I6T-MC-AMAH Statistical Analysis Plan Version 2

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)

NCT03556202

Approval Date: 13-Feb-2020

1. Statistical Analysis Plan: 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

Mirikizumab (LY3074828) Plaque Psoriasis

Study AMAH is a Phase 3, 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.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I6T-MC-AMAH
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 13-Dec-2018
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 13-Feb-2020 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table of Contents

Figure **Page**

3. Revision History

Statistical Analysis Plan (SAP) Version 1 is approved prior to the first patient unblinding.

SAP Version 2 was approved after the unblinding to the external safety Data Monitoring Committee (DMC), and prior to the first unblinding to the study team. The changes made to the SAP are as follows:

- updated secondary endpoints and Table AMAH.3.1 to align with amendment (a) of Study AMAK and amendment (b) of Study AMAJ
- added clarification regarding the inclusion of Study AMBK
- updated details on the use of psoriasis therapy during Post-Treatment Follow-Up period
- added clarification surrounding the inclusion in and use of the ITT population
- updated the details for the handling of dropouts or missing data
    - included non-responder imputation as a method for handling missing data
- added a summary for treatment disposition
- added patient characteristic reporting for Visit 1 of Study AMAH in addition to the baseline of originating studies for measures that may change over time
- included definition and summary for prior medications
- updated Table AMAH.5.3 and Table AMAH.5.4 with additional details, including:
    - clarification of definitions of missing components
    - addition of sPGA(0)
    - addition of PASI 75
    - addition of PSS signs score
    - addition of PSSI score = 0
    - addition of NAPSI score = 0
    - addition of PPASI 50, PPASI 75, and PPASI 100
    - addition of DLQI (0,1) and DLQI total score ≥5 improvement from baseline
- added summaries to characterize patients that increase dosing
- added the analysis section for Japan submission and the Appendix of Analysis Plan for the Japan Addendum
- updated guidelines on interim database locks
- made other minor typographical corrections and clarifications not affecting content

4. Study Objectives

Table AMAH.4.1 shows the protocol defined objectives and endpoints of the study. The estimand (ICH E9 R1) associated with each endpoint/analysis is documented in the following places:

- The population and cohort of interest is described in the protocol inclusion/exclusion criteria and in this document in Section 6.1.1.
- The endpoints/variables are listed in Table AMAH.4.1, Table AMAH.6.3 and Table AMAH.6.4.
- The handling of intercurrent events is summarized in Sections 6.3.
- Population level summary measures are described in Section 6.9 and Table AMAH.6.4.

Table AMAH.4.1. Protocol Defined 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 Psoriasis Symptoms Scale (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 a Dermatology Life Quality Index (DLQI) total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5* • Change in Palmoplantar Psoriasis Severity Index (PPASI) total score in patients with palmoplantar involvement at baseline* • Change in Psoriasis Scalp Severity Index (PSSI) total score in patients with scalp involvement at baseline* • Change in Nail Psoriasis Severity Index (NAPSI) total score in patients with fingernail involvement at baseline*

Objectives	Endpoints
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.

* Secondary objectives have been updated to align with a protocol amendment (a) to Study AMAK and protocol amendment (b) to Study AMAJ. Since Study AMAH has not had another protocol amendment, changes have been reflected in this SAP but differ from those listed in the Study AMAH protocol amendment (a).

5. Study Design

Study AMAH is a long-term study in which patients completing one of the originator studies (AMAF, AMAJ, AMAK, or AMBK) will receive 250 mg or 125 mg mirikizumab every 8 weeks (Q8W), administered subcutaneous (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.
At the time of SAP Version 2, Study AMBK had not begun. In the event that Study AMBK begins while Study AMAH is ongoing, participants from Study AMBK may be allowed to participate in Study AMAH, and this SAP will be amended accordingly.

5.1. Summary of Study Design

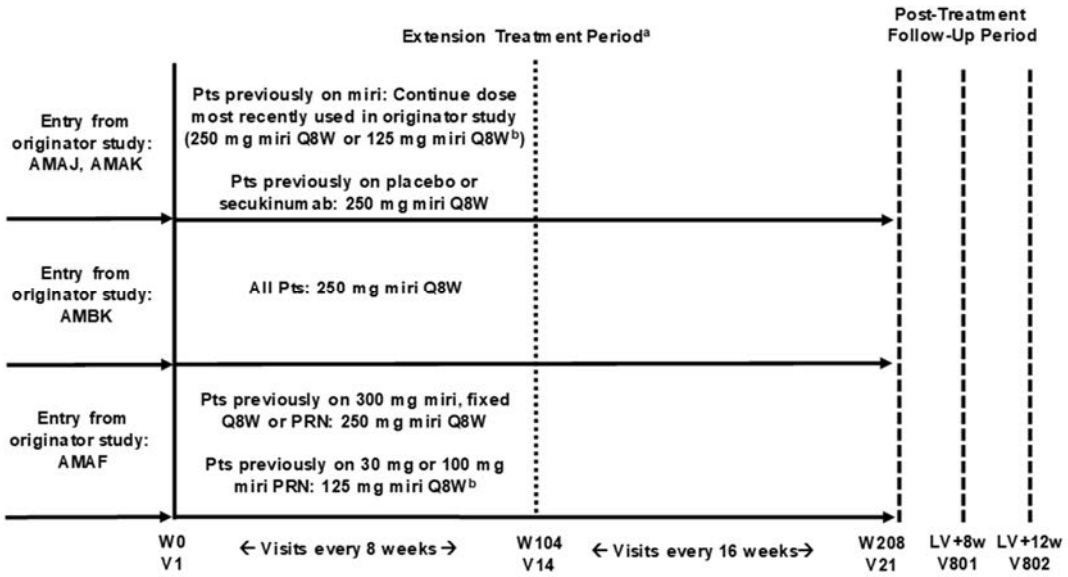
Patients who qualify for Study AMAH may enter directly into the study upon the last visit of a qualifying study treatment period (LVTP) of the originator study. For most patients, Week 52 of the originating study (AMAJ and AMAK) will be the LVTP and will coincide with Week 0 (Visit 1) for Study AMAH.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

Figure AMAH.5.1 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;

Figure AMAH.5.1. Illustration of study design for Clinical Protocol I6T-MC-AMAH.

Screening: There will be no screening period for Study AMAH. Visit 1 (Week 0) of Study AMAH may occur at the last visit, and within 12 weeks after the last visit, of the originator study.

Treatment Period: All patients participating in Study AMAH will receive mirikizumab 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 (Week 0) and continues to Visit 21 (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 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 achieve 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 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.

5.2. Determination of Sample Size

The sample size for Study AMAH will be determined by the number of patients who enroll in 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.

5.3. Method of Assignment to Treatment

All patients participating in Study AMAH will receive mirikizumab Q8W SC. The dose used in Study AMAH will depend on the treatment patients were receiving during the qualifying period of the originator study.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter, Lilly) or its designee. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) will be used.

Analyses and summaries from assessment of endpoints described in Table AMAH.4.1 of this Statistical Analysis Plan are planned to be included in the clinical study report (CSR). Analyses and summaries for key safety data are also planned to be included in the CSR. Results from additional efficacy analysis pre-defined below and other safety analyses may also be provided in the CSR, as deemed appropriate. Any analysis or summary not included in the CSR will be available upon request.

Any change to the data analysis methods described in the protocol will require a protocol 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 CSR.

Additional exploratory analyses of the data may be conducted, as deemed appropriate. Some of these additional supplementary analyses will be prespecified in a separate supplemental SAP.

Some of the analyses described in this document will be incorporated into interactive display tools instead of or in addition to static displays.

The Schedule of Activities outlined in the protocol specifies the allowable windows for assessments. Assessments performed outside these windows will not be excluded from any analysis.

6.1.1. Analysis Populations

Patient populations are defined in Table AMAH.6.1 along with the analysis they will be used to conduct. Patients will be analyzed according to the treatment to which they were assigned for all populations.

Table AMAH.6.1. Definition of Population

Population	Description
All Entered Patients	All patients who have signed the informed consent.
Intent-to-Treat (ITT) Population	All enrolled patients defined as those who have signed the informed consent and have been assigned to treatment in interactive web-response system (IWRS). Patients will be analyzed according to the treatment to which they were assigned. All efficacy and safety analyses will use ITT population.

Patients will be grouped based on the following 3 patient 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 assigned to 250 mg mirikizumab Q8W SC in Study AMAH who received secukinumab during the qualifying period of their originating study.

All efficacy analyses, including health outcome endpoints, will be conducted separately in patients of cohort (1), (2), and (3) on the ITT population. All safety analyses will be conducted on ITT population by cohort.

6.1.2. Baseline Definition

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 (that is, the study in which the patient received their first dose for this program).

6.1.3. Analysis Methods

For assessments of the primary endpoints and other binary efficacy and health outcomes, proportions for each cohort along with the 95% 2-sided asymptotic (i.e., not continuity corrected) confidence intervals (CIs) will be provided. Modified Non-responder Imputation (mNRI) method will be used to estimate the percentage of patients achieving response across post-baseline visits (see Section 6.3.4). In addition, multiple imputation (MI), Non-responder Imputation (NRI), and as Observed methods will be used as secondary analysis (see Section 6.3.1, Section 6.3.2, Section 6.3.1).

For continuous efficacy and health outcomes, MI method will be used for summaries.

Summaries based on observed data at each post-baseline visit will be provided (see Section 6.3.1).

6.2. Adjustments for Covariates

The analysis on the primary outcome is descriptive. No adjustments for covariates will be needed.

6.3. Handling of Dropouts or Missing Data

Intercurrent events [ICH E9(R1)] are events which occur after the treatment initiation and preclude observation of a variable or affect how it should be interpreted. Examples of such events include treatment discontinuation due to death or adverse events (AEs), rescue treatment, and loss to follow-up. This section describes missing data imputation methods handling intercurrent events, commonly used in the long-term extension studies (Ratitch 2018), which will be implemented in this study.

6.3.1. As Observed Analysis

The “as observed” strategy is used in so-called “observed cases” or “completers” analysis ubiquitous in the literature but is not one of the recommended strategies in the ICH E9(R1). For this analysis, only data from completers at the visit are relevant, and therefore the analysis does not need to deal with missing data. This estimand is based on the subset of patients who would complete treatment through visit T if assigned to it. Therefore, this estimand is conditional and targets the effect of treatment conditional on completion of treatment through the time point of interest. Because the estimand is defined for a subpopulation conditional on an intercurrent

event, it is not causal. Summary based on observed data at each post-baseline visit will be provided.

6.3.2. Multiple Imputation

The multiple imputation (MI) can be used to implement the hypothetical strategy [ICH E9(R1)] for handling intercurrent events. This strategy is used to assess the effect of study treatment in a hypothetical trial where all patients have complete data and continue to take study treatment as directed without dropping out of the study or receiving rescue therapy. The MI method will be used to impute missing data with values mimicking what observations would have been had the patient not discontinued, but instead continued receiving their assigned treatment. The method assumes the data are missing at random, meaning missingness can be accounted for by collected variables. Missing outcomes for a discontinued patient are assumed to resemble those of a patient who remained in the trial and had similar baseline scores and outcomes during visits prior to the patient's discontinuation. The MI method will be the primary analysis method for longitudinal continuous outcomes and the secondary analysis for binary outcomes.

Non-monotone (that is, intermittent missingness) and monotone (that is, missingness due to treatment discontinuation) missing data will be imputed separately within each cohort under ITT population. Non-monotone missing data will be imputed using a Markov chain Monte Carlo method based on multivariate normal distribution for all outcomes. Monotone missing data will be imputed using a sequential predictive mean matching (PMM) method. The PMM method chooses a value randomly from a set of plausible observed values (e.g., in the case of sPGA, these are integers 0,1,2,3,4,5). The set consists of measured patient outcomes whose predicted values are close to the predicted value for the missing value from the simulated regression model (Heitjan and Little 1991; Schenker and Taylor 1996).

The steps of the MI method are as follows:

1. The intermittent/non-monotone missing data will be imputed with Markov chain Monte Carlo method with the imputation model based on multivariate normal distribution for the baseline and post-baseline scores. Values will be imputed until the dataset has a monotone missing pattern. Imputation will occur by calling SAS® PROC MI.
2. The monotone missing data will be imputed with the PMM method by calling SAS® PROC MI (with MONOTONE statement and option REGPMM). Imputation will occur sequentially beginning at visit 1 and proceed through visit T (t=1,.., T) utilizing previous outcomes for visits 1 to t-1 and baseline scores. Specifically:
    a. First, predicted values for both observed and missing values are obtained from a regression model with coefficients sampled from the posterior predictive distribution of the parameters. The covariates of the model include the baseline score and previous outcomes of the variable of interest.
    b. Following, a set is produced consisting of the k observations whose predicted values are closest to the predicted value for the missing observation at visit t. The missing value is then replaced by a value drawn randomly from this set. The value of k will be set at 5.
3. The above steps will be repeated for m times with different seed values to create m imputed complete data sets. The value of m will be set at 100.

4. For binary outcomes, imputation of the underlying continuous score will be completed first, as outlined in the above steps. The binary response will then be derived from the imputed complete data.
5. The final summary and inference will be conducted from the multiple datasets using Rubin's combining rules, as implemented in SAS® PROC MIANALYZE.

6.3.3. Non-Responder Imputation

The non-responder imputation (NRI) method will be used to implement the composite strategy [ICH E9(R1)] for handling intercurrent events. This strategy is used to assess the combination of the effect of the study treatment with the occurrence of an intercurrent event. In this strategy patients are defined as responders only if they meet the clinical requirements for response at the predefined time AND they remain on the assigned study treatment. Failing either criteria by definition makes them nonresponders.

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. Enrolled patients without at least 1 observation within Study AMAH will also be defined as nonresponders for the NRI analysis. Analysis of binary categorical efficacy and health outcome variables may be assessed using an NRI method.

6.3.4. Modified Non-responder Imputation

The modified non-responder imputation (mNRI) method will be used to implement the composite strategy [ICH E9(R1)] for handling intercurrent events. This strategy is used to assess the combination of the effect of study treatment with the occurrence of an intercurrent event. For the mNRI method, the patient's response status is defined based on if the patient meets the clinical requirements for response at the predefined time AND the treatment-related contraindication reasons of discontinuation. The outcomes after the discontinuation for treatment-related reasons are considered failure/nonresponse, as in nonresponder imputation (NRI). Discontinuation for reasons that are considered unrelated to study treatment will not be considered a contraindication, thus the resulting outcomes will be imputed by MI. Patients will be considered as non-responders for the mNRI analysis at the analysis time point if they do not meet the clinical response criteria or have missing clinical response data due to discontinuation from study treatment with a reason of adverse event (AE) including death, or lack of efficacy. For patients discontinuing treatment with any other reason, the MI method (Section 6.3.2) will be used. The mNRI method will be the primary analysis method for categorical efficacy and health outcome variables.

6.4. Multiple Comparisons/Multiplicity

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

6.5. Patient Disposition

A detailed description of patient disposition from the study will be listed by timing and summarized with reasons for discontinuation by cohort for the ITT population. Frequency counts and percentages of patients discontinuing the treatment and study will be presented.

6.6. Patient Characteristics

Patient demographic variables, baseline characteristics and baseline clinical measures will be summarized for the baseline of the originating study and, for measurements that are expected to change over time, Visit 1 of Study AMAH by the cohorts described in Section 6.1.1. Table AMAH.6.2 describes the specific variables and how they will be summarized. The summary of additional patient characteristics and subgroup analysis will not require an amendment to the SAP.

Table AMAH.6.2. Patient Characteristics

Variable	Quantitative Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAH
Demographic Characteristics				
Age[a]	Yes	<65 years, ≥65 years	X	X
		<40 years, ≥40 years	X	X
Sex	No	Male, Female	X	
Age within Sex	No	Male <40 years, Male ≥40 years, Female <40 years, Female ≥40 years	X	X
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino	X	
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X	
Geographic Region	No	North America (Canada, Puerto Rico, United States), Europe (Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, United Kingdom), Other (Argentina, Australia, Israel, Japan, Korea, Mexico, Russia, Taiwan)	X	X
	No	By Country	X	X
	No	Asia (Israel, Japan, Korea, Taiwan), North America (Canada, Puerto Rico, United States), Australia, Central America/South America (Argentina, Mexico), Europe (Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, Spain, United Kingdom)	X	X
Height (cm)	Yes	None	X	

Variable	Quantitative Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAH
Weight (kg)	Yes	<80 kg, ≥80 kg	X	X
		<100 kg, ≥100 kg	X	X
BMI[b]	Yes	Underweight (<18.5 kg/m^2), Normal (≥18.5 and <25 kg/m^2), Overweight (≥25 and <30 kg/m^2), Obese (≥30 and <40 kg/m^2), Extreme obese (≥40 kg/m^2)	X	X
Alcohol use	No	Never, Current, Former	X	X
Caffeine use	No	Never, Current, Former	X	X
Tobacco use	No	Never, Current, Former	X	X
Prior Psoriasis Therapy				
Prior systemic therapy[d]	No	Never used, Ever used	X	
Prior biologic therapy[c]	No	Never used, Ever used	X	
Number prior biologics	No	0, 1, 2, >2	X	
Prior non-biologic systemic therapy[d]	No	Never used, Ever used	X	
Number of non-biologic systemic therapies[d]	No	0, 1, 2, >2	X	
Psoriasis Duration and Age at Onset				
Duration of psoriasis (years) [e]	Yes	<15, ≥15	X	X
Duration of diagnosis (years) [f]	Yes	None	X	X
Age at onset (years) [g]	Yes	<25, ≥25	X	
Area of Involvement				
Facial involvement	No	Yes, No	X	
Nail involvement	No	Yes, No	X	
Scalp involvement	No	Yes, No	X	
Palmoplantar involvement	No	Palm involvement only, Sole Involvement only, Both, either	X	
		Yes, No	X	
Baseline Psoriatic Arthritis	No	Yes, No	X	

Variable	Quantitative Summary	Categorical Summary	Baseline Summary	
			Originating Studies	Study AMAH
Baseline Disease Severity				
Baseline PASI score	Yes	<20, ≥20	X	
		<15, ≥15	X	
Baseline sPGA score	No	Clear (0), Minimal (1), Mild (2), Moderate (3), Severe (4), or Very severe (5)	X	
Baseline BSA (%)	Yes	<20%, ≥20%	X	
Baseline PSSI	Yes	None	X	
Baseline NAPSI	Yes	None	X	
Baseline PPASI	Yes	None	X	
Baseline PSS sign scores	Yes	0, 0 to 1, ≥1	X	
Baseline PSS symptom score	Yes	0, 0 to 1, ≥1	X	
Baseline DLQI total score	Yes	0 or 1, >1	X	
		≤10, >10	X	
		<5, ≥5	X	

Abbreviations: BMI = body mass index; BSA = body surface area; eCRF = electronic case report form; IL-17 = interleukin 17; MCS = mental component score; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PCS = physical component score; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; PUVA = psoralen and ultraviolet A; sPGA = Static Physician Global Assessment; TNF = tumor necrosis factor; UVB = ultraviolet B.

[a] Age in years will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the informed consent date.

[b] Body Mass Index (BMI) will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ (m))^2$.

[c] Biologic systemic therapies include: Efalizumab, Ustekinumab, Infliximab, Etanercept, Alefacept, Adalimumab, Golimumab, Certolizumab pegol, Secukinumab, Ixekizumab, Brodalumab, and other biologic agents.

[d] Non-biologics systemic therapies include: Cyclosporine, Methotrexate, Corticosteroids, Acitretin, Fumaric acid derivatives, Apremilast, other systemic agents, and psoralen and ultraviolet A (PUVA).

[e] Duration of psoriasis is calculated as: (date of informed consent – date of psoriasis onset)/365.25.

[f] Duration of psoriasis diagnosis is calculated as: (date of informed consent – date of psoriasis diagnosis)/365.25.

[g] Age at diagnosis in years will be calculated as the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the date of psoriasis diagnosis.

6.7. Treatment Compliance

Treatment compliance for each patient will be calculated as:

$$Treatment\ compliance\ (\%) = 100 \times \frac{Total\ number\ of\ injections\ administered}{Total\ number\ of\ injections\ prescribed}$$

- The total number of injections prescribed can be derived from the Interactive Web Response System (IWRS) study drug dispense dataset.

- The total number of injections administered will be derived using the response to the question "Was dose administered?" on the *Exposure as Collected* eCRF page.

A patient will be considered overall compliant with study treatment within each treatment period if he/she misses no more than 20% of the expected doses and does not miss 2 consecutive doses. In the case a patient missed more than 20% of the prescribed doses during the study because of the investigator temporarily interrupted the treatment, the patient will not be considered as noncompliant.

The patient compliance will be summarized by cohort.

6.8. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) Drug Dictionary. Medication start and stop dates will be compared to the date of first dose of treatment in Study AMAH to allow medications to be classified as concomitant for each treatment period.

Prior medications are those medications that start and stop prior to the date of first dose of study treatment. *Concomitant medications* are those medications that start before, on, or after the first day of study treatment of the defined treatment period and continue into the treatment period. For the ITT population, prior and concomitant medications will be summarized separately by preferred term in descending frequency. Additional summaries will be given for the use of (1) topical therapies, (2) topical steroid therapy, and (3) systemic corticosteroid therapy as concomitant therapies. The drugs included in these classes are defined by compound level safety standards.

6.9. Efficacy Analyses

Table AMAH.6.3 includes the description and derivation of the efficacy/health outcomes measures and endpoints.

Table AMAH.6.4 provides the detailed analyses including analysis type, method and imputation, population, and time point for efficacy/health outcomes analyses**.**

Table AMAH.6.3. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
sPGA	Static Physician Global Assessment (sPGA): the physician's global assessment of the patient's psoriasis lesions at a given time point. 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).	sPGA score	Range from 0 to 5: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	Single item, missing if missing. For the duplicate individual score at the same visit, choose the latest results.
		sPGA (0,1)	An sPGA assessed as either 0 or 1 with at least a 2-point improvement from baseline, which represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.	Missing if sPGA is missing.
		sPGA (0)	An sPGA assessed as 0 with at least a 2-point improvement from baseline, which represents a clinically important endpoint indicating complete resolution of plaque psoriasis.	Missing if sPGA is missing.
PASI	Psoriasis Area and Severity Index (PASI): combines assessments of the extent of body-surface involvement in 4 anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness, T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease (Fredriksson and Pettersson 1978).	PASI score	The composite PASI score is calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the 4 resulting quantities as follows: $PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l$ Where, R_h, R_u, R_t, R_l = redness score of plaques on the head, upper limb, trunk, and lower	If any individual score is missing, the PASI score will not be calculated, hence, missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
	Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for very severe involvement): 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe The body is divided into 4 anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement; up to 6 for 90% - 100% involvement): 0 = 0% (clear) 1 = >0% to <10% 2 = 10% to <30% 3 = 30% to <50% 4 = 50% to <70% 5 = 70% to <90% 6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of body surface area.		limb, scored 0-4 respectively; T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper limb, trunk, and lower limb, scored 0-4 respectively; A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper limb, trunk, and lower limb, respectively. PASI scores are treated as a continuous score, with 0.1 increments within these values.	
		PASI change from baseline	Calculated as: observed PASI – baseline PASI.	Missing if baseline or observed value is missing.
		PASI percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing if baseline or observed value is missing.
		PASI 75	A clinically meaningful response; ≥75% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
		PASI 90	Higher level of clearance; PASI 90 is a ≥90% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.
		PASI 100	Complete resolution of plaque psoriasis; a 100% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.
PSS	The Psoriasis Symptoms Scale (PSS) is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms. The overall severity for each individual symptom from patient's psoriasis is indicated by selecting the number from an NRS of 0 to 10 that best describes the worst level of each symptom in the area in the past 24 hours, where 0 (= no severity) and 10 (worst imaginable severity). 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, discomfort, stinging,	PSS item scores	The PSS score for each item as collected during office based assessment. itch, pain, discomfort, stinging, burning, redness, scaling, and cracking	The item is missing if it is not present in the data.
		PSS symptoms score	Calculated by summing the individual item scores as follows: itch NRS + pain NRS + stinging NRS + burning NRS.	If any of the 4 relevant item scores are missing, the score is missing.
		PSS signs score	Calculated by summing the individual item scores as follows: redness NRS + scaling NRS + cracking NRS	If any of the 3 relevant item scores are missing, the score is missing.
		PSS symptoms score of 0	Free of itch, pain, stinging, and burning.	Missing if PSS symptoms score is missing.
		PSS signs score of 0	Free of redness, scaling, and cracking	Missing if PSS signs score is missing.
		PSS symptoms, signs score change from baseline	Change from baseline = Observed PSS score – Baseline PSS score. Here "PSS score" could refer to the items, symptoms or signs score. Negative change indicates improvement and a positive change indicates deterioration of the condition.	Missing if either observed or baseline PSS score is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
	burning, redness, scaling, and cracking.			
PSSI	Psoriasis Scalp Severity Index (PSSI): in patients with scalp psoriasis at baseline. The scalp will be assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows: Erythema, Induration, and Desquamation: 0 = Absent 1 = Slight 2 = Moderate 3 = Severe 4 = Severest Possible Percent of Scalp Involved: 0 = none 1 = <10% 2 = 10 – 29% 3 = 30 – 49% 4 = 50 – 69% 5 = 70 – 89% 6 = 90 – 100%	PSSI score	The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 to 72.	If any individual score is missing, the PSSI score will not be calculated, hence missing. For the duplicate individual score at the same visit, choose the latest results.
		PSSI score change from baseline	Calculated as: observed PSSI – baseline PSSI	Missing if baseline or observed value is missing.
		PSSI score = 0	A PSSI assessed as 0, which represents the absence of scalp psoriasis.	Missing if PSSI score is missing.
NAPSI	Nail Psoriasis Severity Index (NAPSI): in patients with fingernail psoriasis involvement at baseline, NAPSI will be used to evaluate the severity of fingernail bed psoriasis and fingernail matrix psoriasis by area of involvement in the fingernail unit. The	NAPSI score	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), usually indicated as NAPSI score.	For each fingernail, if either bed or matrix score is missing or not done, the score for that finger is missing. If <50% of the finger scores from 10 fingers are missing, the

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
	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: 0 = None 1 = present in one quadrant of nail 2 = present in two quadrants of nail 3 = present in three quadrants of nail 4 = present in four quadrants of nail			imputation will be performed by using the average score of the remaining fingernails. If ≥50% of the finger scores are missing, the NAPSI score will be left as missing. For the duplicate scores at the same visit, choose the latest results
		NAPSI score change from baseline	Calculated as: observed NAPSI – baseline NAPSI	Missing if baseline or observed value is missing.
		NAPSI score = 0	A NAPSI assessed as 0, which represents the absence of nail psoriasis.	Missing if NAPSI score is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
PPASI	Palmoplantar Psoriasis Area and Severity Index (PPASI): in patients with palmoplantar psoriasis at baseline, both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows: Erythema (E), Induration (I), and Desquamation (D): 0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe Percent of Palm and Sole Area Covered: 0 = None 1 = <10% 2 = 10 – 29% 3 = 30 – 49% 4 = 50 – 69% 5 = 70 – 89% 6 = 90 – 100%	PPASI score	The PPASI score is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of palm and sole area involvement. The range is 0 to 72. $PPASI = 0.2(E_{rp} + I_{rp} + D_{rp})A_{rp} + 0.2(E_{lp} + I_{lp} + D_{lp})A_{lp} + 0.3(E_{rs} + I_{rs} + D_{rs})A_{rs} + 0.3(E_{ls} + I_{ls} + D_{ls})A_{ls}$ where: E_{rp}, E_{lp}, E_{rs}, E_{ls} = Erythema score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; I_{rp}, I_{lp}, I_{rs}, I_{ls} = Induration score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; D_{rp}, D_{lp}, D_{rs}, D_{ls} = Desquamation score of plaques on the right palm (rp), left palm (lp), right sole (rs), left sole (ls), scored 0-4 respectively; A_{rp}, A_{lp}, A_{rs}, A_{ls} = numerical value translation of % area covered for the right palm, left palm, right sole, and left sole, respectively.	If any individual score is missing, the PPASI score will not be calculated, hence, missing. For the duplicate scores at the same visit, choose the latest results.
		PPASI change from baseline	Calculated as: observed PPASI – baseline PPASI.	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
		PPASI percent improvement from baseline	Calculated as: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ \ PPASI - Observed\ \ PPASI}{Baseline\ \ PPASI}$ If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	Missing if baseline or observed value is missing.
		PPASI 50	A ≥50% improvement in PPASI score from baseline	Missing if baseline or observed value is missing.
		PPASI 75	A ≥75% improvement in PPASI score from baseline	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing/duplicate Components
		PPASI 100	a 100% improvement in PPASI score from baseline	Missing if baseline or observed value is missing.
DLQI	Dermatology Life Quality Index (DLQI): is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related QoL. This questionnaire has 10 items that are grouped in 6 domains, including 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 and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0	DLQI total score	A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a post-baseline DLQI total score of 0 or 1. A DLQI total score of 0 to 1 is considered as having no effect on a patient's HRQoL (Khilji et al. 2002; Hongbo et al. 2005).	Missing if DLQI total score is missing.
		DLQI (0,1) and DLQI total score ≥5 improvement from baseline	Patient is a DLQI (0,1) responder and reduction/decrease of ≥5 points from baseline	Missing if baseline or the total score is missing.

Abbreviations: DLQI = Global Assessment Dermatology Life Quality Index; HRQoL = health-related quality of life; NRS = Numeric Rating Scales; SAP = statistical analysis plan; PASI = Psoriasis Area and Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; sPGA = Static Physician Global Assessment.

Table AMAH.6.4. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point
PASI	PASI 90 (Primary)	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT - patients who entered Study AMAH with a PASI 90 response	All visits in corresponding Periods
	PASI 75; PASI 90; PASI 100 (Secondary)	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT	All visits in corresponding periods
sPGA	sPGA (0,1) (Primary)	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT - patients who entered Study AMAH with sPGA (0,1)	All visits in corresponding periods
	sPGA (0); sPGA (0,1) (Secondary)	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT	All visits in corresponding periods
PSS	PSS symptoms score of 0;	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with a PSS symptoms score ≥1 at Baseline	All visits in corresponding periods
	PSS signs score of 0;	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with a PSS signs score ≥1 at Baseline	All visits in corresponding periods
PSSI	PSSI change from baseline	Descriptive analysis with Observed and Multiple Imputation	ITT - patients with Scalp Involvement at Baseline	All visits in corresponding periods
	PSSI = 0	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with Scalp Involvement at Baseline	All visits in corresponding periods
PPASI	PPASI change from baseline	Descriptive analysis with Observed and Multiple Imputation	ITT - patients with Palmoplantar Involvement at Baseline	All visits in corresponding periods

Measure	Variable	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Time Point
	PPASI 50; PPASI 75; PPASI 100	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with Palmoplantar Involvement at Baseline	All visits in corresponding periods
NAPSI	NAPSI change from baseline	Descriptive analysis with Observed and Multiple Imputation	ITT - patients with Nail Psoriasis Involvement at Baseline	All visits in corresponding periods
	NAPSI = 0	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with Nail Psoriasis Involvement at Baseline	All visits in corresponding periods
DLQI	DLQI (0,1)	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT - patients with Baseline DLQI > 1	All visits in corresponding periods
	DLQI (0,1) and ≥5-point reduction from Baseline	Descriptive analysis with Observed, NRI, mNRI and Multiple Imputation	ITT – patients with DLQI ≥5 at Baseline	All visits in corresponding periods

Abbreviations: DLQI = Global Assessment Dermatology Life Quality Index; mNRI = modified non responder imputation; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/90%/100% improvement from baseline in the Psoriasis Area and Severity Index; PPASI = Palmoplantar Psoriasis Severity Index; PPASI 50/75/100 = ≥50%/75%/100% improvement from baseline in the Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; sPGA = Static Physician Global Assessment.

6.9.1. Primary Outcome and Methodology
Primary outcomes, sPGA (0,1) and PASI 90 and their analyses are described in Table AMAH.6.3 and Table AMAH.6.4.

6.9.2. Additional Analyses of the Primary Outcome
Additional analyses of the primary outcomes are described in Table AMAH.6.3 and Table AMAH.6.4.

After Study AMAH dosing is no longer blinded, patients may be increased from 125 mg mirikizumab Q8W to 250 mg mirikizumab Q8W. Additional summaries to characterize the patients that increase dosing will be presented. These summaries include:

- The number of patients who increase dosing of mirikizumab by visit
- sPGA and PASI scores or other measurements at the visit prior to titration of mirikizumab

6.9.3. Multiple Testing Controlled Secondary Efficacy Analyses
Not Applicable.

6.9.4. Secondary Efficacy Analyses
Other secondary analyses of efficacy are described in Table AMAH.6.3 and Table AMAH.6.4.

6.9.5. Sensitivity Analyses
Not Applicable.

6.10. Health Outcomes/Quality-of-Life Analyses
Secondary analysis of health outcomes/quality of life are described in Table AMAH.6.3.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods
Details of pharmacokinetic/pharmacodynamic (PK/PD) analyses can be found in a separate PK/PD analysis plan.

6.12. Safety Analyses
For the purpose of Study AMAH alone, the following are planned:

- Listing of Serious Adverse Events (SAEs)
- Listing of adverse events leading to permanent discontinuation of study drug
- Summary of SAEs (with different columns for cohorts specified in Section 6.1.1)
- Summary of AEs leading to permanent discontinuation of study drug (with different columns for cohorts specified in Section 6.1.1)

The safety data from this study will also be used as part of integrated safety assessments and ongoing safety review through study end.

6.12.1. Extent of Exposure
The exposure will be calculated as:

Date of last study visit during the treatment period – Date of first dose for the treatment period of Study AMAH+1 day

Overall exposure will be summarized in total patient years (PY), derived in the following manner:

Exposure in PY = Sum of duration of exposure in days (for all patients in treatment group) / 365.25.

Total PY of exposure will be reported. Descriptive statistics will be provided for patient-weeks of exposure and the frequency of patients falling into different exposure ranges will be summarized:

- >0; ⩾24 weeks; ⩾48 weeks; ⩾72 weeks;⩾96 weeks; ≥120 weeks; ≥152 weeks; ≥152 weeks; ≥184 weeks; ≥208 weeks
- >0 to <24 weeks; ≥24 weeks to <48 weeks; ≥48 weeks to < 72 weeks; ≥ 72 weeks to < 96; ≥ 96 weeks to < 120; ≥ 120 weeks to < 152; ≥152 weeks to < 184 weeks; ≥184 weeks to <208 weeks; ≥208 weeks.

Additional exposure ranges may be considered, if necessary. No p-values will be reported in these tables as they are intended to describe the study populations, rather than test hypotheses about them.

A by-patient listing of assigned treatments will be provided.

6.12.2. 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.

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample anti-drug antibodies (ADA) assay result and potentially a sample neutralizing anti-drug antibodies (NAb) assay result. A patient has treatment-emergent anti-drug antibodies (TE-ADA) when ADA are induced or boosted by exposure to study drug; i.e., when at least one postbaseline ADA sample has a 4-fold increase in titer, compared to baseline (if ADA were present at baseline) or has a titer 2-fold greater than the minimum required dilution of 1:10 (if no ADA were present at baseline).

Compound level safety standards will be followed in the analyses of immunogenicity. The summary of TE ADA and neutralizing antibody (NAb) status will be produced for the ITT population (including originating studies and Study AMAH).

6.13. Protocol Deviations

Protocol deviations will be identified throughout the study. Important protocol deviations are defined as those deviations from the protocol likely to have a significant impact on the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

A separate document known as the "The AMAH Trial Issues Management Plan" describes the categories and subcategories of important protocol deviations and whether or not these deviations are important protocol violations.

The number and percentage of patients having important protocol deviation(s) will be summarized within category and subcategory of deviations by cohort for ITT population.

A by-patient listing of important protocol deviations will be provided.

6.14. Analysis for Japan Addendum

Protocol Addendum I6T-MC-AMAH(1.1) is performed in Japan to enable the inclusion of patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) to fulfill the needs for Japan submission. Appendix 1 provides the details of analysis for the Japan Addendum.

6.15. Interim Analyses and Data Monitoring

Data Monitoring Committee (DMC): One DMC, consisting of members external to Lilly, will be established for interim safety monitoring across Studies I6T-MC-AMAK, I6T-MC-AMAJ, I6T-MC-AMAH and I6T-MC-AMBK in patients with psoriasis. This committee will consist of a minimum of 3 members, including a physician with expertise in dermatology and a statistician. No member of the DMC may have contact with study sites. A Statistical Analysis Center (SAC) will prepare and provide unblinded safety data to the DMC. The SAC members may be Lilly employees or from third-party organizations designated by Lilly. However, they will be external to the study team and will have no contact with sites and no privileges to influence any change in the ongoing study. Access to the unblinded safety data will be limited to the DMC and the SAC or their designees. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded data. The purpose of the DMC is to advise Lilly regarding continuing patient safety; however, the DMC may request key efficacy data to put safety observations into context and to confirm a reasonable benefit/risk profile for ongoing patients in the study. Study sites will receive information about interim assessments ONLY if they need to know for the safety of their patients. This committee will make recommendations as to whether it is scientifically and ethically appropriate to continue enrollment, discontinue a treatment group, or discontinue the study. Details outlining the roles and responsibilities of the DMC will be finalized in the DMC charter.

Interim Database Lock: An unblinded interim analysis may be performed to support a regulatory submission. Additional yearly or ad-hoc interim analysis may be performed along with the 4-month safety update or to meet any external regulatory needs.

Final Database Lock: A final database lock will occur after the Post-Treatment Follow-Up Period is completed.

6.16. Annual Report Analyses

Based on regulatory requirements for the Development Safety Update Report (DSUR), reports will be produced (if not already available from the study CSR) for the reporting period covered by the DSUR.

6.17. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized by treatment group, by MedDRA preferred term.

- An AE is considered "Serious," whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each SAE and "Other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Refer to a separate blinding and unblinding plan.

8. References

Fredriksson T, Petterson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.

Heitjan F. and Little RJA. (1991), Multiple imputation for the fatal accident reporting system. *Applied Statistics*. 1991;40:13–29.

PhUSE resouces page. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Summary Documents. 2015. Available at http://www.phusewiki.org/docs/CSS%20White%20Papers%202016/CS_WhitePaper_Outliers Shifts_v1.0.pdf. Accessed September 18, 2017.

Ratitch B, Lipkovich I, Erickson JS, Zhang L, Mallinckrodt CH. Points to consider for analyzing efficacy outcomes in long-term extension clinical trials. *Pharmaceutical Statistics*. 2018:1–16. DOI: https://doi.org/10.1002/pst.1888

Schenker N. and Taylor JMG. (1996), Partially parametric techniques for multiple imputation. *Computational Statistics and Data Analysis*. 1996;22:425–446.

9. Appendices

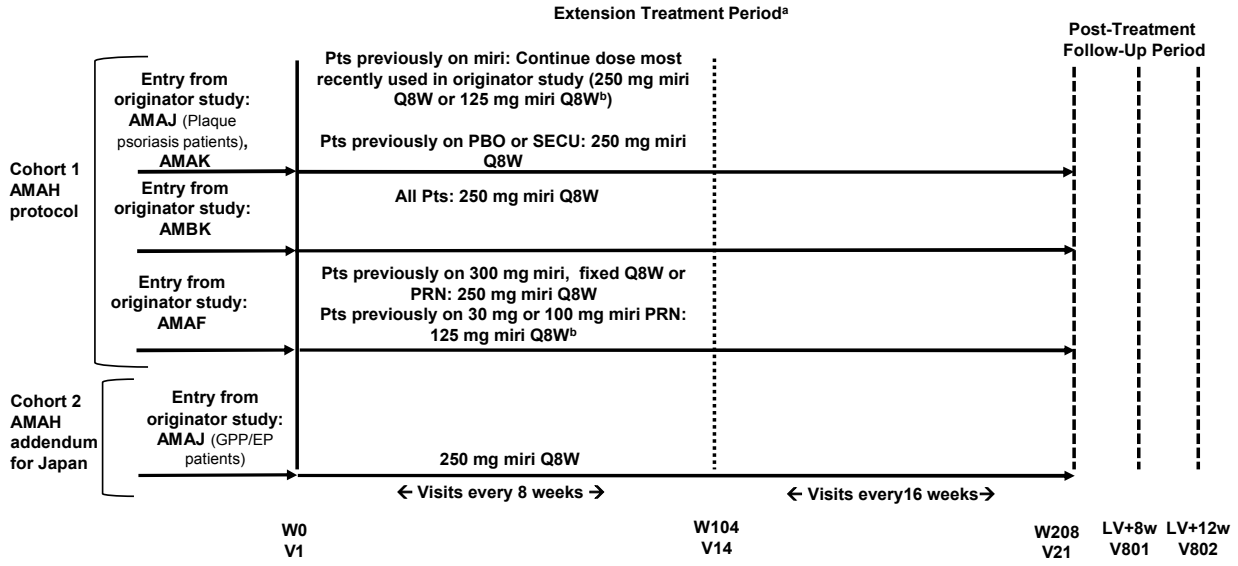
Appendix 1. Analysis Plan for Japan Addendum

App 1.1. Japan Addendum Design and Objecties

The main protocol for Study AMAH enrolls patients with plaque psoriasis (Cohort 1). AMAH(1.1) addendum will enroll Japanese patients originating from Study AMAJ who are diagnosed as GPP by the Japanese Dermatological Association or EP who have ≥80% body surface area (BSA) involvement (with inflammatory erythema). These patients will continue to receive 250 mg mirikizumab every 8 weeks (Q8W) SC for up to a total of 208 weeks (Cohort 2).

Approximately 8 patients with generalized pustular psoriasis (GPP) or erythrodermic psoriasis (EP) will enroll in AMAJ. The number of patients in Cohort 2 will be determined by the number who continue into Study AMAH from Study AMAJ who reside in Japan and have a diagnosis of GPP or EP.

Objectives in the main protocol are not applied to GPP and EP patients. Selected endpoints in the main protocol are applied to GPP and EP patinets. Table AMAH.App.1 shows the addendum objectives and endpoints which are added to the study as exploratory objectives:



Abbreviations: AMAF = I6T-MC-AMAF; AMAJ = I6T-MC-AMAJ; AMAK = I6T-MC-AMAK; AMAH = I6T-MC-AMAH; AMBK = I6T-MC-AMBK; LV = last study visit; miri = mirikizumab given as subcutaneous injection (SC); PBO = placebo; PRN=as needed; pts = patients; Q8W =every 8 weeks; SECU = secukinumab; 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

Table AMAH.App.1. Japan Addendum Objectives and Endpoints

Exploratory To assess the efficacy of mirikizumab in patients with GPP.	**GPP ONLY** Time course of response to treatment as measured by the following measures: • global improvement score • assessment of dermal symptoms for GPP • change from baseline in PASI • change from baseline in DLQI total score
To assess the efficacy of mirikizumab in patients with EP	**EP ONLY** Time course of response to treatment as measured by the following measures: • global improvement score • change from baseline in PASI • change from baseline in DLQI total score

Abbreviations: DLQI = Dermatology Life Quality Index; EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis; PASI = Psoriasis Area and Severity Index.

App. 1.2. Japan Addendum General Considerations

The benefit/risk profile to support global registrations will be based on the analysis of Cohort 1.

Patients enrolled in Cohort 2 will not be included in the analysis supporting global registrations. To support registration in Japan, efficacay and safety analyses for plaque psoriasis, GPP, and EP will be conducted separately.

The Japan Addendum Intent-to-Treat (ITT) Population – Patients with GPP or EP is defined as all GPP and EP patinets who enrolled in the Japan addendum, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. All patients are assigned to mirikizumab treatment. Efficacy and safety analyses will be conducted on this population. GPP and EP patients will be reported separately.

The definitions of the baselines for efficacy and safety analyses in the Japan addendum are the same as in the main protocol/SAP.

No formal inferential statistics will be performed. Data will be summarized for GPP and EP patients separately. The methods of summary are the same as in the main SAP.

The following general summaries and/or listings will be provided based on Japan Addendum ITT Population – Patients with GPP or EP:

- Patient disposition including treatment disposition and study disposition
- Patient demographics and other baseline characteristics

    - Add baseline GPP dermal symptom total score
- Prior medications and concomitant medications
- Study treatment exposure
- Listing of randomization/treatment assignment
- Important protocol deviations
- Treatment compliance

App. 1.3. Japan Addendum Efficacy/Health Outcomes

Table AMAH.App.2 includes the description and derivation of the additional efficacy measures and endpoints that are collected in the Japan Addendum.

Table AMAH.App.3 provides the detailed analyses for efficacy/health outcomes analyses in the Japan Addendum.

Table AMAH.App.2 Description and Derivation of Additional Efficacy/Health Outcomes Measures and Endpoints for Japan Addendum

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
Global Improvement Score	• Collected for patients with GPP or EP from Week 2. • Assessed in the 4 grades by comparing the psoriatic findings: (1) resolved, (2) improved, (3) unchanged, (4) worsened. • Assessed based on the comparison of the psoriatic findings, sPGA, PASI score, and other evaluations with those at the baseline.	Global improvement score	As collected	Single item, missing if missing.
Assessment of dermal symptoms	• According to the Japanese Dermatological Association GPP revised criteria.[a] • Performed only for patients with GPP. • Skin symptoms are assessed by the score with the area of erythema (on a 0-3 scale), the area of erythema with pustules (on a 0-3 scale), and the area of skin edema (on a 0-3), where 0 = none; 1 = mild; 2 = moderate; 3 = severe.	GPP dermal symptom total score	Sum of scores of the area of erythema, the area of erythema with pustules, and the area of skin edema. Range from 0-9.	If any individual score is missing, the total score will not be calculated, hence missing.

Abbreviations: EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment.

[a] (Terui et al. [WWW]).

Table AMAH.App.3. Description of Efficacy/Health Outcomes Analyses for Japan Addendum

Measure	Variable	Analysis Method	Population	Time Point and Period
Global Improvement Score	Global improvement score	Descriptive analysis with Observed	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits
GPP dermal symptom total score	GPP dermal symptom total score change from baseline	Descriptive analysis with Observed	Japan Addendum Intent-to-Treat Population – Patients with GPP	All scheduled visits
PASI	PASI change from baseline	Descriptive analysis with Observed	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits
DLQI	DLQI total score change from baseline	Descriptive analysis with Observed	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits

Abbreviations: DLQI = Dermatology Life Quality Index; EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis; PASI = Psoriasis Area and Severity Index.

App. 1.4. Japan Addendum Safety Analyses

The following safety summaries will be provided for the Japan Addendum Intent-to-Treat (ITT) Population – Patients with GPP or EP:

- Listing of Serious Adverse Events (SAEs)
- Listing of adverse events leading to permanent discontinuation of study drug
- Summary of SAEs
- Summary of AEs leading to permanent discontinuation of study drug

References

Terui T, Akiyama M, Ikeda S, Ozawa A, Kanekura T, Kurosawa M, Komiyane M, Sano S, Nemoto O, Muto M, Yamanishi K, Iwatsuki K. Practice Guidelines 2014 for generalized pustular psoriasis (GPP). Japanese Dermatological Association web site. Available at: https://www.dermatol.or.jp/uploads/uploads/files/guideline/nouhouseikansenguideline.pdf. Accessed January 16, 2017.

Umezawa Y, Ozawa A, Kawasima T, Shimizu H, Terui T, Tagami H, Ikeda S, Ogawa H, Kawada A, Tezuka T, Igarashi A, Harada S. Therapeutic guidelines for the treatment of generalized pustular psoriasis (GPP) based on a proposed classification of disease severity. *Arch Dermatol Res*. 2003;295(suppl 1):S43-S54.

Leo Document ID = 60334e62-b120-46a3-a98f-1f59c9437d5b

Approver: PPD

Approval Date & Time: 13-Feb-2020 14:39:18 GMT

Signature meaning: Approved