 1-mL placebo PFS[b])
AMAK	250 mg miri Q8W or placebo	250 mg miri (2 x 1-mL miri PFS)
	125 mg miri Q8W	125 mg miri[a] (1 x 1-mL miri PFS plus 1 x 1-mL placebo PFS[b])

Abbreviations: miri = mirikizumab; PFS = prefilled syringe; PRN = as needed; Q4W = every 4 weeks; Q8W = every 8 weeks.

[a] Patients receiving 125 mg Q8W may be eligible to escalate to 250 mg Q8W (see Section 7.4)

[b] Placebo will be administered only until study treatments are unblinded (see Section 7.3 describing how long treatments are blinded).

Administration:

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 until Visit 14, at which time site staff will train patients on self-injection and will provide them with a log to track their doses at home.

Following Visit 14, injections will be self-administered SC by the patient or caregiver. It is recommended that these injections be administered away from the investigational site. If the patient or caregiver is not able to administer any dose throughout the study, study site staff may administer that injection.

Refer to the appropriate *Manual Syringe Directions for Use* provided by the sponsor for the investigational product. Note that in the case a study drug injection is performed in an arm, it is not to be given in the same arm from which patient blood samples, including PK samples, are drawn at relevant visits.

Study Drug Administration Logs will be dispensed to each patient for recording pertinent data about each injection; details of the use of these logs are provided in Section 7.2.1. Possible injection sites are identified in the *Manual Syringe Directions for Use*. The injection site may be rotated to another area for subsequent doses.

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 Eli Lilly and Company (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

At the time of unblinding, patients, site personnel and the Sponsor will become unblinded so that patients on the 125 mg miri can stop receiving a 1 x 1-mL placebo PFS (see Table AMAH.3).

7.1.1. Packaging and Labeling

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 in prefilled syringes containing mirikizumab or placebo. The 1-mL syringe of mirikizumab is manufactured to contain 125 mg of the drug.

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 assigned to double-blind treatment at Visit 1 based on the ending treatment regimen of the originating study (see Table AMAH.3). The interactive web-response system (IWRS) will be used to assign prefilled syringes containing investigational product to each patient. Investigational product will be dispensed according to the Schedule of Activities (Section 2). Site personnel will confirm that they have located the correct prefilled syringes by entering a confirmation number found on the prefilled syringes into the IWRS.

7.2.1. Selection and Timing of Doses

Study visits at which the 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). Study drug will be administered by site personal at Visits 1-13. Starting with Visit 14 patients should self-administer study drug on the day of the visit, and then every 8 weeks thereafter, preferably on the same day of the week.

7.3. Blinding

This is a double-blind study until the originating studies AMAJ and AMAK have had database lock and dosing for those studies is no longer blinded. The blinding applies to patients, site personnel, and Sponsor personnel.

Personnel in the originator Studies AMAF and AMAJ performing unblinded tasks (e.g., study drug dosing/dispensing) will by default know the treatment assignments of individual patients in Study AMAH by the protocol design. If these unblinded site personnel in the originator Studies AMAF and AMAJ also have a role in Study AMAH, they must assume the same responsibilities taken in the originator study for these patients and **must not** be involved in any patient assessment activities, seek any information related to these patients beyond their allowed activities, discuss the treatment assignment with the patient or with the blinded personnel. Principal Investigators will need to ensure that the blinded conditions of the originating studies are maintained during Study AMAH until database lock has occurred and dosing for those studies is no longer blinded.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. 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 before the study dosing is no longer blinded, the patient may continue the study, unless there are safety or benefit/risk reasons for the patient not to continue the study as determined by the principal investigator or Sponsor.

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's 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

After Study AMAH dosing is no longer blinded, patients who in the opinion of the investigator have experienced significant clinically meaningful loss of efficacy during study participation may be increased from 125 mg mirikizumab Q8W to 250 mg mirikizumab Q8W if it is determined by the patient and the investigator that the patient might benefit from additional study drug in order to maintain satisfactory disease control. All patients who increase dosing to 250 mg mirikizumab Q8W will remain on this dose until completion of the study or early discontinuation. No other dose adjustments are permitted in Study AMAH.

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 the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study-treatment accountability, reconciliation, and record maintenance (such as, receipt, reconciliation, and final disposition of 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 destroyed according to applicable regulations.

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

7.6. Treatment Compliance

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 the study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient.

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. 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.

Patients taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study, unless changes need to be made because of AEs. Additional systemic drugs are to be avoided during the study, unless required to treat AEs. If the need for concomitant medication arises for an AE or for appropriate medical management (including the limited use of therapeutic agents which, if used under treatment regimens other than for treating an AE or for appropriate medical management, might be considered psoriasis therapies), 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 AMAH.4 below (also see the section Exclusion Criteria [Section 6.2]).

Table AMAH.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 *(including, but not limited to, corticosteroids, 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)*	N	N	
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	.

Drug Class	Allowed for Chronic Use	Allowed with Restrictions	Conditions for Allowed Use
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 AMAH or complete 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 the 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 (assess 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 5.1.3 (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, the following:

- Development of:
    - Serious or opportunistic infections, as described in Section 9.2.3).
    - Hypertension (see Section 9.4.2.1).
    - Latent tuberculosis (TB) infection (LTBI) (see Section 9.4.5.2).
    - Positive hepatitis B virus (HBV) deoxyribonucleic acid (DNA) results that are below the level of quantification (see Section 9.4.5.3).
    - 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 alanine aminotransferase (ALT), alkaline phosphatase (ALP) or total bilirubin level (TBL) include one of the following (Section 9.4.6.1):
        - ALT ≥3xupper limit of normal (ULN) and TBL <2xULN
        - ALP ≥2xULN and TBL <2xULN
        - TBL ≥2xULN without increase from baseline in ALT/aspartate aminotransferase (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 the study treatment. If the investigator and the Sponsor-designated medical monitor agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor-designated 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 this 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:

- **Patient Decision**
  - The patient requests to be either discontinued from 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 >8xULN
  - ALT or AST >5xULN for more than 2 weeks
  - ALT or AST >3xULN and TBL >2xULN or international normalized ratio (INR) >1.5
  - ALT or AST >3xULN, with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3xULN
  - ALP >2.5xULN and TBL >2xULN

- ALP >2.5xULN, 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 count <2000 cells/μL (<2.00x10^3/μL or <2.00 GI/L).
  - Lymphocyte count <500 cells/μL (<0.50x10^3/μL or <0.50 GI/L).
  - Platelet count <50,000 cells/μL (<50x10^3/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 of this protocol).
  - 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 a 12-month period).
  - Any patient who has a change in disease phenotype at any time (for example, a change to pustular psoriasis).
  - 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 if:

    1. 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

    2. The patient 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 Columbia-Suicide Severity Rating Scale [C-SSRS])

    OR

3. The patient 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 positive or hepatitis C virus (HCV) ribonucleic acid (RNA) positive. The patient should be referred to a specialist physician (see Sections 8.1.2 and 9.4.5.3 for HBV, and Section 9.4.5.4 for HCV).

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

Patients permanently discontinuing from the 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 5.1.3 (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 to assess the proportion of patients maintaining efficacy achieved in the originator studies are as follows:

9.1.1.1. Static Physician's Global Assessment

The static Physician's Global Assessment (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 the 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 4 years. 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 4 years. 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 body surface area (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 threshold (Khilji et al. 2002; Hongbo et al. 2005).

9.1.2.7.2. 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 from 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.

9.1.2.7.3. 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).

9.1.3. 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 of 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 them 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 informed consent form (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 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 any 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 the investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving the 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's 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 subjects once they have discontinued and/or completed the study (the patient disposition case report form has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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 suicide ideations 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 9.1.2.7.3) 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.
- Retain the investigational product 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.
- Follow the instructions outlined in the Product Complaint Form 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, electrocardiograms (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 1 of AMAH]; 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 child-bearing potential.

Patients determined to be pregnant will be discontinued from the study.

Patients will undergo urine pregnancy testing at the clinic during designated scheduled visits (see Section 2), which will be performed locally. Between visits, urine pregnancy tests are to be performed monthly at home.

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 the follow-up period, at the discretion of the investigator or if this is required by local regulations.

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, ADA, and additional exploratory markers of hypersensitivity (see Section 7.8.2.1). 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

Diagnosis of LTBI During Study

Tuberculosis testing in Study AMAH 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.

Patients diagnosed with LTBI, based on a positive interferon-γ release assay test result or a positive purified protein derivative response ≥5 mm of induration, and no evidence of active TB, during the study will temporarily discontinue investigational product and be offered treatment, if clinically appropriate. These patients can be considered for resumption of investigational product after completing the first 4 weeks of appropriate ongoing prophylactic therapy for LTBI based on national or international guidelines, for example, United States Centers for Disease Control and Prevention (CDC [WWW]); or the World Health Organization (WHOa [WWW]), and no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2xULN). These patients must continue with and complete a full course of treatment for latent TB in order to continue on investigational product. Noncompliance with LTBI treatment during the study is a reason for permanent discontinuation from study drug.

Active TB

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

9.4.5.3. Hepatitis B Monitoring

Any enrolled patient who tested positive for hepatitis B core antibody (HBcAb+) in the originator study will undergo periodic monitoring of HBV DNA as per the Schedule of Activities (Section 2).

In addition to the above, any enrolled patient who tested HBcAb+ in the originator study and who experiences an elevated ALT or AST level >3xULN 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.

9.4.5.4. Hepatitis C Monitoring

Any enrolled patient with a history of HCV infection (tested positive for HCV antibody in the originator study) who develops elevated ALT level >3xULN, will be tested for HCV RNA.

Any patient diagnosed with hepatitis C, as demonstrated by a positive HCV RNA test 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.

Data from Study AMAH may be included in a psoriasis program level DMC if this data is available at the time DMC meets.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT level ≥3xULN, ALP level ≥2xULN, or elevated TBL ≥2xULN, 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 levels 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 level to ≥5xULN on 2 or more consecutive blood tests
- Elevated serum TBL to ≥ 2xULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP level to ≥2xULN 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 OR Genetics

9.7.1. Whole Blood and/or Saliva Sample for Pharmacogenetic Research

Not applicable.

9.8. Biomarkers

Not applicable.

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

The samples size for Study AMAH will be determined by the number of patients who continue into Study AMAH from the originator studies. Approximate planned sample sizes for Studies AMAF, AMAJ, AMAK, and AMBK are respectively 205, 1440, 500, and 300. Based on the assumption that 80% to 90% of patients complete the originator studies and 80% to 90% of the completers continue on into Study AMAH, Lilly anticipates that approximately 1600 to 2000 patients will enter Study AMAH.

10.2. Populations for Analyses

For all safety, efficacy and healthy outcomes analysis, the intent-to-treat (ITT) population will be used unless otherwise stated. The ITT population includes all enrolled patients who are assigned to receive treatment, 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. Additional populations for further analysis may be defined in the SAP.

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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

For all safety, efficacy and health outcomes analysis, the ITT population will be used unless otherwise stated.

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. The analysis will be focused on point estimates and confidence intervals. Thus, no hypothesis testing will be performed, and control for multiplicity is not applicable. Efficacy and safety summaries will be provided by the following 3 cohorts:

(1) Patients assigned to 250 mg mirikizumab Q8W SC in Study AMAH, excluding patients who received secukinumab during the qualifying period of their originating study.
(2) Patients assigned to 125 mg mirikizumab Q8W SC in Study AMAH
(3) Patients who received secukinumab during the qualifying period of their originating study.

Additional cohorts for further analysis may be defined in the SAP and summarized. Sensitivity analyses may be done by excluding from Cohort (1) patients who were receiving placebo during the qualifying period of their originator study.

Unless otherwise specified, all references to baseline for efficacy and health outcomes related endpoints in this study protocol refer to baseline values of the originating study. Detailed definitions of baseline for safety, vital sign, laboratory, and immunogenicity related analyses will be described in the SAP prior to first unblinded analysis.

For assessment of categorical efficacy endpoints, proportions and 95% confidence intervals will be reported using the simple asymptotic method, without continuity correction (that is, normal approximation to the binomial distribution).

For continuous efficacy and health outcome variables with multiple post-baseline measurements, the mean response over time will be estimated using mixed-effects model for repeated measures (MMRM). When MMRM is used, the model includes cohort (defined above), baseline value, visit, the interaction of cohort-by-visit as fixed factors, originating study, previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America, Europe, or Other). 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. Least squares (LS) means for each cohort will be reported along with the 95% confidence intervals.

For continuous efficacy and health outcome variables with a single post-baseline time point, the mean response will be estimated using analysis of covariance (ANCOVA) with the following in the model: cohort (defined above), baseline value and previous exposure to originating study, biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America, Europe, or Other). Type III tests for LS means will be used for statistical comparison between treatment groups. The LS means for each cohort will be reported along with the 95% confidence intervals. Missing data imputation method for the ANCOVA model will be specified in the SAP.

Continuous safety data, including vital sign and laboratory values, will be analyzed by 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 Responses:* 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. This is the primary analysis method for all binary efficacy endpoints.

- *Mixed Model Repeated Measures (MMRM) for Continuous Outcomes:* This analysis will be the primary analysis method for longitudinal continuous measurements. It assumes that the data is missing at random and that the bias caused by missing data can be attenuated by modeling random effects using the within-patient error correlation structure.

In addition, estimation based on observed data only will be used. Additional methods for the primary endpoints will be discussed in the SAP.

10.3.1.2. Multiple Comparisons/Multiplicity

The analysis will be focused on point estimates and confidence intervals. Thus, no hypothesis testing will be performed, and multiple testing will not need to be accounted for.

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. Reasons for discontinuation from the study will be summarized by cohort.

10.3.2.2. Patient Characteristics

Patient characteristics and baseline clinical measures will be summarized for both the baseline of the originating study and the baseline of Study AMAH by the cohorts described in Section 10.3.1. Baseline characteristics will include gender, age, age category, weight, race, geographic region (US/Non-US), 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 total score, BSA, PSSI, PSS symptom and sign total scores, DLQI total score, Short Form 36-item Health Survey (SF-36) (physical component summary), and SF-36 (mental component summary).

10.3.2.3. Concomitant

Previous and concomitant medications will be summarized for patients who enter Study AMAH by the cohorts described in Section 10.3.1. Summaries will be presented using the latest version of the World Health Organization drug dictionary.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who enter Study AMAH by the cohorts described in Section 10.3.1. A patient will be considered as having missed the visit if he or she fails to attend for administration of 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 and not missing 2 consecutive doses.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

For assessment of the primary endpoints and other categorical efficacy endpoints, proportions and 95% confidence intervals will be reported. Further details to be provided in the SAP. For the primary endpoint, missing data will be handled in at least 2 different ways: (1) proportions, calculated using only observed data, and (2) non-responder imputation (NRI). For the NRI method, all patients who do not meet the clinical response criteria or have missing clinical response data at the analysis time point will be defined as nonresponders.

10.3.3.2. Secondary Analyses

The secondary efficacy and health outcome endpoints of the trial are presented in Table AMAH.2. Details of the analysis methods that will be utilized are provided in Section 10.3.1. Additional analyses of the secondary efficacy and health outcome endpoints may be considered and will be fully detailed in the SAP.

10.3.3.3. Tertiary/Exploratory Analyses

The exploratory efficacy and health outcome endpoints of the trial are presented in Table AMAH.2. Details of the analysis methods that will be utilized are provided in Section 10.3.1. Additional analyses of the secondary efficacy and health outcome endpoints may be considered and will be fully detailed in the SAP.

10.3.4. Safety Analyses

Safety assessments will include AEs, laboratory analytes, vital signs, ECGs, and C-SSRS. Safety data assessments will be summarized for the cohorts described in Section 10.3.1

Adverse events will be coded according to the *Medical Dictionary for Regulatory Activities* 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 study 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 table of TEAEs. 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 plan for analyzing AESIs will be described in the Program Safety Analysis Plan and SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

No PK/pharmacodynamics (PD) analyses are planned.

Serum drug level sampling will support the assessment of immunogenicity (simultaneous sampling with immunogenicity sampling). Serum drug level samples are taken as an aliquot from the immunogenicity sample.

10.3.6. Evaluation of Immunogenicity

Immunogenicity will be evaluated cumulatively, using data both from the patient's originating study and from the present study. Baseline for ADA assessment will be the baseline ADA assessment from the originating study, and postbaseline will be time after initiation of mirikizumab. The frequency and percentage of patients with preexisting (baseline) ADA and with treatment-emergent ADA to mirikizumab will be tabulated. For patients with treatment-emergent ADA, 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

10.3.7.1. Subgroup Analyses

The primary analysis will focus on the cohorts described in Section 10.3.1. Additional subgroups for further analysis may be defined in the SAP.

10.3.8. Interim Analyses

As previously mentioned, Study AMAH is a double-blind study until the originating studies AMAJ and AMAK have had database lock and dosing for those studies is no longer blinded. After Study AMAH treatment is unblinded, multiple interim analyses will be performed as described in the SAP. To protect the study integrity during the blinded period, 1 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 an 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 members of the SAC will be internal to Lilly, but external to the study team. The study team will not have access to the 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. Study sites will receive information about interim assessments ONLY if they need to know for the safety of their patients. The DMC 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 will be done prior to the first unblinded assessment.

An unblinded interim analysis may be performed to support a regulatory submission when the originator studies have completed. Additional yearly interim analysis may be performed along with the 4-month safety update.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
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 events 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.
BP	blood pressure
BSA	body surface area
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
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.
ERB	Ethical Review Board
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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	intent-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
LS	least squares
LTBI	latent tuberculosis infection
LVTF	last visit of a qualifying study treatment period
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

PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic(s)
PK	pharmacokinetic(s)
PPASI	Palmoplantar Psoriasis Severity Index
PRN	as needed
PSS	Psoriasis Symptoms Scale
PSSI	Psoriasis Scalp Severity Index
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
SAP	statistical analysis plan
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	Short Form 36-item Health Survey
Spga	static Physician's Global Assessment
study drug	See "investigational product"
SUSARs	suspected unexpected serious adverse reactions
TB	Tuberculosis
TBL	total bilirubin level

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
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin	Total protein
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Cell morphology	Alanine aminotransferase (ALT)
Absolute Counts and Percentage of:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
Absolute Counts and Percentage of:	Glucose
Platelets	Albumin
	Cholesterol (total)
Urinalysis:	Low-density lipoprotein (LDL)
Specific gravity	High-density lipoprotein (HDL)
Ph	Triglycerides
Protein	Creatine kinase (CK)
Glucose	
Ketones	**Other:**
Bilirubin	HBV DNA test[b]
Urobilinogen	HCV RNA test[b]
Blood	Urine pregnancy test (females only; assayed locally by clinical study site)
Nitrite	PPD or QuantiFERON®-TB Gold test or T-SPOT®.TB test[c]
Urine leukocyte esterase	Anti-mirikizumab antibodies (immunogenicity)[a]
Microscopic examination of sediment	Serum mirikizumab concentration (PK)[a]
	Tryptase[a]

	Complement panel (C3 and C4)[a]
	Cytokine panel[a]
	High-sensitivity C-reactive protein (hsCRP)

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

Note: Tuberculosis testing will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure), and as required by local regulations and/or local standard of care.

[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] 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.

[c] Tuberculosis 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 the following:

- 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

Eli Lilly and Company (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 Investigator's Brochure (IB) and updates during the course of the study
- ICF
- 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 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 with 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 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. The CRF 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 or electrocardiogram 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-AMAH 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: WHOb [WWW]

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-AMAH(a) Summary (A Multicenter, Long-Term Extension to Evaluate the Long-Term Safety and Maintenance of Treatment Effect of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis [OASIS-3])

Overview

Protocol I6T-MC-AMAH (A Multicenter, Long-Term Extension to Evaluate the Long-Term Safety and Maintenance of Treatment Effect of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis [OASIS-3]) 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:

- Text has been added to Section 7.3 (Blinding). This text clarifies the roles and responsibilities of site personnel who know the treatment assignments of patients in Study AMAH, through their work in an originating study
- 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-AMAH Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Global	Various typos fixed and clarifications made	
Section 2. Schedule of Activities	1. Added "temperature" to Vital Signs 2. Added immunogenicity and associated PK sample to V1, for patients with no sample within prior 4 weeks	1. Regulatory request from US FDA 2. Ensures continuity of immunogenisity sampling
Section 5.1.3. 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 6.1. Inclusion Criteria	Added that local contraception guidelines must be followed	Allow sites to meet local regulatory requirements
Section 7.3. Blinding	Added text to clarify the roles and responsibilities of site personnel who know the treatment assignments of patients in Study AMAH, through their work in an originating study	Original protocol assumed all personnel start the study blinded, which is not necessarily true as patients continue from an originator study into this one with the same site personnel.
Section 7.8.2.1. Management of Hypersensitivity Events, Inlcuding 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 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 rest of the protocol. 2. Alignment with commitment to US FDA

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~~."	Alignment with commitment to US FDA
Section 9.4.4. Immunogenicity Assessments	Added that immunogenicity samples will be evaluated for PK, ADA, and additional exploratory markers of hypersensitivity.	To provide information in the event of a hypersensitivity event
Section 9.4.5.1. Physical Examination and Section 2. Schedule of Activities	Added peripheral lymph nodes to list for symptom-directed evaluation	New safety guideline
Section 9.4.5.2. Tuberculosis	Added expectation on timing of clinical assessments of TB risk	Clarification
Appendix 2. Clinical Laboratory Tests	1. Added "Gamma-glutamyl transferase (GGT)" to list of clinical chemistry. 2. Exploratory hypersensitivity biomarkers added	1. Regulatory request from US FDA 2. To provide information in the event of a hypersensitivity event
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 2. Schedule of Activities (overleaf)

Table AMAH.1. Schedule of Activities (Table Truncated)

Procedure[a]	Treatment Period (Visits 1-14, every-8-week visits)													
Visit Number	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Week Relative to Study Drug Initiation	**0**	**8**	**16**	**24**	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**1 ± 5**	**57 ± 5**	**113 ± 5**	**169 ± 5**	**225 ± 5**	**281 ± 5**	**337 ± 5**	**393 ± 5**	**449 ± 5**	**505 ± 5**	**561 ± 5**	**617 ± 5**	**673 ± 5**	**729 ± 5**
Vital signs (BP, temperature, and heart rate)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity for mirikizumab[n]	Xo	X	X	X			X			X			X	
Serum for mirikizumab concentrations (PK)[p]	Xo	X	X	X			X			X			X	

Procedure[a]	Treatment Period (Visits 15-21, every-16-week visits)							ETV[r]	Follow-up Period (Visits 801 and 802)	
Visit Number	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**		**V801**	**V802**
Week Relative to Study Drug Initiation	**120**	**136**	**152**	**168**	**184**	**200**	**208**		**LV +4W**	**LV +12W**
Day Relative to Study Drug Initiation, with Visit Tolerance Interval	**841 ± 5**	**953 ± 5**	**1065 ± 5**	**1177 ± 5**	**1289 ± 5**	**1401 ± 5**	**1457 ± 5**		**29 ± 5**	**~~112~~85 ± 5**
Vital signs (BP, temperature, and heart rate)[d]	X	X	X	X	X	X	X	X	X	X

[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 Visit 1. 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) (see Section 9.4.5.1.) Physical examination does not need to be performed again if Visit 1 occurs on the same date as the last visit of the originator study and if physical examination was performed at the last visit of the originator study.

[e] Tuberculosis testing will be conducted based on clinical assessment of TB risk (symptoms/signs/known or suspected TB exposure; risk factors detailed in Appendix 5), determined by the principal investigator, and according to local regulations and/or local standard of care (Section 9.4.6). Tuberculosis 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 the 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 Section 9.4.5.2.

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

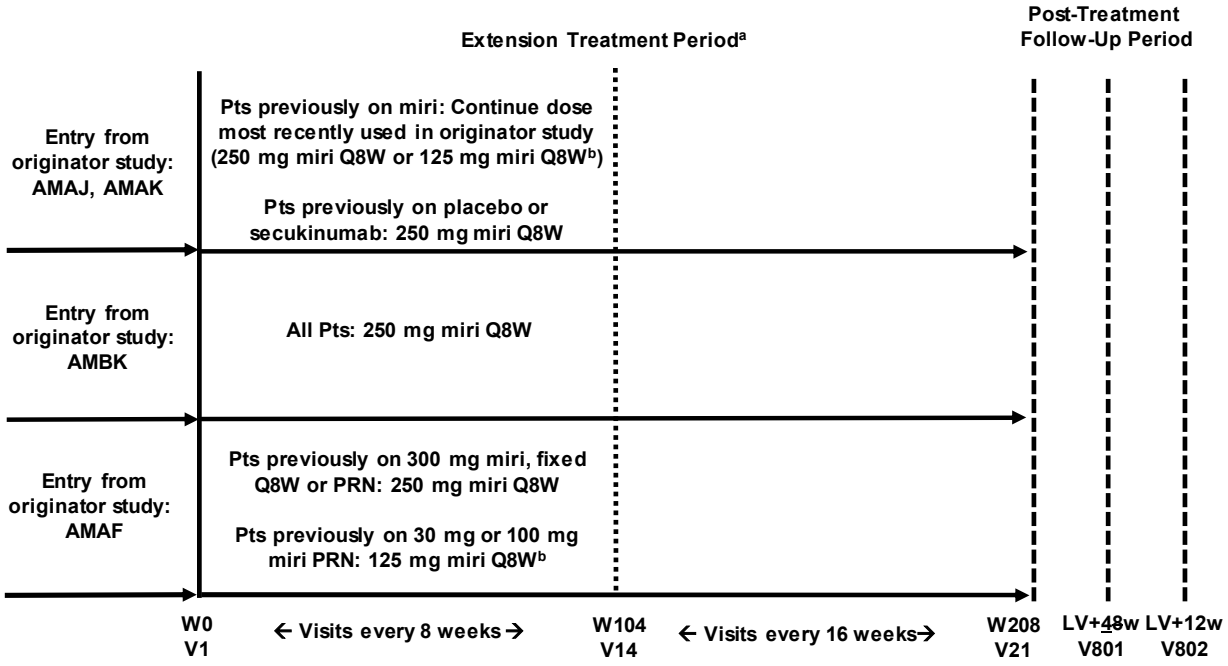
o Sample from last vist of originator study should be used. If no sample <4 weeks old is available, then a baseline sample should be collected in this study.

p Scheduled ~~P~~pharmacokinetic samples are taken as an aliquot from the immunogenicity sample. Unscheduled pharmacokinetic 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.

Section 5.1.3. Post-Treatment Follow-Up Period (12 Weeks)

All patients, whether they discontinue early for any reason or complete study treatment, will enter the 12-week Post-Treatment Follow-Up Period (Visit 801 and Visit 802) of Study AMAH.

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.



[a]Patients will remain blinded to treatment until the last patient completes the last originator study.
[b]Patients receiving 125 mg Q8W may be eligible to escalate to 250 mg Q8W, see section 7.4

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

Section 6.1. Inclusion Criteria

Patient Characteristics

[2b] Female Patients

Women of child-bearing potential:

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

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

Section 7.1. Treatments Administered

Table AMAH.3. Treatment Regimens

Originator Study	Treatment at End of Originating Study	Treatment in Study AMAH (Q8W)*
AMBK	250 mg miri Q4W	250 mg miri (2 x 1-~~ml~~ mL miri PFS)
AMAF	300 mg miri, Q8W fixed or PRN	250 mg miri (2 x 1-~~ml~~ mL miri PFS)
	30 mg or 100 mg miri PRN	125 mg miri[a] (1 x 1-~~ml~~ mL miri PFS plus 1 x 1-mL placebo PFS[b])
AMAJ	250 mg miri Q8W or secukinumab	250 mg miri (2 x 1-~~ml~~ mL miri PFS)
	125 mg miri Q8W	125 mg miri[a] (1 x 1-~~ml~~ mL miri PFS plus 1 x 1-mL placebo PFS[b])
AMAK	250 mg miri Q8W or placebo	250 mg miri (2 x 1-~~ml~~ mL miri PFS)
	125 mg miri Q8W	125 mg miri[a] (1 x 1-~~ml~~ mL miri PFS plus 1 x 1-mL placebo PFS[b])

…At the time of unblinding, patients, site personnel and the Sponsor will become unblinded so that patients on the 125 mg miri can stop receiving~~recieving~~ a 1 x 1-mL placebo PFS (see Table AMAH.3).

Section 7.3. Blinding

This is a double-blind study until the originating studies AMAJ and AMAK have had database lock and dosing for those studies is no longer blinded. The blinding applies to patients, site personnel, and Sponsor personnel.

Personnel in the originator Studies AMAF and AMAJ performing unblinded tasks (e.g., study drug dosing/dispensing) will by default know the treatment assignments of individual patients in Study AMAH by the protocol design. If these unblinded site personnel in the originator Studies AMAF and AMAJ also have a role in Study AMAH, they must assume the same responsibilities taken in the originator study for these patients and **must not** be involved in any patient assessment activities, seek any information related to these patients beyond their allowed activities, discuss the treatment assignment with the patient or with the blinded personnel.

Principal Investigators will need to ensure that the blinded conditions of the originating studies are maintained during Study AMAH until database lock has occurred and dosing for those studies is no longer blinded.

Section 7.7. Concomitant Therapy

Table AMAH.4. Excluded Classes of Concomitant Medications or Classes with Restricted Use (Table Truncated)

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, certolizu~~a~~mab)*	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 ~~months or 12~~ weeks~~, respectively,~~ after discontinuation of study drug).*	N	N	

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 the 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 (assess 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:

- ~~Opportunistic~~ Infections, including 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, electrocardiograms (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.

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, ADA, and additional exploratory markers of hypersensitivity (see Section 7.8.2.1). 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.

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

Diagnosis of LTBI During Study

Tuberculosis testing in Study AMAH 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.

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests (Table Truncated)

Clinical Chemistry[a]
Serum Concentrations of:
Gamma-glutamyl transferase (GGT)
Other
Tryptase[a]
Complement panel (C3 and C4)[a]
Cytokine panel[a]

[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.

[c] Tuberculosis 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 ~~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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