Statistical Analysis Plan Version 3

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

NCT03482011

Approval Date: 28-Mar-2019

1. Statistical Analysis Plan: I6T-MC-AMAK: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Withdrawal Maintenance Dosing Period to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderate-to-Severe Plaque Psoriasis OASIS-1

Mirikizumab (LY3074828) Plaque Psoriasis

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

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I6T-MC-AMAK
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 07 October 2018
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 12 December 2018
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 28-Mar-2019 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to the first unblinding.

The following updates were made in Version 2, prior to the first unblinding to external safety DMC:

1. Added the following analyses in Table AMAK.6.6 of Section 6.10:
   - Dermatology Life Quality Index (DLQI) (0,1) analysis for Patients with Study Baseline DLQI ≥5,
   - Time to first loss of 100% improvement in Psoriasis Area and Severity Index from baseline (PASI 100),
   - Analysis of covariance (ANCOVA) for percentages of scheduled visits with 90% improvement in PASI from baseline (PASI 90) response among all scheduled visits,
   - ANCOVA for percentages of weeks with PASI 90 response in maintenance period,
   - Cumulative time with PASI 100 response after re-randomization through Week 52,
   - Psoriasis Symptoms Scale (PSS) Symptoms Score of 0 by consistent maintenance of PASI 90 / PASI 100 at Week 52,
   - PSS Signs Score of 0 by consistent maintenance of PASI 90 / PASI 100 at Week 52,
   - DLQI (0,1) by consistent maintenance of PASI 90 / PASI 100 at Week 52,
   - Consistent Maintenance of PASI 100 up to Week X.
2. Removed major protocol deviation definition in Table AMAK.6.1 and Section 6.15.
3. Updated Table AMAK.6.7.
4. Removed "including deaths and SAEs temporally associated or preceding deaths" from SAE definition in Section 6.13.3.
5. Updated Opportunistic Infections analysis to be by treatment-emergent opportunistic infections (OI) by narrow terms and broad terms separately in Section 6.13.8.2.
6. Updated Hypersensitivity in Section 6.13.8.3.
7. Updated Injection Site Reaction in Section 6.13.8.4.

SAP Version 3 was approved prior to the first unblinding to the efficacy primary endpoint for Week 16. The overall changes made in Version 3 were according to Protocol Amendment (a). The summary of changes is as follows:

- Dermatology Life Quality Index (DLQI) (0,1) analysis with at least a 5-point improvement (reduction) from baseline for Patients with Study Baseline DLQI ≥5. The endpoint in the graphical approach to control type I error rate has updated with this revised endpoint.

- Updated Table 6.2 the treatment group descriptions and Table 6.3 the Study Period definition.
- Modified the study baseline definition to be more conclusive.
- Removed the last observation carried forward analysis. Updated the details for categorical MMRM and tipping point analysis.
- Modified multicenter studies to be subgroup analysis.
- Updated the prior psoriasis therapy and others in the Table 6.4 patient characteristics and variables for subgroup analysis.
- Included the AEs occurring prior to the first dose for preexisting conditions.
- Updated Table 6.5 and 6.6. with additional details, including:
    - changed the description of consistent maintenance to be a stability analysis
    - revised the analysis for the Patient's Global Assessment of Psoriasis, and Facial psoriasis
    - revised SF-36 domain score analysis with the Responder Definition
    - added analysis to EQ-5D dimension scores.
- Made other minor typographical corrections and clarifications without affecting content in the document.

4. Study Objectives

Table AMAK.4.1 shows the protocol defined objectives and endpoints of the study. In addition, the analysis of some non-protocol defined endpoints is described in Section 6.10 to provide supportive evidence of efficacy.

The estimand (ICH E9 R1) associated with each endpoint/analysis is documented in the following places:

- The population of interest is described in the protocol inclusion/exclusion criteria and in this document in Table AMAK.6.1 and Table AMAK.6.6.
- The endpoints/variables are listed in Table AMAK.4.1, Table AMAK.6.5, and Table AMAK.6.6.
- The handling of intercurrent events is summarized in Section 6.3 and Table AMAK.6.6.
- Population summary measures are described in Section 6.10 and Table AMAK.6.6.

Table AMAK.4.1. Protocol Defined Objectives and Endpoints

Objectives	Endpoints
Primary[a,b] To assess whether mirikizumab induction dosing is superior to placebo in the treatment of patients with respect to high levels of clinical response	At Week 16: • Proportion of patients with an sPGA (0,1) with at least a 2-point improvement from baseline • Proportion of patients achieving a ≥90% improvement in PASI from baseline (PASI 90)
Major Secondary[a,b] To assess whether mirikizumab induction dosing is superior to placebo with respect to an early, clinically meaningful response	At Week 4: • Proportion of patients achieving a 75% improvement in PASI (PASI 75)
To assess whether the mirikizumab induction dosing is superior to placebo with respect to clinically meaningful response and the highest levels of clinical response	At Week 16: • Proportion of patients achieving PASI 75 • Proportion of patients achieving a 100% improvement in PASI (PASI 100)
To assess whether mirikizumab induction dosing is superior to placebo with respect to body surface area (BSA) affected by psoriasis	At Week 16: • Proportion of patients with ≤1% of BSA with psoriasis involvement
To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5.

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

Objectives	Endpoints
Exploratory To evaluate the potential development of anti-mirikizumab antibodies and their potential relationship with efficacy, TEAEs, and mirikizumab exposure	At Week 16 and Week 52: • Relationship between TE-ADA and efficacy (sPGA and PASI) • Relationship between TE-ADA and TEAEs • Relationship between TE-ADA and mirikizumab pharmacokinetics.

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

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

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

5. Study Design

Study I6T-MC-AMAK (AMAK) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, multi-period study in which approximately 500 patients will be randomized to treatment groups involving different mirikizumab doses and regimens or placebo. The study is comprised of 2 treatment periods (Induction and Maintenance with Randomized Withdrawal), which together last for up to 52 weeks, followed by a 12-week Post-Treatment Follow-Up period. Figure AMAK.5.1 illustrates the study design.

Screening Period: Patients will be evaluated for study eligibility ≤28 days before the baseline visit (Visit 2). Electronic diary collection will begin at screening.

Baseline and Double-Blind Induction Period (Week 0 to Week 16): At Visit 2 (Week 0; baseline), patients who meet the study eligibility criteria will be randomized 4:1 to receive 250 mg mirikizumab or matching placebo subcutaneously (SC), respectively, at Weeks 0, 4, 8, and 12. Patients who discontinue the study for any reason during this period will stop treatment and continue to the early termination visit (ETV) and then complete the 12-week Post-Treatment Follow-up Period.

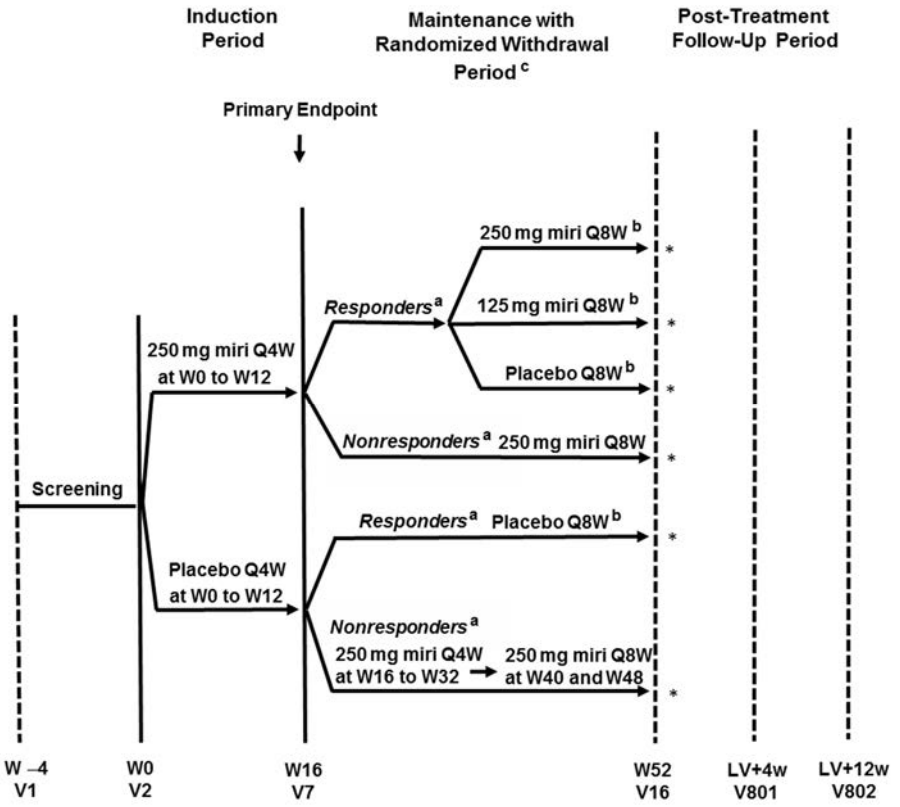
Double-Blind Maintenance Period (Week 16 to Week 52): All patients who complete the Induction Period may continue in the Maintenance Period. The Maintenance Dosing Period will be a double-blind treatment period with randomized withdrawal. The first injection of study drug for this period will be at Week 16, with the last injection at Week 48. At Week 16 (Visit 7), patients who enter the Maintenance Period will be classified as a responder (Psoriasis Area and Severity Index [PASI] ≥90) or non-responder (PASI <90). All patients will receive injections once every 4 weeks (Q4W) at Weeks 16 through 48 in order to maintain study blind across the study treatment groups. Patients will be treated as follows:

- Patients who were responders to mirikizumab in the blinded Induction Period (responder definition is PASI 90 at Week 16) will be re-randomized 1:1:1 to 250 mg mirikizumab once every 8 weeks (Q8W), 125 mg mirikizumab Q8W, or placebo Q8W, according to their randomized treatment assignment at Week 16. Patients who relapse during the blinded Maintenance Period (see relapse criterion defined in Table AMAK.6.5) will remain on, or will be switched to, 250 mg mirikizumab for the remainder of the study and will be monitored for recapture of efficacy response. These patients will begin retreatment with mirikizumab at the visit at which relapse is identified and will receive another mirikizumab treatment at the next visit 4 weeks later. Subsequent mirikizumab treatments will be given at Q8W intervals.
- Patients who received placebo in the blinded Induction Period who are responders at Week 16 (Visit 7) will continue to receive placebo during the Maintenance Period until relapse.
- Patients who were not responders to mirikizumab in the blinded Induction Period will receive 250 mg mirikizumab Q8W. Continued blinded treatment for nonresponders is provided so that partial or slow responders may remain in the study beyond Week 16, thus, maintaining the study blind while patients continue to receive potentially beneficial longer-term treatment with mirikizumab.

- Patients who received placebo in the blinded Induction Period who are nonresponders at Week 16 (Visit 7) will receive 250 mg mirikizumab Q4W for Weeks 16 through 32 and mirikizumab treatments Q8W, thereafter.

At Week 52, patients may enter the long-term extension study, I6T-MC-AMAH (AMAH), or discontinue study treatment and complete Study AMAK's 12-week Post-Treatment Follow-Up Period. Patients who discontinue the study will stop treatment and continue to the ETV and then complete the 12-week Post-Treatment Follow-Up Period.

Post-Treatment Follow-Up Period (12 Weeks): Patients who do not enroll into Study AMAH or who discontinue early from study treatment in Study AMAK will complete the Post-Treatment Follow-Up Period (Visit [V] 801 and V802) of Study AMAK.



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

Note: Randomizations occur at Week 0 and Week 16.

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

a Patients may receive placebo injections during the Maintenance Period to maintain the study blind across treatment groups.

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

c First Maintenance Period dosing at Week 16.

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

5.1. Determination of Sample Size

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

There are multiple primary endpoints in this study: static Physician's Global Assessment (sPGA) (0,1) and PASI 90 at Week 16. The assumed sPGA (0,1) responses are 70% for the mirikizumab arm and 5% for the placebo arm. The assumed PASI 90 responses are 70% for the mirikizumab arm and 3% for the placebo arm. These assumptions are based upon the results of

the mirikizumab Phase 2 Study AMAF (Reich et al. 2017) and review of historical clinical studies in psoriasis (Langley et al. 2014; Gordon et al. 2016; Blauvelt et al. 2017; Papp et al. 2017; Reich et al. 2017).

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

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

5.2. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Week 0 and to re-randomize patients at Week 16. Stratified block randomization will be implemented using a computer-generated sequence within an interactive web-response system (IWRS). Randomization will be stratified, based on previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other). The IWRS will be used to assign prefilled syringes containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct carton(s) of pre-filled syringes by entering a confirmation number found on the carton(s) into the IWRS.

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 the protocol (e.g., described in Table AMAK.4.1 and in Section 4 of AMAK protocol) 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. Patient Populations for Analysis

Patient populations are defined in Table AMAK.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 AMAK.6.2 describes the treatment groups and the comparisons for each study period and the analysis population.

Table AMAK.6.1. Patient Populations for Analysis

Population	Description
All Entered Patients	All patients who signed informed consent.
Induction ITT	All randomized patients, even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise noted, efficacy and health outcomes analyses for the induction period will be conducted on this population.
Induction Safety	All randomized patients *who received at least 1 dose of study treatment.* Safety analyses for the induction period will be conducted on this population.
Re-randomized Maintenance ITT	All Induction ITT patients who received at least 1 induction dose of study treatment and have been re-randomized at Week 16. Efficacy and health outcomes analyses for the maintenance period will be conducted on this population.
Re-randomized Maintenance Safety	All Induction ITT patients who received at least 1 induction dose of study treatment, have been re-randomized at Week 16 *and have received at least 1 maintenance dose.* Safety analyses for the maintenance period will be conducted on this population.
Non-re-randomized Maintenance ITT	All Induction ITT patients who received at least 1 induction dose of study treatment, have *not* been re-randomized at Week 16, and have entered the maintenance period (Table AMAK.6.3). Efficacy analyses for the maintenance period will be conducted on this population.
Maintenance ITT	Pooled re-randomized and Non-re-randomized populations.
Re-randomized Relapsed	All *Re-randomized* Maintenance ITT patients who relapse during the Maintenance Period and received a 250-mg dose. These patients will be analyzed for recapture of efficacy response.
All Miri Safety	All randomized patients *who received at least 1 dose of mirikizuma*b. Patients who received placebo for the entire study are not included.
Induction PPS	All randomized patients who do not have important protocol deviations excluded from per protocol analysis (IPDPP) in the induction period. IPDPP are described in a separate document: "The AMAK Trial Issues Management Plan." These patients will be used as a sensitivity analysis for the primary endpoints only.

Abbreviations: ETV = early termination visit; ITT = intent-to-treat; PPS = per protocol set.

Table AMAK.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Groups	Inferential Comparisons
Induction	Induction ITT Induction Safety Induction PPS	placebo Q4W; 250 miri Q4W	250 miri Q4W vs. placebo Q4W
Maintenance	Re-randomized Maintenance ITT; Re-randomized Maintenance Safety	placebo Q8W[e]; 125 miri Q8W; 250 miri Q8W; Total miri*	125 miri Q8W vs. placebo Q8W; 250 miri Q8W vs. placebo Q8W
	Re-randomized Relapsed	placebo Q8W[a e]; 125 miri Q8W[a]; 250 miri Q8W[a]; Total miri*	No comparison
	Non-re-randomized Maintenance	miri nonresponder[b]; placebo nonresponder[c] placebo responder[d]	No comparison
	Maintenance ITT	placebo Q8W[e]; 125 miri Q8W; 250 miri Q8W; miri nonresponder[b]; placebo responder[d] placebo nonresponder[c];	No comparison
All	All Miri Safety	all miri [f]; all miri + placebo withdrawal[e f]; all miri + placebo withdrawal[e] + FUP[f]	No comparison

Abbreviations: FUP = follow-up; ITT = intent-to-treat; miri = mirikizumab; PASI 90 = ≥90% improvement from baseline in the Psoriasis Area and Severity Index; PPS = per protocol set; Q4W = administration once every 4 weeks; Q8W = administration once every 8 weeks; vs. = versus.

* For safety related analysis only.

a Treatment is the treatment patient was receiving immediately before relapse.

b Patients randomized to mirikizumab in induction who do not achieve PASI 90 at Week 16 receive 250 mg Q8W.

c Patients randomized to placebo in induction who do not achieve PASI 90 at Week 16 receive 250 mg Q8W.

d Patients randomized to placebo in induction who achieve PASI 90 at Week 16 continue to receive placebo.

e Patients re-randomized to Placebo in Maintenance Period.

f Technically, there is only 1 treatment group. However, all summaries utilizing the "All Miri Safety" will include a summary for different periods:

- all miri: only the period of exposure to miri treatment.
- all miri + placebo withdrawal: period of exposure to miri treatment + placebo withdrawal.
- all miri + placebo withdrawal + FUP: period of exposure to miri treatment + placebo withdrawal + follow up.

6.1.2. Study Time Intervals

Table AMAK.6.3 displays a list of study periods along with the definition of which patients will be considered to have entered the study period and when the individuals start and end the study period. The table shows both a date and a time.

To calculate the length of any time interval or time period in this study, the following formula will be used:

$$Length\ of\ interval\ (days) = End\ Date - Interval\ Start\ Date + 1$$

To convert any time length from days to years, the following formula will be used:

$$Length\ of\ interval\ (years) = Length\ of\ interval\ (days)/365.25$$

To convert any time length from days to weeks, the following formula will be used:

$$Length\ of\ interval\ (weeks) = Length\ of\ interval\ (days)/7$$

Only for the purpose of calculating the length of study period time intervals, the words "prior to" in Table AMAK.6.3 should be understood to mean "the day before," while the word "after" should be understood to mean "the day after."

Table AMAK.6.3. Definition of Study Period Time Intervals

Study Period	Start Definition	End Definition
Screening: All patients who sign informed consent are considered as entering the Screening Period.	Informed consent date	Prior to the start of induction.
Induction Period Interval: All patients who are randomized to the study are considered as entering the Induction Period.	At the first injection date/time[a] following randomization. For patients who are randomized but not dosed, the Induction Period starts on the date of randomization.	Prior to the start of maintenance. For patients who discontinue before or on the Week 16 visit, the induction period ends at the last date of treatment discontinued date or last treatment visit date.
Maintenance Period Interval: All patients who had any Week 16 to Week 52 visits (except the ones who discontinued the study at Week 16) are considered to have entered the Maintenance Period.	At the Week 16 dosing date/time[a]. If a patient is unable to be dosed at the Week 16 visit, the Maintenance Period starts at the Week 16 visit. If the patient misses the Week 16 visit, the Maintenance Period starts at Day 118.	After the Week 52 visit date. If patients discontinued prior to Week 52, the Maintenance Period ends at the last date of treatment disposition date or last treatment visit date. If the patient relapsed, the Maintenance Period ends before the patient entered the relapse period.
Relapse Period Interval: All patients who responded during induction and meet the relapse criteria and receive a 250 mg dose during maintenance will be considered to have entered the Relapse Period.	The date/time[a] the patient received the first dose[a] after the patient was measured to meet the relapse criteria.	After the Week 52 visit date. If patients discontinued prior to Week 52, the Relapse Period ends after the early treatment discontinuation visit date.
Placebo Withdrawal Interval: All patients who are re-randomized ***to placebo*** will be considered to have entered the placebo withdrawal period.	Same as start of the maintenance period.	Same as end of the maintenance period.
Follow-up Period Interval: All patients who had Visit 801 or 802 are considered to have entered the Follow-up Period.	The latest of the following dates: (1) after the end of the Induction Period; (2) after the end of the Maintenance Period; (3) after the end of end of the Relapse Period.	The last date of the last study visit and study disposition date.

Study Period	Start Definition	End Definition
All Miri[b]: All patients who are treated with mirikizumab are considered to have entered this period.	The date/time[a] of first injection with mirikizumab (i.e., injection with placebo does not start the period).	If the patient is not re-randomized to Placebo, then the All Miri Period ends the latest of the following dates: (1) after the end of the Induction Period; (2) after the end of the Maintenance Period; (3) after the end of end of the Relapse Period. If the patient is re-randomized to Placebo, then the All Miri Period is the combination [b] of the Induction and Relapse Periods (if the patient relapses).
All Miri + Placebo Withdrawal Period: All patients who are treated with mirikizumab are considered to have entered this period.	The date/time[a] of first injection with mirikizumab (i.e., injection with placebo does not start the period).	The latest of the following dates: (1) after the end of the Induction Period; (2) after the end of the Maintenance Period; (3) after the end of end of the Relapse Period.
All Miri + Placebo Withdrawal + FUP Period: All patients who are treated with mirikizumab are considered to have entered this period.	Same as the "All Miri + Placebo Withdrawal Period."	After the last study visit.

Abbreviations: FUP = follow-up; Miri = mirikizumab.

[a] Missing dose time will be imputed as the earliest time that is consistent with available data about dose time. For example, suppose the minutes are missing but hour is present. In this case, we would impute the minutes to be 0.

[b] The "All Miri Period" by definition excludes "the Placebo Withdrawal Period." Thus, for patients who are re-randomized to placebo and then relapse, the "All Miri Period" is actually made up of two separate time periods with two separate start and end dates.

6.1.3. Definition of Study Baseline

For efficacy and health outcomes, study baseline is defined as the last non-missing assessment (including unscheduled visits) before the first injection, which in most cases will be the measure recorded at Week 0 (Visit 2). For efficacy/health outcome measures, if the patient does not take any injection, the last available value on or prior to the randomization date will be used. In cases where baseline measurements are taken on the same day as the injection, the baseline measurements are used as the baseline for data analysis.

For the Psoriasis Symptom Scale (PSS), the weekly average of at least 4 days of the consecutive 7 days prior to the first injection (or randomization, if the patient does not take any injection) will be the study baseline score.

Baseline for safety analysis is described in the Safety section (Section 6.13).

6.1.4. Analysis Methods

For assessments of the primary endpoints and other binary efficacy and health outcomes endpoints, the following will be provided:

- Crude proportions for each treatment group along with the 95% 2-sided asymptotic (i.e., not continuity corrected) confidence intervals (CIs) will be provided.
- The estimated common risk difference along with 95% CIs. The common risk difference (Agresti 2013) is the difference in proportions adjusted for the stratification factors as

mentioned in Section 6.2. SAS PROC FREQ will be used for the estimates and CIs, where the CIs are calculated by using Mantel-Haenszel-Sato method (Sato 1989).

- Cochran–Mantel–Haenszel (CMH) test will be used to compare the treatment groups while adjusting for the stratification factors as mentioned in Section 6.2. The CMH p-value will be reported, and the CMH adjusted odds ratio along with the 95% 2-sided asymptotic (i.e., not continuity corrected) CIs.

When specified as a sensitivity analysis for binary endpoints, logistic regression with a Firth penalized likelihood will be used. The model will include the treatment groups and the covariates described in Section 6.2. Firth correction is equivalent to specifying Jeffrey's prior and seeking the mode of the posterior distribution. Roughly, it adds one-half of an observation to the data set, assuming that the true values of the regression parameters are equal to 0. The likelihood function is adjusted by a fixed quantity which reduces the positive bias of small samples. The fixed quantity is a function of the information which goes to 0 as sample size increases. Firth correction can be implemented in PROC Logistic by including *"firth"* as an option in the model statement. The odds ratio and the corresponding 95% CIs, as well as the treatment differences and the corresponding 95% CIs, will be reported.

In addition, when specified as a sensitivity analysis, pseudo-likelihood-based mixed-effects model of repeated measures (Categorical MMRM) estimating the percentage of patients achieving response across postbaseline visits may be used. When MMRM is used, the model includes treatment, baseline value (continuous), visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the induction/maintenance covariates mentioned in Section 6.2 as fixed factors. The binomial distribution and the logit link function will be used. The residual pseudo-likelihood with a subject-specific expansion (RSPL) will be used, which is equivalent to restricted maximum likelihood (REML). An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. 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 approximation will be used to estimate the denominator degrees of freedom. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The probability of response, the corresponding 2-sided 95% CI, and the p-value for the treatment comparisons at postbaseline visits will be reported.

Treatment comparisons of continuous efficacy and health outcome variables with multiple postbaseline measurements will be made using mixed-effects model for repeated measures (MMRM). When MMRM is used, the model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the induction/maintenance covariates mentioned in Section 6.2 as fixed factors. 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 restricted maximum likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least squares (LS) means will be used for the statistical comparison; the 95% confidence interval will also be reported.

Treatment comparisons of continuous efficacy and health outcome variables with a single postbaseline time point will be made using analysis of covariance (ANCOVA) with the following in the model: treatment group, baseline value, and Induction Period/Maintenance Period covariates mentioned in Section 6.2. Type III tests for LSMeans will be used for statistical comparison between treatment groups. The LSMean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported. Analysis of covariance may also be used in addition to the MMRM approach, by repeating analysis for each time point.

The Kaplan-Meier (KM) product limit method will be used to estimate the survival for several time to event analyses. The hazard ratio and log-rank test stratified by covariates mentioned in Section 6.2 will be reported. Time for all analysis will be described in units of weeks.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that do not correspond to the planned collection schedule will be excluded from the MMRM analysis (Andersen and Millen 2013). For by-visit summaries/displays, such as boxplots, the weeks when data was not scheduled to be collected may not be displayed. However, unscheduled assessments within any defined study period will still be used in the shift analyses, and for imputing values for the change from baseline to modified baseline observation carried forward (mBOCF) endpoint analyses.

6.2. Adjustments for Covariates

Unless otherwise specified, the statistical analysis models for the Induction Period efficacy will include adjustment for the covariates: previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America or Other). In all models, the adjustment for covariates will be performed by coding each of 8 possible combinations of the covariates as a separate strata, and the strata will be actual the variables adjusted for. Similarly, unless otherwise specified, the statistical analysis models for the Maintenance Period efficacy will adjust for the covariate body weight (<100 kg or ≥100 kg). These covariates correspond to the stratification factors to be used during randomization. When MMRM or ANCOVA is used, additional covariates, such as baseline, will be used, as described in Section 6.1.4.

6.3. Handling of Dropouts or Missing Data

Intercurrent events (ICH E9R1) are events which occur after the treatment initiation and make it impossible to measure a variable or influence 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. The missing data methods described below handle intercurrent events in different ways.

6.3.1. Non-Responder Imputation (NRI)

The NRI method can be justified based on the composite strategy (ICH E9R1) for handling intercurrent events. 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 non-responders.

Analysis of binary efficacy and health outcome variables will be assessed using an NRI method. Patients will be considered as non-responder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized patients with no postbaseline observations will also be defined as non-responders for the NRI analysis.

For the Maintenance Period, patient who relapse (see definition in Table AMAK.6.5) after re-randomization during the maintenance period will be considered to have entered the relapse period and will be non-responders for all subsequent visits of maintenance efficacy analysis.

For the Relapse Period, the response rates will be summarized by the weeks after relapse based on the number of patients with planned scheduled visit during the Relapse Period._Patients who complete the Week 52 treatment visit will, thereafter, not be counted in the numerator when calculating the response rate.

6.3.2. Mixed-effects Model for Repeated Measures (MMRM)

The MMRM method can be justified based on the hypothetical strategy (ICH E9R1) for handling intercurrent events. In this strategy, the scientific question of interest is to assess the effect of study treatment in a hypothetical trial where all patients have complete data and continue to take study treatment without dropping out of the study or receiving rescue therapy.

MMRM will be used where specified for longitudinal continuous measurements. It assumes missing data can bias results, but the bias can be attenuated by modeling random effects using the within-patient error correlation structure. These correlations between the repeated measurements provide the platform used to account for the bias from patient dropout. MMRM model details are provided in Section 6.1.4.

If patients enter the Relapse Period, only the visits prior to entering the Relapse Period will be included in the MMRM model for the Maintenance Period efficacy analysis.

6.3.3. Modified Baseline Observation Carried Forward (mBOCF)

An mBOCF analysis will be performed on specified continuous efficacy endpoints. For patients discontinuing investigational product due to an AE, the baseline observation for the endpoint will be carried forward to the corresponding visit for all missing observations after the patient discontinued study treatment. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding visit for all missing observations after the patient discontinued. For all patients with sporadically missing observations prior to discontinuation, the last non-missing observation before the sporadically missing observation will be carried forward to the corresponding visit. Randomized patients without at least 1 postbaseline observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE.

The mBOCF can be justified based on the composite strategy (ICH E9R1) for handling intercurrent events. It handles the intercurrent event of discontinuing study drug due to an

adverse event by defining the patient as not receiving any benefit from study drug after the event. That is, the patient is defined as reverting back to baseline regardless of any continuing efficacy benefits they may still have received after the event. For other intercurrent events (e.g., rescue treatment and discontinuation due to reasons other than an AE) the while on treatment strategy is applied. That is, the endpoint is defined as the last observed value at or before the visit of interest while the patient was still on study drug.

6.3.4. As Observed

Summary based on observed data at each postbaseline visit will be provided for some endpoints. Descriptive statistics will be reported without inferential comparisons. 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 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 (post-randomization) event, it is not causal. The strategy used in this estimand is the one behind the so-called "observed cases" or "completers" analysis ubiquitous in the literature but is not one of the recommended strategies in the ICH E9(R1).

6.3.5. Tipping Point Analysis

Tipping point analysis will be conducted as sensitivity analysis for primary endpoints including PASI 90 and sPGA (0,1) at Week 16.

Within each analysis, the most extreme case will be considered, in which all missing data for patients randomized to mirikizumab will be imputed using the worst possible outcomes and all missing data for patients randomized to placebo will be imputed with the best possible outcomes:

- Missing responses in the mirikizumab group will be imputed with a range of response probabilities, including probabilities of 0, 0.2, 0.4, 0.6, 0.8, and 1.0.
- For missing responses in the placebo group, a range of response probabilities, probabilities of 0, 0.2, 0.4, 0.6, 0.8, and 1.0, will be used to impute the missing values. Multiple imputed data sets will be generated for each response probability.

Treatment differences between mirikizumab and placebo will be analyzed for each imputed data set using Cochran-Mantel-Haenszel test (Section 6.1.4). Results across the imputed data sets will be aggregated using SAS® Proc MIANALYZE in order to compute a p-value or 95% CI for the treatment comparisons for the given response probability. If the probability values do not allow for any variation between the multiple imputed datasets (for example, all missing responses in the placebo and mirikizumab groups are imputed as responders and nonresponders, respectively), then the p-value from the single imputed dataset will be used.

6.4. Multicenter Studies

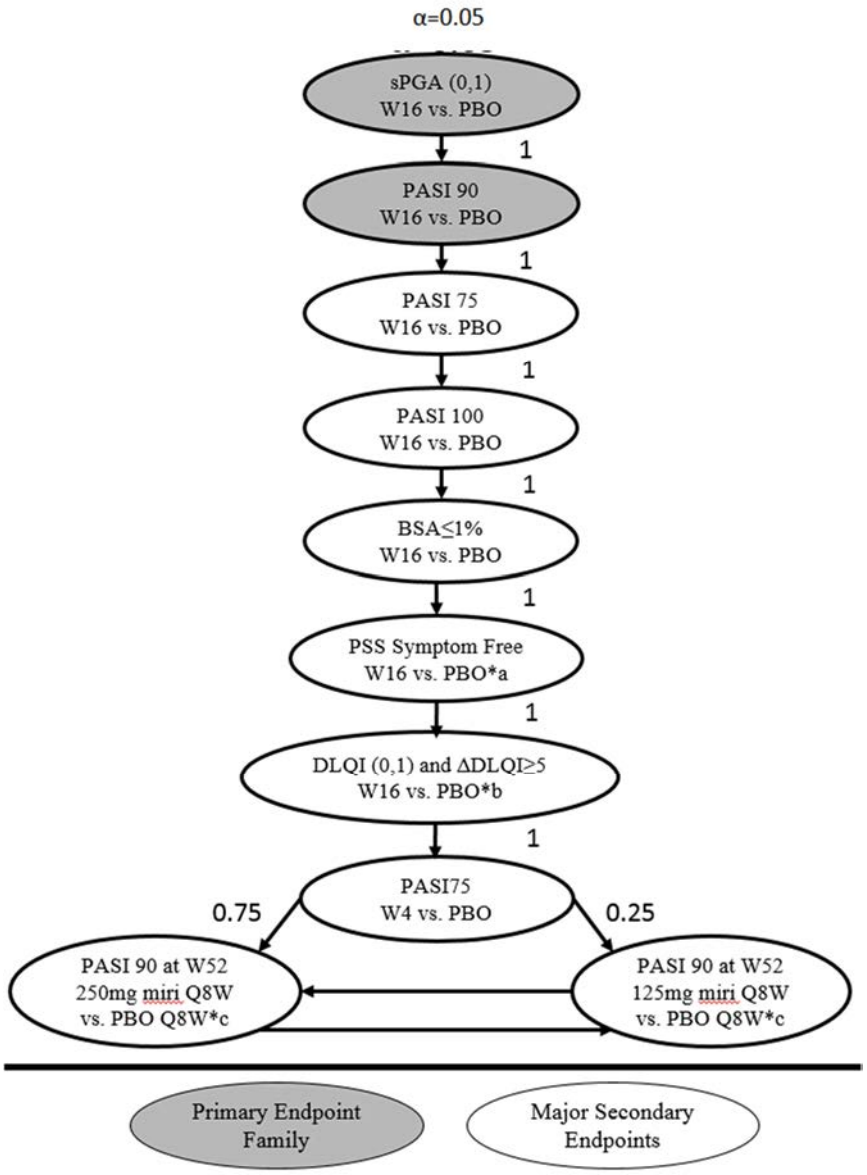
This study will be conducted by multiple investigators at multiple sites internationally. Typically, a logistic regression with treatment, center, and treatment-by-center may be used to

assess the consistence of treatment effect in center. However, due to a large number of sites in the study, this logistic regression model will not likely converge. Instead, the subgroup analysis on the country, and the region will be evaluated. The countries will be categorized into geographic regions: Asia (Japan, Korea, Taiwan), North America (United States, Puerto Rico), Central America/South America (Mexico), and Europe (Germany, Poland, Russia). Subgroup analysis details are provided in Section 6.14.1.

If the treatment-by-country or treatment-by-region interaction is significant at a 2-sided alpha level of 0.1, the nature of this interaction will be inspected as to whether it is quantitative (i.e., the treatment effect is consistent in direction across all countries or regions, but not in size of treatment effect) or qualitative (the treatment is beneficial in some, but not all countries or regions). If the treatment-by-country or treatment-by-region interaction effect is found to be quantitative, results from the primary model will be presented. If the treatment-by-country or treatment-by-region interaction effect is found to be qualitative, further inspection will be used to identify in which countries or regions mirikizumab is found to be more beneficial.

6.5. Multiple Comparisons/Multiplicity

A prespecified graphical multiple testing approach (Bretz et al. 2009, 2011) will be implemented to control the overall Type I error rate at 2-sided alpha of 0.05, for all primary and major secondary endpoints. More specifically, we will calculate multiple testing adjusted p-values using "Algorithm 2" described by Bretz et al. (2009), and any hypothesis tests with a multiple testing adjusted p-value of less than 0.05 will be considered statistically significant. This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Bretz et al. 2009, 2011; Alosh et al. 2014). Each hypothesis is represented as a node in a graph. Directed arrows between the nodes with associated weights represent how alpha is passed from its initial allocation to other nodes. The testing scheme will be fully specified by the graph (including nodes, arrows, and weights) along with the initial alpha allocation. Figure AMAK.6.1 describes the graphical scheme, and all of our alphas will be allocated to the sPGA (0,1) endpoint initially. The testing scheme will be finalized before the first unblinding of efficacy data.



Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; miri = mirikizumab; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/=100% improvement in PASI from baseline; PBO = placebo; PSS = Psoriasis Symptoms Scale; Q8W = every 8 weeks; sPGA = static Physician's Global Assessment; vs. = versus; W = Week.

[a] PSS Symptom Free at Week 16 is performed for patients with study baseline PSS symptom score ≥1 in Induction ITT population.

[b] DLQI (0,1) and reduction in DLQI ≥5 at Week 16 is performed for patients with study baseline DLQI ⩾5 in Induction ITT population.

[c] Re-randomized Maintenance ITT population.

Figure AMAK.6.1. Graphical approach to control type 1 error rate for Study AMAK.

6.6. Patient Disposition

Patient flow will be summarized for the number of patients who: entered; failed screening; were randomized to each treatment; completed induction; were re-randomized to each treatment group or were not re-randomized; and completed the maintenance period. Of the treatment completers, the numbers who enter AMAH, complete the post-treatment follow-up, or discontinue the study will be summarized.

More specifically, the following summaries will be produced. The screen failures and reason for screen failure will be summarized. The *treatment disposition* will be summarized for the Induction intent-to-treat (ITT) population during the induction period. Patients who entered the maintenance period (Table AMAK.6.3) will be considered to have completed the induction period. The *treatment disposition* will be summarized for the Maintenance ITT population. Summaries will be by treatment group (Table AMAK.6.2). Summaries will also include reason for discontinuation from the study tabulated by treatment group. The *study disposition* of all patients who are randomized (i.e., in the Induction ITT population) will be summarized along with the reason for discontinuation. The completers will be categorized into those completers who entered AMAH and those who did not.

All patients who are randomized (i.e., in the Induction ITT population) and discontinued from study treatment during any period from the study will be listed, and the timing of discontinuing the study will be reported. If known, a reason for their discontinuation will be given.

Patient allocation by region, country, and center/site will be summarized with number of patients who entered the study, number of ITT patients for each treatment group, number of patients discontinued from study treatment, and number of patients discontinued from study.

6.7. Patient Characteristics

Patient demographic variables and baseline characteristics will be summarized by dose and overall for the Induction and Maintenance ITT populations with the baseline values. The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline covariates across treatment groups will be performed. By-patient listings of basic demographic characteristics (i.e., age, sex, race, racial subgroup, ethnicity, ethnic subgroup, country, body weight) for the Induction ITT population will be provided.

Table AMAK.6.4 describes the specific variables and how they will be summarized. The final two columns specify variables used for the efficacy subgroup analysis described in Section 6.14.1. The summary of additional patient characteristics and subgroup analysis will not require an amendment to the SAP.

Table AMAK.6.4. Patient Characteristics (and Variables for Subgroup Analysis)

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Induction	Maintenance
Demographic Characteristics				
Age[b]	Yes	<65 years, ≥65 years	X	X
		<40 years, ≥40 years	X	X
Sex	No	Male, Female	X	X
Age within Sex	No	Male <40 years, Male ≥40 years, Female <40 years, Female ≥40 years		
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	X
Geographic Region	No	North America (United States, Puerto Rico), Other	X	
	No	By Country (listed in other documents)	X	
	No	Asia (Japan, Korea, Taiwan), North America (United States, Puerto Rico), Central America/South America (Mexico), and Europe (Germany, Poland, Russia)	X	X
Height (cm)	Yes	None		
Weight (kg)	Yes	<80 kg, ≥80 kg	X	X
		<100 kg, ≥100 kg	X	X
BMI[c]	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		
Caffeine use	No	Never, Current, Former		
Tobacco use	No	Never, Current, Former	X	
Prior Psoriasis Therapy				
Prior systemic therapy[d,e]	No	Never used, Ever used	X	
Prior biologic therapy[d]	No	Never used, Ever used	X	X
Number prior biologic therapies	No	0, 1, 2, >2	X	X
Prior non-biologic systemic therapy[e]	No	Never used, Ever used	X	
Number of prior non-biologic systemic therapies[e]	No	0, 1, 2, >2		
Prior conventional systemic therapy[l]	No	Never used, Ever used	X	
Number of prior conventional systemic therapies[l]	No	0, 1, 2, >2		
Prior anti-TNF alpha[f]	No	Never used, Ever used	X	X
Prior anti-IL 17[g]	No	Never used, Ever used	X	
Prior anti-TNF alpha[f] and/or Prior anti-IL 17[g]	No	Anti-IL-17 only, Anti-TNF only, Both, Neither		
Prior topical therapy	No	Never used, Topical prescription therapy, Topical non-prescription therapy		
Prior phototherapy	No	Never used, Ever used	X	
Prior systemic therapy or phototherapy	No	Never used, Ever used	X	
Prior non-biologic systemic therapy or phototherapy	No	Never used, Ever used	X	
Prior biologic inadequate response (among those who had	No	Yes, No	X	

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Induction	Maintenance
prior biologic therapy)				
Prior biologic loss of response (among those who had prior biologic therapy)	No	Yes, No	X	
Prior biologic intolerance (among those who had prior biologic therapy)	No	Yes, No	X	
Prior biologic inadequate response, loss of response, or intolerance (among those who had prior biologic therapy)	No	Yes, No	X	
Prior biologic failure[h] (among those who had prior biologic therapy)	No	Failed, Not failed	X	
Prior biologic failure[h] relative to prior biologic exposures	No	Not exposed, Exposed but not failed, Exposed and failed		
Prior systemic failure[h] (among those who had prior systemic therapy)	No	Failed, Not failed	X	
Prior failure, contraindication or intolerance to non-biologic systemic agents or phototherapy	No	Yes, No	X	X
Psoriasis Duration and Age at Onset				
Duration of psoriasis (years)[i]	Yes	<15, ≥15	X	
Duration of diagnosis (years)[j]	Yes	None		
Age at onset (years)[k]	Yes	<25, ≥25	X	
Area of Involvement				
Baseline facial involvement	No	Yes, No	X	
Baseline nail involvement	No	Yes, No	X	
Baseline scalp involvement	No	Yes, No	X	
Baseline palmoplantar involvement	No	Palm involvement only, Sole Involvement only, Both, Neither		
		Yes, No	X	
Baseline Psoriatic Arthritis	No	Yes, No	X	
Baseline Disease Severity				
Baseline PASI score	Yes	<20, ≥20	X	
		<15, ≥15	X	
Baseline sPGA score	Yes	Moderate (3), Severe (4), or Very severe (5)	X	
Baseline BSA (%)	Yes	<20%, ≥20%	X	
Baseline PSSI	Yes	None		
Baseline NAPSI	Yes	None		
Baseline PPASI	Yes	None		
Baseline PSS sign scores	Yes	0, ≥1		
Baseline PSS symptom score	Yes	0, ≥1		
Baseline PatGA	No	0 (Clear), 1, 2, 3, 4, 5 (Severe)		
Baseline DLQI total score	Yes	0 or 1, >1		
		≤10, >10		
		<5, ≥5		
Baseline SF-36 PCS	Yes	None		
Baseline SF-36 MCS	Yes	None		
Baseline WPAI-PSO employment status	No	Yes, No		
Baseline WPAI-PSO score	Yes	None		

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Induction	Maintenance
Baseline QIDS-SR16 score	Yes	<11, ≥11	X	
		None (0 – 5), Mild (6 – 10), Moderate (11 – 15), Severe (16 – 20), Very severe (21 – 27)		

Abbreviations: BMI = body mass index; eCRF = electronic case report form; IL-17 = interleukin 17; PUVA = psoralen and ultraviolet A; TNF = tumor necrosis factor; UVB = ultraviolet B.

[a] Subgroup analysis will be used for efficacy endpoints only. See Section 6.14.1 for more details.
[b] 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.
[c] Body Mass Index (BMI) will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ (m))^2$.
[d] Biologic systemic therapies include: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, and other biologic agent.
[e] Non-biologic systemic therapies include: cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, apremilast, other systemic agent, and psoralen and ultraviolet A (PUVA).
[f] Anti-TNF alpha biologics include: infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol.
[g] Anti-IL 17 biologics include: secukinumab, ixekizumab, and brodalumab.
[h] Reasons for discontinuation are loss of response or inadequate response.
[i] Length of the interval (see Section 6.1.2) from the date of psoriasis onset to the date of informed consent.
[j] Length of the interval (see Section 6.1.2) from the date of psoriasis diagnosis to the date of informed consent.
[k] 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.
[l] Conventional systemic therapies include: cyclosporine, methotrexate, corticosteroids, acitretin, fumaric acid derivatives, and other systemic agent.

6.7.1. Historical Illnesses and Preexisting Conditions

Historical illness/condition is defined as the condition/event recorded on the Pre-existing Conditions and Medical History electronic case report form (eCRF) page or on a Prespecified Medical History eCRF page with an end date prior to the date of informed consent. *Preexisting condition* is defined as the condition/event recorded on the Pre-existing Conditions and Medical History eCRF page or on a Prespecified Medical History eCRF page with a start date prior to the date of informed consent, and no end date (i.e., the event is ongoing) or an end date on or after the date of informed consent. In addition, the AEs occurring prior to first dose are also included. Notice: if a preexisting condition worsens in severity on or after the date of informed consent, it will be recorded as an AE on AE eCRF page from the date of worsening onward.

The number and percentage of patients with preexisting conditions will be summarized by treatment using MedDRA Preferred Term (PT) nested within System Organ Class (SOC). These summaries will be done for the Induction ITT and Maintenance ITT populations.

The number and percentage of patients with prespecified medical history (hypertension, diabetes type 1, insulin-requiring type II diabetes mellitus, diabetes mellitus type II non-insulin dependent, coronary artery disease, stroke, dyslipidemia, psoriatic arthritis, ulcerative colitis, Crohn's disease) by treatment and overall for the Induction ITT and Re-randomized Maintenance ITT Populations.

6.8. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who enter the Induction and Maintenance Periods. Treatment compliance for each patient will be calculated as:

$$Treatment\ compliance\ (\%) = 100\ \times \frac{Total\ number\ of\ injections\ administered\ within\ window}{Total\ number\ of\ injections\ planned\ per\ protocol}$$

Here, the planned injections per protocol is based on the number visits before the patient discontinued study drug, and the total number of injections administered within the protocol defined window will be derived using the response to the question, "Was dose administered?" on the Exposure eCRF page along with the eCRF dose start date. A patient will be considered noncompliant if he/she fails to attend for administration of study medication within the required treatment window as defined in the protocol schedule of activities. Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses. Proportions of patients who demonstrate overall compliance during the Induction Period will be compared between treatment groups using Fisher's exact test.

Patient treatment compliance will be summarized for the ITT and Maintenance populations.

6.9. 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 each treatment period 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. Concomitant medications are assigned to the treatment period in which they are actually ongoing. For example, if a patient is receiving concomitant medication during the Induction Period, but has a stop date during the Induction Period, the same medication would not be listed as a concomitant medication during the latter periods unless the patient has a new start date. For all summary tables of concomitant medications, preferred terms of concomitant medication will be sorted by descending frequency. Summary tables include the following:

- For the Induction ITT population during the Induction Period, summary tables with the number and frequency of patients by treatment group will be presented for:
    - All prespecified prior therapies in the "Prior Therapy: Indication" eCRF within the categories used in the eCRF. The number and percentage of patients with each reason for discontinuation of previous psoriasis therapy will be summarized by type and therapy.
    - Preferred names of prior therapies (reported before randomization), ordered by frequency

    - Preferred names of concomitant therapies (use during the induction period), ordered by frequency
- For the Re-randomized Maintenance ITT population during the Maintenance Period, summary tables with the number and frequency of patients by treatment group will be presented for preferred names of concomitant therapies (use during the maintenance period), ordered by frequency.
- For the All Miri Safety population, a frequency table will be presented with concomitant therapy for the following categories: current concomitant therapy (used while assigned to active treatment); current concomitant therapy, including placebo withdrawal period (Table AMAK.6.3); and current concomitant therapy, including placebo withdrawal period and post-treatment follow-up.
- A summary of concomitant medications within classes of interest will also be provided for the Induction ITT and Re-randomized Maintenance ITT Populations. This will include: (1) topical therapy; (2) topical steroid therapy; and (3) systemic corticosteroid therapy. Definition of these three classes of interest will be based on compound level safety standards.

6.10. Efficacy Analyses

Table AMAK.6.5 includes the description and derivation of the efficacy/health outcomes measures and endpoints.

Table AMAK.6.6 provides the detailed analyses including analysis type, method and imputation, population, time point, and treatment comparisons for efficacy/health outcomes analyses.

Table AMAK.6.5. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
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). 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	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 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.	If any individual score is missing, the PASI score will not be calculated, hence, missing.
		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: $Percent\ improvement\ from\ aseline\ = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	their respective proportion of body surface area.		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.	
		PASI 75	A clinically meaningful response; at least a 75% improvement in PASI score from baseline.	Missing if baseline or observed value is missing.
		PASI 90 (Primary)	Higher level of clearance; at least 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.
		Stability of PASI 90 / PASI 100 from Week 16 to each visit up to Week 52	Patient has PASI 90 / PASI 100 for all non-missing visits starting from Week 16 to (and including all between scheduled visits if any) each visit up to Week 52.	Missing if PASI 90 / PASI 100 is missing any of Week 16 to each visit up to Week 52. Also missing when patient has relapsed/ discontinued study treatment at or before the analysis visit.
		Time to first achieving PASI 100, PASI 90 or PASI 75 (i.e., 3 different analyses) during Induction Period	For patients who are observed to meet the response criteria during the Induction Period, time will be from the start of the Induction Period to the first measurement date where the patient met the response criteria.	Patients not observed to meet response criteria during the Induction Period will be censored after the date of their last measurement during the Induction Period.
		Time to first loss of PASI 90 or relapse (i.e., 2 different analyses) after re-	For patients who are observed to relapse/lose response during the Maintenance Period, time will be from the start of the Maintenance Period to the first measurement date where the patient relapsed.	Patients who are not observed to relapse/lose response during the Maintenance Period will be censored after the date

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
		randomization		of their last visit during the Maintenance Period.
		Time to first regaining PASI 90 or PASI 100 (i.e., 2 different analyses) after relapse	For patients who are observed to regain response during the Relapse Period, time will be from the start of the Relapse Period to the first measurement date where response was achieved.	Patients who are not observed to regain response will be censored after the date of their last visit during the Maintenance Period.
		Cumulative time with PASI 90 response after re-randomization through Week 52	Area under the curve (AUC) of PASI 90 response over time using trapezoidal rule (i.e. 100% when patients are PASI 90 responders at the visit and 0% when patients are non PASI 90 responders at the visit.) percentages of scheduled visits with PASI 90 response among all scheduled visits percentages of weeks with PASI 90 response	NRI if the observed value is missing.
		Relapse	The loss, at any visit, of ≥50% of the Week 16 PASI improvement from baseline. That is, a patient will have relapsed during the Maintenance Period if their PASI score increases to greater than or equal to the midpoint between their baseline and Week 16 PASI score.	Missing if baseline, Week 16 or observed value is missing.
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.
		sPGA (0,1) (Primary)	An sPGA assessed as either 0 or 1, 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, which represents a clinically important endpoint indicating complete resolution of plaque psoriasis.	Missing if sPGA is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
		Time to first achieving sPGA (0,1) During Induction Period	For patients who are observed to meet the response criteria during the Induction Period, time will be from the start of the Induction Period to the first measurement date where the patient met the response criteria.	Patients not observed to meet response criteria during the Induction Period will be censored after the date of their last measurement during the Induction Period.
BSA	Percentage of Body Surface Area (BSA): The investigator will evaluate the percentage involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), in which 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb).	BSA	Collected as a single scale as part of PASI electronic case report form (eCRF). Range from 0% to 100%.	Single item, missing if missing.
		BSA ≤1%	BSA assessed as ≤1% with psoriasis involvement.	Missing if BSA is missing.
		BSA change from baseline	Calculated as: observed BSA – baseline BSA.	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,	PSS item scores	The PSS score for each item as reported in daily diaries from Visit 1 up to Visit 7. For each week up to Visit 7, a mean score will be calculated. See Appendix 1 for details on the study period associate with each week and calculation details. The PSS will be collected only during office visits for the remaining visits.	For daily diary assessments, at least 4 (out of up to 7) assessments must be averaged. Otherwise, the item is missing. For office-based assessments, 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.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	stinging, burning, redness, scaling, and cracking.	PSS Signs Score of 0	Free of redness, scaling and cracking.	Missing if PSS Signs Score is missing.
		PSS (Signs, Symptoms, items) Score change from baseline	Change from baseline = Observed PSS Score – Baseline PSS Score. Here "PSS Score" could refer to the Signs, Symptoms, or an item Score. Negative change indicates improvement and a positive change indicates deterioration of the condition.	Missing if either observed or baseline PSS score is missing.
PSSI	Psoriasis Scalp Severity Index (PSSI): will be used if the patient has 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.
		PSSI score change from baseline	Calculated as: observed PSSI – baseline PSSI	Missing if baseline or observed value is missing
		PSSI score = 0	A PSSI response is defined as a PSSI score of 0, which is also referred to as scalp clearance.	Missing if PSSI score is missing
NAPSI	Nail Psoriasis Severity Index (NAPSI): in patient with baseline fingernail psoriasis involvement, 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 fingernail is divided with imaginary	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

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	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			10 fingers are missing, the 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.
		NAPSI score change from baseline	Calculated as: observed NAPSI – baseline NAPSI	Missing if baseline or observed value is missing
		NAPSI score =0	A NAPSI response is defined as a NAPSI score of 0, which is also referred to as nail clearance.	Missing if NAPSI score is missing

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
PPASI	Palmoplantar Psoriasis Area and Severity Index (PPASI): will be used if the patient has 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.
	PPASI change from baseline	Calculated as: observed PPASI – baseline PPASI.	Missing if baseline or observed value is missing.
	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.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
		PPASI 50	At least a 50% improvement in PPASI score from baseline.	Missing if baseline or observed value is missing.
		PPASI 75	At least a 75% improvement in PPASI score from baseline.	Missing if baseline or observed value is missing.
		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 postbaseline 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 total score ≥5 improvement from baseline	Reduction/Decrease of ≥5 points from baseline. A 5-point change from baseline is considered as the minimal clinically important difference threshold.	Missing if baseline or observed value is missing.
		DLQI (0,1) and DLQI total score ≥5 improvement form 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.
		DLQI total score and domain scores change from	Calculated as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
		baseline		
		DLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been? #2. How embarrassed or self-conscious have you been because of your skin?	If 1 question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions #3 and #4: #3. How much has your skin interfered with you going shopping or looking after your home or garden? #4. How much has your skin influenced the clothes you wear?	If 1 question in a domain is missing, that domain is missing.
		DLQI leisure domain	Sum of responses of questions #5 and #6: #5. How much has your skin affected any social or leisure activities? #6. How much has your skin make it difficult for you to do any sport?	If 1 question in a domain is missing, that domain is missing.
		DLQI work and school domain	Sum of responses of questions question #7A and #7B: #7A. Has your skin prevented you from working or studying? #7B. If No: how much has your skin been a problem at work or studying?	If the answer to question #7A is missing, this domain is missing. If #7A is No, and #7B is missing, this domain is missing.
		DLQI personal relationships domain	Sum of responses of questions #8 and #9: #8. How much has your skin created problems with your partner or any of your close friends or relatives? #9. How much has your skin caused any sexual difficulties?	If 1 question in a domain is missing, that domain is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
		DLQI treatment domain	Response of question #10: #10. How much of a problem has the treatment for your skin been, for example, by making your home messy, or by taking up time?	If 1 question in a domain is missing, that domain is missing.
WPAI-PSO	The Work Productivity and Activity Impairment-Psoriasis (WPAI-PSO) Questionnaire is a patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (psoriasis). It contains 6 items that measure: 1) employment for pay status; 2) hours missed from work due to the psoriasis; 3) hours missed from work for other reasons; 4) hours actually worked; 5) degree of health affected-productivity while working; and 6) degree of health-affected productivity in regular unpaid activities. Greater scores indicate greater impairment (Reilly Associates Health Outcomes Research [WWW]).	Employment Status	Yes/No	Missing if question is missing.
		Absenteeism Score (%)	$\frac{Q2}{(Q2+Q4)} \times 100$	Missing if Q2 or Q4 are missing. Also missing if Employment Status is No.
		Presenteeism Score (%)	$\frac{Q5}{10} \times 100$	Missing if Q5 is missing. Also missing if Employment Status is No.
		Work Productivity Loss Score (%)	$\left[\frac{Q2}{Q2+Q4} + \left(1 - \frac{Q2}{Q2+Q4}\right)\frac{Q5}{10}\right] \times 100$	Missing if Q2, Q4, or Q5 is missing. Also missing if Employment Status is No.
		Activity Impairment Score (%)	$\frac{Q6}{10} \times 100$	Missing if Q6 is missing. May still be present and non-missing if patient is unemployed.
Rebound	Derived from multiple other measurements mentioned in this table.	Rebound	Defined as having one or more of the following: worsening of psoriasis severity over baseline static Physician's Global Assessment (sPGA) score, worsening of psoriasis severity over baseline PASI score by 125%, or change in psoriasis phenotype (i.e., from plaque psoriasis to any of guttate, pustular or erythrodermic psoriasis) after randomization to placebo at Week 16.	Missing if baseline or observed value of sPGA or PASI is missing.
		Rebound within 12 Weeks, post re-randomized to placebo	Defined has having rebound for any non-missing visit between Week 16 to (and including) Week 28 (12 weeks post re-randomized to placebo).	Missing if rebound is missing for all Visits, Week 16 to Week 28.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
SF-36	The 36-Item Short Form Health Survey (SF-36) is a 36-item, patient-completed measure designed to be a short, multipurpose assessment of health (The SF Community – SF-36 Health Survey Update). The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 comprises 8 domain scores and 2 overarching component scores. SF-36 domain scores are: (1) Physical functioning; (2) Role-physical; (3) Role-emotional; (4) bodily pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health. The component scores are: (1) the Physical Component Summary (PCS); and (2) Mental Component Summary (MCS). The SF-36 acute version will be used, which has a 1 week recall period. Responder Definitions were determined in the user's manual (Maruish 2011).	SF-36 Domain scores and SF-36 Component Scores	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. No missing-imputation method will be used. Both, raw and domain scores without missing-data imputation will be recorded in the SDTM dataset; however, only the domain scores will be used for analyses specified in this SAP.	Missing data handling offered by SF-36. No missing-imputation
		SF-36 change from baseline for domain and component scores	Calculated as: observed SF-36 score – baseline SF-36 score.	Missing if baseline or observed value is missing.
		SF-36 Domain score Responder Definition	Domain score increase (change from baseline) (1) Physical functioning >4.3; (2) Role-physical > 4.0; (3) Role-emotional >4.6; (4) bodily pain > 5.5; (5) vitality > 6.7; (6) social functioning > 6.2; (7) mental health > 6.7; and (8) general health > 7.0	Missing if baseline or observed value is missing.
		SF-36 PCS Responder Definition	PCS component score increase (change from baseline) > 3.8.	Missing if baseline or observed value is missing.
		SF-36 MCS Responder Definition	MCS component score increase (change from baseline) > 4.6.	Missing if baseline or observed value is missing.
PatGA	The Patient's Global Assessment of Psoriasis	PatGA (0)	A PatGA assessed as 0	Missing if baseline or

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	(PatGA) is a patient-reported, single item scale on which patients are asked to rank, by selecting a number on a 0-to-5 NRS, the severity of their psoriasis "today" from 0 (clear, no psoriasis), to 5 (severe).			observed value is missing.
		PatGA (0,1) and PatGA ≥ 2 improvement from baseline	A PatGA assessed as either 0 or 1, and the reduction (change from baseline) ≥ 2.	Missing if baseline or observed value is missing.
EQ-5D-5L + Bolt On	European Quality of Life–5 Dimensions–5 Level (EQ-5D-5L) + Bolt On: is a standardized measure of health status used to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his/her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: Item 1: mobility Item 2: self-care Item 3: usual activities Item 4: pain/discomfort Item 5: anxiety/depression The Bolt On is an addition to the EQ-5D-5L that consists of 2 dimensions specific to psoriatic disease: Item 6: skin irritation Item 7: self-confidence The dimensions of Bolt On supplement the existing 5 dimensions of the EQ-5D in an attempt to better address specific burdens associated with psoriatic disease. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in	EQ-5D-5L + Bolt On Item Scores	Seven health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a primary score.	Each dimension is a single item, missing if missing. Note: score of 9 is missing.
		EQ-5D-5L UK Population-based index score	Uses the concatenation of the value of each EQ-5D-5L dimension score in the order of: Item 1; Item 2; Item 3; Item 4; Item 5. Derive EQ-5D-5L UK Population-based index score by using the UK algorithm (Szende et al. 2006) to produce a patient-level index score between -0.59 and 1.0 (continuous variable): https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/	If any of the items is missing or equal to 9, the index score is missing
		EQ-5D-PSO index score	The value sets and psychometric properties of the EQ-5D + psoriasis Bolt On has been proposed and validated based on the UK population (Swinburn et al. 2013). The psychometric analysis indicated the extra dimensions, skin irritation, and self-confidence, successfully captured additional information for	If any of the items is missing or equal to 9, the index score is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	each of the 5 dimensions.		psoriasis patients.	
		EQ-5D VAS	Range from 0 = "worst imaginable health state" to 100 = "best imaginable health state.". Note: higher value indicates better health state.	Single item, missing if missing.
		Change from baseline of EQ-5D VAS or index scores	Change from baseline = Observed score – Baseline score	Missing if baseline or observed value is missing.
TSQM	The Treatment Satisfaction Questionnaire for Medication (TSQM) is a self-administered 9-item measure to evaluate patient treatment satisfaction with medication in 3 domains: Effectiveness Item 1: prevention or treatment of condition Item 2: symptom relief Item 3: time to start working Convenience Item 4: difficulty of use Item 5: difficulty in planning Item 6: convenience Global Satisfaction Item 7: confidence that medication is good Item 8: certain that good outweighs bad Item 9: overall satisfaction The recall period is the last 2-3 weeks or since the medication was last taken. Item formats include both a 1- to 7-point and a 1- to 5-point Likert scale. Higher scores indicate greater satisfaction (Bharmal et al. 2009).	TSQM Global Satisfaction	Let "S" be the sum of all non-missing items 7 to 9. TSQM Global Satisfaction is calculated as: $100 * (S - 3)/14$ If either Item 7 or 8 is missing: $100 * (S - 2)/10$ If Item 9 is missing: $100 * (S - 2)/8$	If more than 1 of the 3 items are missing, then missing.
		TSQM Effectiveness	Let "S" be the sum of all non-missing items, 1 to 3. TSQM Effectiveness is calculated as: $100 * (S - 3)/18$ If one item is missing: $100 * (S - 2)/12$	If more than 1 of the 3 items are missing, then missing.
		TSQM Convenience	Let "S" be the sum of all non-missing items, 4 to 6. TSQM Effectiveness is calculated as: $100 * (S - 3)/18$ If one items is missing: $100 * (S - 2)/12$	If more than 1 of the 3 items are missing, then missing.
QIDS-SR16	The 16-item Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR16) is a self-administered, 16-item instrument intended to	QIDS-SR16 Total Score	The QIDS-SR16 total score is the sum of the domain scores below. The total score has a range of 0 to 27.	The total score will be missing if any domain score is missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
	assess the existence and severity of symptoms of depression. A patient is asked to consider each item as it relates to the way he/she has felt over the last week. There is a 4-point scale for each item ranging from 0 (best) to 3 (worst). The domains assessed by the instrument include: (1) sleep disturbance (initial, middle, and late insomnia or hypersomnia); (2) sad mood; (3) decrease/increase in appetite/weight; (4) concentration; (5) self-criticism; (6) suicidal ideation; (7) interest; (8) energy/fatigue; (9) psychomotor agitation/retardation	Sleep disturbance (initial, middle, and late insomnia or hypersomnia)	The highest score recorded for the four sleep items: #1 (falling asleep), #2 (sleep during the night), #3 (waking up too early) and #4 (sleeping too much).	Domain is missing if all items are missing.
		Sad mood	Item #5 (feeling sad).	Domain is missing if the item is missing.
		Decrease/increase in appetite/weight	The highest score recorded for the appetite/weight items: #6 (decreased appetite), #7 (increased appetite), #8 (decreased weight within the last two weeks), and #9 (increased weight within the last two weeks).	Domain is missing if all items are missing or not applicable.
		Concentration	Item #10 (concentration / decision making).	Domain is missing if the item is missing.
		Self-criticism	Item #11 (view of myself).	Domain is missing if the item is missing.
		Suicidal ideation	Item #12 (thoughts of death or suicide).	Domain is missing if the item is missing.
		Interest	Item #13 (general interest).	Domain is missing if the item is missing.
		Energy/fatigue	Item #14 (energy level).	Domain is missing if the item is missing.
		Psychomotor agitation/retardation	The highest score recorded for the two psychomotor items: #15 (feeling slowed down) and #16 (feeling restless).	Domain is missing if all items are missing.
		QIDS-SR16 Response	≥50% improvement in the QIDS-SR16 total score from baseline.	If total score is missing for baseline or visit, then missing.
		QIDS-SR16 Remission	QIDS-SR16 Total Score of 0 to 5.	If total score is missing, then missing.

Measure	Description	Variable	Derivation/Comment	Definition of Missing Components
Facial Psoriasis	Physician assessed presence or absence of facial psoriasis.	Facial Psoriasis	Response is either Yes or No.	Missing if question is missing.

Abbreviations: BSA = body surface area; DLQI = Global Assessment Dermatology Life Quality Index; EMA = European Medicines Agency; HRQoL = health-related quality of life; MCID = Minimal Clinically Important Difference; MCS = Mental Component Score; NRS = Numeric Rating Scales; PASI = Psoriasis Area and Severity Index; PatGA = Patients Global Assessment of Psoriasis; PCS = Physical Component Score; Ps = psoriasis; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; SAP = statistical analysis plan; SDTM = study data tabulation model; sPGA = Static Physician Global Assessment; UK = United Kingdom; VAS = visual analog scale.

Table AMAK.6.6. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
PASI	PASI 90 (Primary and Sensitivity)	CMH analysis with NRI	Induction ITT; Induction PPS	Week 16 (and all visits in corresponding Periods)
		Logistic regression analysis with NRI	Induction ITT	Week 16 (and all visits in corresponding Periods)
		Categorical MMRM	Induction ITT	Week 16 (and all visits in corresponding Periods)
	PASI 75; PASI 90; PASI 100	CMH analysis with NRI	Induction ITT; Re-randomized Maintenance ITT;	All visits in corresponding periods
		Summary statistics with NRI and as observed	Non-re-randomized Maintenance; Re-randomized Relapsed	All visits in corresponding periods
	Time to first achieving PASI 100, PASI 90, or PASI 75 (i.e., 3 different analyses)	KM analysis (censoring described in Table AMAK.6.5)	Induction ITT;	All visits in corresponding periods
	Time to first loss of PASI 90	KM analysis (censoring described in Table AMAK.6.5)	Re-randomized Maintenance ITT	All visits in corresponding periods
	Time to first loss of PASI 100	KM analysis (censoring described in Table AMAK.6.5)	Re-randomized Maintenance ITT in patients achieved PASI 100 at Week 16	All visits in corresponding periods
	Stability of PASI 90 up to Week 52	CMH analysis with NRI	Re-randomized Maintenance ITT	All visits in corresponding periods
	Stability of PASI 100 up to Week 52	CMH analysis with NRI	Re-randomized Maintenance ITT in patients achieved PASI 100 at Week 16	All visits in corresponding periods
	PASI ≤5; PASI ≤3; PASI ≤2; PASI ≤1	CMH analysis with NRI	Induction ITT; Re-randomized Maintenance ITT;	All visits in corresponding periods

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
	PASI change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT;	All visits in corresponding periods
		Summary statistics (As observed)	Non-re-randomized Maintenance; Re-randomized Relapsed	All visits in corresponding periods
	Percent improvement from baseline	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	All visits in corresponding periods
		Summary statistics (As observed)	Non-re-randomized Maintenance; Re-randomized Relapsed	All visits in corresponding periods
	Cumulative time with PASI 90 response after re-randomization through Week 52	ANCOVA for AUC of PASI 90 response over time; ANCOVA for percentages of scheduled visits with PASI 90 response among all scheduled visits ANCOVA for percentages of weeks with PASI 90 response in maintenance period	Re-randomized Maintenance ITT	All visits in corresponding periods through Week 52
	Cumulative time with PASI 100 response after re-randomization through Week 52	ANCOVA for AUC of PASI 100 response over time ANCOVA for percentages of scheduled visits with PASI 100 response among all scheduled visits ANCOVA for percentages of weeks with PASI 100 response in maintenance period	Re-randomized Maintenance ITT in patients achieved PASI 100 at Week 16	All visits in corresponding periods through Week 52

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
	Time to relapse	KM analysis (censoring described in Table AMAK.6.5)	Re-randomized Maintenance ITT	All visits in corresponding periods
	Regaining PASI 90 within 16 weeks after relapse and retreatment	Summary statistics (As observed)	Re-randomized Relapsed	16 weeks after relapse
	Time to first regaining PASI 90 after relapse	KM analysis (censoring described in Table AMAK.6.5)	Re-randomized Relapsed	All visits in corresponding periods
sPGA	sPGA (0,1) (Primary and Sensitivity)	CMH analysis with NRI	Induction ITT; Induction PPS	Week 16 (and all visits in corresponding Period)
		Logistic regression analysis with NRI	Induction ITT	Week 16 (and all visits in corresponding Period)
		Categorical MMRM	Induction ITT	Week 16 (and all visits in corresponding Period)
	sPGA (0,1); sPGA (0)	CMH analysis with NRI	Induction ITT; Re-randomized Maintenance ITT;	All visits in corresponding periods
		CMH analysis with NRI	Re-randomized Maintenance ITT - In Patients who Achieve sPGA (0,1) at Week 16	All visits in corresponding periods
		Summary statistics with NRI and as observed	Non-re-randomized Maintenance; Re-randomized Relapsed	All visits in corresponding periods
	Time to first loss of sPGA (0,1)	KM product limit curve (censoring described in Table AMAK.6.5)	Re-randomized Maintenance ITT - In Patients who Achieve sPGA (0,1) at Week 16	All visits in corresponding periods
	Time to first achieving sPGA (0,1)	KM product limit curve (censoring described in Table AMAK.6.5)	Induction ITT	All visits in corresponding periods
BSA	Proportion of patients with ≤1% of BSA with psoriasis involvement	CMH analysis with NRI	Induction ITT; Re-randomized Maintenance ITT	All visits in corresponding periods
		Summary statistics with NRI and as observed	Non-re-randomized Maintenance	All visits in corresponding periods
	BSA change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	All visits in corresponding periods

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
PSS	PSS Symptoms Score of 0	CMH analysis with NRI	Induction ITT - In Patients with Baseline PSS Symptom Score ≥1	All weeks in Induction Period
		CMH analysis with NRI	Re-randomized Maintenance ITT - In Patients with Baseline PSS Symptom Score ≥1	All visits in corresponding period
		Summary statistics with NRI and as observed	Non-re-randomized Maintenance - In Patients with Baseline PSS Symptom Score ≥1	All visits in Maintenance Periods
	PSS Signs Score of 0	CMH analysis with NRI	Induction ITT - In Patients with Baseline PSS Signs Score ≥1	All weeks in Induction Period
		CMH analysis with NRI	Re-randomized Maintenance ITT - In Patients with Baseline PSS Signs Score ≥1	All visits in corresponding period
		Summary statistics with NRI and as observed	Non-re-randomized Maintenance- In Patients with Baseline PSS Signs Score ≥1	All visits in Maintenance Periods
	Change from baseline for PSS Item Scores, Symptoms Score, Signs Score	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	All visits in corresponding periods
	PSS Symptoms Score of 0 by stability of PASI 90 / PASI 100 at Week 52	CMH analysis with NRI	Re-randomized Maintenance ITT - In Patients with Baseline PSS Symptom Score ≥1	Week 52
	PSS Signs Score of 0 by stability of PASI 90 / PASI 100 at Week 52	CMH analysis with NRI	Re-randomized Maintenance ITT – In Patients with Baseline PSS Signs Score ≥1	Week 52
PSSI	PSSI change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT - In Patients with Scalp Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Scalp Involvement at Baseline	All visits in corresponding periods
	PSSI score = 0	CMH analysis with NRI	Induction ITT - In Patients with Scalp Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Scalp Involvement at Baseline	All visits in corresponding periods

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
PPASI	PPASI change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT - In Patients with Palmoplantar Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Palmoplantar Involvement at Baseline	All visits in corresponding periods
	PPASI 50; PPASI 75; PPASI 100	CMH analysis with NRI	Induction ITT - In Patients with Palmoplantar Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Palmoplantar Involvement at Baseline	All visits in corresponding periods
NAPSI	NAPSI change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT - In Patients with Nail Psoriasis Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Nail Psoriasis Involvement at Baseline	All visits in corresponding periods
	NAPSI score = 0	CMH analysis with NRI	Induction ITT - In Patients with Nail Psoriasis Involvement at Baseline; Re-randomized Maintenance ITT - In Patients with Nail Psoriasis Involvement at Baseline	All visits in corresponding periods
DLQI	DLQI (0,1) and ≥5 point reduction from baseline	CMH analysis with NRI	Induction ITT - In Patients with Baseline DLQI>=5 Re-randomized Maintenance ITT - In Patients with Study Baseline DLQI >=5	All visits in corresponding periods
		Summary statistics (as observed)	Non-re-randomized Maintenance - In Patients with Study Baseline DLQI >=5	All visits in corresponding periods
	DLQI (0,1)	CMH analysis with NRI	Induction ITT - In Patients with Study Baseline DLQI >1 ; Re-randomized Maintenance ITT - In Patients with Study Baseline DLQI >1	All visits in corresponding periods
	DLQI total score ≥5 point reduction from baseline	CMH analysis with NRI	Induction ITT - In Patients with Study Baseline DLQI ≥5 ; Re-randomized Maintenance ITT - In Patients with Study Baseline DLQI ≥5	All visits in corresponding periods
	DLQI total score and domain scores change from baseline	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	All visits in corresponding periods

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
	DLQI (0,1) by stability of PASI 90 / PASI 100 at Week 52	CMH analysis with NRI	Re-randomized Maintenance ITT	Week 52
SF-36	SF-36 change from baseline for Domain Scores and PCS and MCS Component Scores	ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	Last visit in corresponding periods
	SF-36 Domain score Responder Definition; SF-36 PCS Responder Definition; SF-36 MCS Responder Definition (Defined in Table AMAK.6.5)	CMH analysis with NRI	Induction ITT; Re-randomized Maintenance IT	Last visit in corresponding periods
PatGA	PatGA(0)	CMH analysis with NRI	Induction ITT - in patients with baseline PatGA >0; Re-randomized Maintenance ITT – in patients with baseline PatGA >0	All visits with scheduled measurements in corresponding periods
	PatGA (0,1) and ≥2 improvement from baseline	CMH analysis with NRI	Induction ITT – in Patients with baseline PatGA ≥2; Re-randomized Maintenance ITT – in patients with baseline PatGA ≥2	All visits with scheduled measurements in corresponding periods
WPAI-PSO	Change from baseline in WPAI-PSO Scores (Absenteeism, Presenteeism, Work Productivity, Activity Impairment)	ANCOVA with mBOCF	Induction ITT - In Patients with Baseline Employment Status of Yes	Week 16 Visit.
		MMRM; ANCOVA with mBOCF	Re-randomized Maintenance ITT - In Patients with Baseline Employment Status of Yes	All visits with scheduled measurements in corresponding period.
TSQM	Mean Effectiveness, Convenience, and Global Satisfaction	ANCOVA with mBOCF	Induction ITT	Week 16 Visit
		MMRM; ANCOVA with mBOCF	Re-randomized Maintenance ITT	All visits with scheduled measurements in corresponding period.
EQ-5D-5L + Bolt On	EQ-5D Dimension Scores	CMH analysis	Induction ITT; Re-randomized Maintenance ITT	All visits with scheduled measurements in corresponding period.

Measure	Variable	Analysis Method (Section 6.1.4)	Population (Section 6.1.1)	Time Point
	Change from baseline of EQ-5D VAS and Index scores	MMRM; ANCOVA with mBOCF	Induction ITT; Re-randomized Maintenance ITT	All visits with scheduled measurements in corresponding periods.
QIDS-SR16	QIDS-SR16 Response; QIDS-SR16 Remission	CMH analysis with NRI	Induction ITT- In Patients with a Baseline Value ≥11; Re-randomized Maintenance ITT - In Patients with a Baseline Value ≥11	All visits with scheduled measurements in corresponding periods.
Facial Psoriasis	Facial Psoriasis	Summary statistics with CMH analysis; Shift table	Induction ITT; Re-randomized Maintenance ITT	Week 16 and Week 52
	No Facial Psoriasis	CMH analysis with NRI	Induction ITT – In Patients with a Baseline Facial Involvement; Re-randomized Maintenance ITT - In Patients with a Baseline Facial Involvement	Week 16 and Week 52
Rebound	Rebound within 12 weeks	Summary statistics analysis as observed	Re-randomized Maintenance ITT	12 weeks after re-randomization to placebo at Week 16

Abbreviations: ANCOVA = analysis of covariance; AUC = area under the drug plasma concentration versus time curve; BSA = body surface area; CMH = Cochran-Mantel-Haenszel test; DLQI = Global Assessment Dermatology Life Quality Index; EQ-5D-5L = European Quality of Life–5 Dimensions–5 Level; ITT = intent-to-treat; KM = Kaplan-Meier; mBOCF = modified baseline observation carried forward; MCID = Minimal Clinically Important Difference; MCS = Mental Component Score; MMRM = mixed model repeating measures; NAPSI = Nail Psoriasis Severity Index; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/100% improvement from baseline in the Psoriasis Area and Severity Index; PatGA = Patients Global Assessment of Psoriasis; PCS = Physical Component Score; PPASI = Palmoplantar Psoriasis Severity Index; PPS = per protocol set; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology – Self-Report; SF-36 = 36-Item Short Form Health Survey; sPGA = Static Physician Global Assessment; TSQM = Treatment Satisfaction Questionnaire for Medication; VAS = visual analog scale; WPAI-PSO = Work Productivity Activity Impairment Questionnaire–psoriasis.

6.10.1. Primary Outcome and Methodology

Primary outcome PASI 90 and its analysis are described in Table AMAK.6.5 and Table AMAK.6.6. The primary analysis is a CMH analysis with NRI.

6.10.2. Additional Analyses of the Primary Outcome

Additional analyses of the primary outcome are described in Table AMAK.6.5 and Table AMAK.6.6.

6.10.3. Multiple Testing Controlled Secondary Efficacy Analyses

Secondary outcomes and their analyses are described in Table AMAK.6.5 and Table AMAK.6.6. The primary analysis for all multiple testing controlled secondary efficacy analyses is a CMH analysis with NRI.

6.10.4. Other Secondary Efficacy Analyses

Other secondary analyses of efficacy are described in Table AMAK.6.5 and Table AMAK.6.6.

6.10.5. Sensitivity Analyses

Sensitivity analyses are described in Table AMAK.6.5 and Table AMAK.6.6.

6.11. Health Outcomes/Quality-of-Life Analyses

See Table AMAK.6.5 and Table AMAK.6.6.

6.12. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Details of pharmacokinetic/pharmacodynamic (PK/PD) analyses can be found in a separate PK/PD analysis plan.

6.13. Safety Analyses

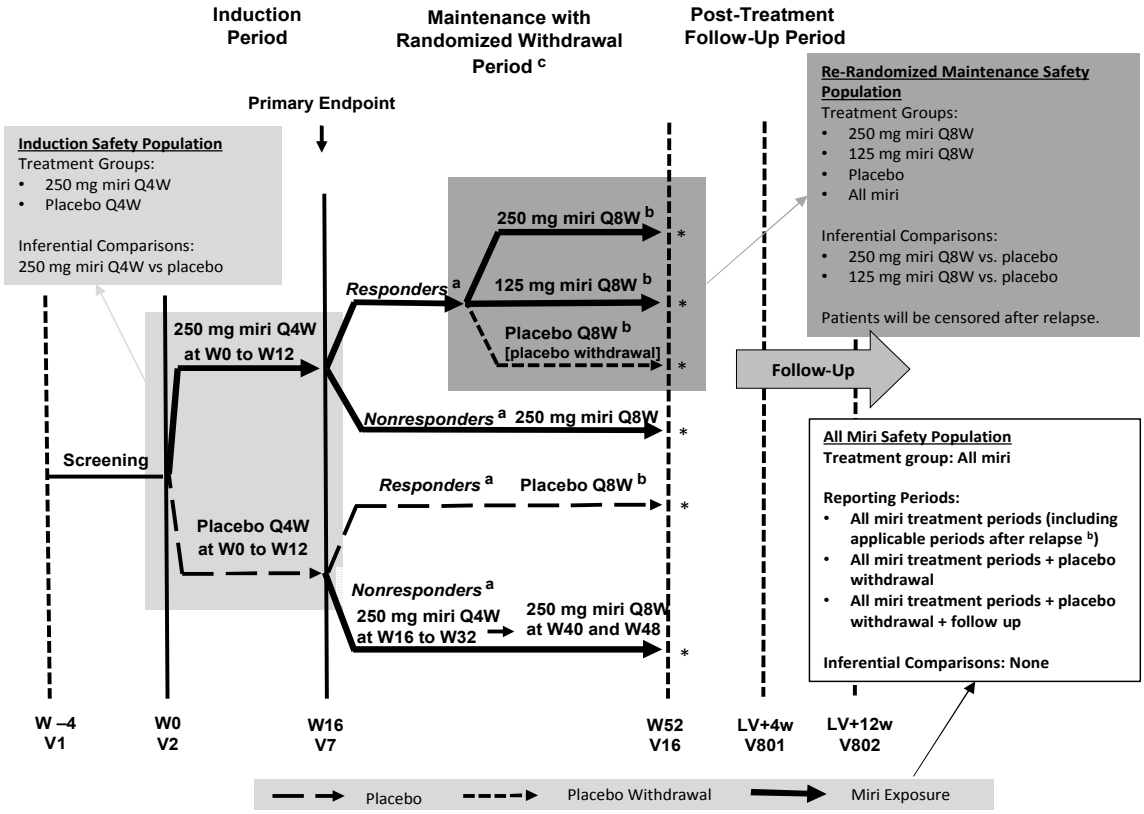
The planned analyses of safety data will be performed with an intent to maintain consistency with compound level safety standards. These standards are based on internal standards which were informed by Clinical Data Interchange Standards Consortium (CDISC) standards, regulatory guidance (e.g., Food and Drug Administration [FDA] Clinical Review Template), and cross-industry standardization efforts (e.g., Pharmaceutical Users Software Exchange [PhUSE] white papers from the Standard Analyses and Code Sharing Working Group provided in the PhUSE Computational Science Deliverables Catalog [WWW]).

All safety evaluations will be based upon the following safety analysis populations with their associated study periods:

- Induction Safety Population
- Re-randomized Maintenance Safety Population
- All Miri Safety Population

These analysis populations are fully defined in Table AMAK.6.1, while Table AMAK.6.2 describes the treatment groups, associated study periods and the comparisons for each analysis

population. Figure AMAK.6.2 gives a graphical depiction of each of the 3 safety populations along with the treatment groups, associated study periods and the comparisons for each analysis population.



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

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

a Patients may receive placebo injections during the Maintenance Period to maintain the study blind across treatment groups.

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

c First Maintenance Period dosing at Week 16.

Figure AMAK.6.2. Illustration of safety populations within the study design.

Unless otherwise noted, Fisher's exact test will primarily be used to compare percentages, and odds ratios will be provided. Odds ratios will be created with mirikizumab treatment as the numerator and placebo as the denominator.

Treatment differences in mean change for continuous measurements will be assessed using an analysis of covariance (ANCOVA) model containing terms for treatment and the continuous covariate of baseline measurement. Type 3 sums of squares will be used. The significance of

within-treatment group changes from baseline will be evaluated by testing whether the treatment group LSMean changes from baseline are different from zero using a t-statistic.

Not all displays described in this section will necessarily be included in the CSRs. Any display described and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display created interactively will be included in the CSR if deemed relevant to the discussion.

6.13.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for each of the three safety analysis populations (i.e., Induction Safety, Re-randomized Maintenance Safety, and All Miri Safety). For the treatment period of interest associated with each safety analysis population, exposure will be calculated as the time period length in years (see Section 6.1.2) with start and end dates described in Table AMAK.6.3. The following periods will be used for calculations:

- For the Induction Safety Population, the Induction Period Interval will be used.
- For the Re-randomized Maintenance Safety Population, the Maintenance Period Interval will be used. As noted in Table AMAK.6.3, patients who relapse after re-randomization during the maintenance period are considered to have left the maintenance period and entered the relapse period.
- For the All Miri Safety Population, we calculate the exposure for 3 different period definitions:
    - Exposure for "all miri" will be calculated by finding the length of the "All Miri Period." For patients who are re-randomized to placebo, the "All Miri Period" may be composed of two non-overlapping periods of time, and the length of the two periods of time will be summed.
    - Exposure for "all miri + placebo withdrawal" will be calculated as the length of the "All Miri + Placebo Withdrawal Period."
    - Exposure for "all miri + placebo withdrawal + follow-up (FUP)" will be calculated as the length of the "All Miri + placebo withdrawal + FUP Period."

Total patient-years (PY) of exposure will be reported for each of the three safety analysis populations by treatment group (see Table AMAK.6.2). Descriptive statistics will be provided for patient-weeks of exposure and the frequency of patients falling into different exposure ranges will be summarized:

- >0; ≥4 weeks; ≥8 weeks; ≥12 weeks; ≥16 weeks; ≥ 24 weeks; ≥32 weeks; ≥40 weeks; and ≥48 weeks
- >0 to <4 weeks; ≥4 weeks to <8 weeks; ≥8 weeks to < 12 weeks; ≥ 12 weeks to < 16; …; ≥48 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.

6.13.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. The maximum severity for each LLT during the baseline period will be used as baseline. The treatment period will be included as postbaseline for the analysis. For events with a missing severity during the baseline period, it will be treated as "mild" in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment-emergence will be determined by comparing to baseline severity. For events occurring on the day of first taking study medication, the start times of the study treatment and AE will be used to determine whether the event was pre- versus post-treatment. If start time for the AE is missing, it will be assumed to have started in the later period.

Summary tables as described in Table AMAK.6.7 will be presented for the three safety populations/ periods, as indicated. Summary tables will include the number and percentage of patients reporting an event. For events that are gender-specific (as defined by MedDRA), the number of participants at risk will include only patients from the given gender. Comparisons will be performed using Fisher's exact test. P-values should be interpreted cautiously due to the fact that multiplicity is not controlled.

For the three safety populations, the baseline period and postbaseline periods (see Figure AMAK.6.2) will be defined as follows:

- *Induction Safety Population*: The baseline period is the Screening Period. The postbaseline period will be the Induction Period.
- *Re-randomized Maintenance Safety Population*: The baseline events are those events which are ongoing at the start of the Maintenance Period (i.e., the baseline period is a moment in time). The postbaseline period is defined as the Maintenance period.
- *All Miri Safety Population*: The baseline period for patients randomized to mirikizumab during induction is the screening period. For all other patients, the baseline events are those events which are ongoing at the time of first injection with mirikizumab. Three different postbaseline periods will be used:
    - For "all miri," the "All Miri Period" will be used. Note that the "All Miri Period" excludes events that began during the "Placebo Withdrawal Period" for patients who were re-randomized to Placebo.
    - For "all miri + placebo withdrawal," the "All Miri + Placebo Withdrawal Period" will be used.
    - For "all miri + placebo withdrawal + FUP," the "All Miri + Placebo Withdrawal + FUP Period" will be used.

Table AMAK.6.7. Summary Tables Related to Adverse Events

Analysis	Population/ Period[a]
Overview of AEs	I; R; A
Summary of TEAE PTs by decreasing frequency	I; R; A
Summary of TEAE PTs occurring in ≥1% of patients by decreasing frequency	I; R
Summary of TEAE PTs by decreasing frequency within SOC	I; R
Summary of TEAE PTs by maximum severity by decreasing frequency within SOC	I; R
Summary of SAE PTs by decreasing frequency	I; R; A
Summary of AEs leading to study discontinuation	I; R; A
Listing of SAEs	I
Listing of Deaths	All Entered patients

Abbreviations: AEs = adverse event; PTs = Preferred Terms; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

[a] Populations are abbreviated as follows: I = Induction Safety; R = Re-randomized Maintenance Safety; A = All Miri Safety.

6.13.2.1. Common Adverse Events

The percentages of patients with TEAEs will be summarized by treatment using MedDRA PT for the common TEAEs (occurred in ≥1% before rounding of treated patients). Events will be ordered by decreasing frequency in the all miri group. See Table AMAK.6.7 and Figure AMAK.6.2.

6.13.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

The number and percentage of patients who reported a serious adverse event (SAE) during the treatment period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency in the all miri group within SOC. This analysis will be conducted for all 3 safety populations. A listing of SAEs will be provided.

The number and percentage of patients who permanently discontinued from study treatment due to an AE (including AEs that led to death) during the treatment period will be summarized by treatment using MedDRA PT nested within SOC. Events will be ordered by decreasing frequency in the all miri group within SOC. This analysis will be conducted for all 3 safety populations.

6.13.4. Clinical Laboratory Evaluation

As described more fully in compound level safety standards and in the laboratory-related PhUSE white papers (PhUSE 2013; PhUSE 2015), the clinical laboratory evaluations will be summarized with the following displays described in Table AMAK.6.8.

Table AMAK.6.8. Summaries/Displays/Analysis for Clinical Laboratory Evaluations

Analysis	Population/ Period[a]
Box plots of observed values (and change from baseline values) by visit. Change from baseline to last observation will be summarized within the box plot of changes (rightmost column), and descriptive summary statistics will be included in a table below the	I; R

box plot along with a p-value using the ANCOVA model described in Section 6.13.	
Treatment-emergent abnormal high lab values (i.e., patients shifting from a normal/low maximum baseline value to a high maximum postbaseline value) or low laboratory values (i.e., patients shifting from normal/high minimum baseline value to a low minimum postbaseline value).	I; R; A
Scatter plot of maximum (minimum) postbaseline value versus maximum (minimum) baseline value.	I; R
Shift tables showing the number of patients who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) postbaseline observation. Here, categories may be low, normal, or high with cut-offs defined in the compound level safety standards.	I; R

Abbreviation: ANCOVA = analysis of covariance.

[a] Populations are abbreviated as follows: I = Induction Safety; R = Re-randomized Maintenance Safety; A = All Miri Safety.

For these displays, the postbaseline periods will be identical to those described in Section 6.13.2. Postbaseline measurement for continuous analysis (e.g., boxplots) will include *only* scheduled measurements, while postbaseline categorical analysis (e.g., shifts) will include *both* scheduled and unscheduled measurements.

Measurements are defined to be in the baseline periods as follows:

- *Induction Safety Population*:
  - For analyses of continuous measurements: the last scheduled or unscheduled non-missing measurement recorded during the screening period.
  - For analyses of categorical measurements: all scheduled or unscheduled non-missing measurements recorded during the Screening Period.
- *Re-randomized Maintenance Safety Population*:
  - For analyses of continuous and categorical measurements: the last scheduled or unscheduled non-missing measurement recorded during the Induction Period (i.e., the baseline period only includes a single assessment).
- *All Miri Safety Population*:
  - For analyses of continuous measurements: (1) the last scheduled or unscheduled non-missing measurement recorded during the Screening Period for the patients randomized to miri during induction; (2) the last scheduled or unscheduled non-missing measurement recorded before first miri treatment for all other patients.
  - For analyses of categorical measurements: (1) all scheduled or unscheduled non-missing measurements recorded during the Screening Period for the patients randomized to miri during induction, (2) the last scheduled or unscheduled non-missing measurement recorded before first miri treatment for all other patients.

For any laboratory test given on the day of first taking study medication at the start of the postbaseline period, the start time of the study treatment will be used to determine whether the laboratory test was pre- versus postbaseline. If time for the laboratory test is missing, it will be assumed to be in the baseline period (i.e., assume the protocol-defined order of procedures was

followed). Following the compound-level safety standards, for some laboratory tests, a safety concern may exist for only high (or only low) values. For these laboratory tests, displays with only maximum (or minimum) values will be used and shift tables will be presented accordingly.

6.13.5. Vital Signs and Other Physical Findings

As described more fully in compound level safety standards and in the vital signs-related PhUSE white papers (PhUSE 2013; PhUSE 2015), vital signs will be summarized similarly to the clinical laboratory evaluation (see Section 6.13.4). For vital signs, the low and high limits are based on a combination of a specified value and a change or percentage change. In this case, the PhUSE white paper recommends providing scatter plots and shifts to low/high. Boxplots will also be presented.

6.13.6. Electrocardiograms

Complete electrocardiogram (ECG) data will not be part of the clinical database for the individual studies. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment will be reported to Lilly or its designee as an AE via eCRF. Aside from standard AE summary tables, no additional analysis of ECG data will be performed.

6.13.7. Immunogenicity

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. Listings of immunogenicity assessments will be provided-along with the summary of specified TEAEs by TE ADA status. The summary of TE ADA and NAb status will be produced for all 3 safety populations, where the post baseline period for reporting is the same as described for AEs in Section 6.13.2. For the Re-randomized Maintenance population the analysis of TEAEs will be cumulative across both the Induction and Maintenance Periods. Additional assessments of the relationship between immunogenicity and efficacy will be performed as part of the integrated analysis including other Phase 3 mirikizumab psoriasis trials.

6.13.8. Special Safety Topics including Adverse Events of Special Interest

This section includes areas of interest, whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, potential adverse events of special interest (AESI) relevant to these special safety topics will be identified by one or more standardized MedDRA query(ies) (SMQs),

by a Lilly defined MedDRA PT listing, based upon the review of the most current MedDRA Version, or by treatment-emergent relevant laboratory changes, as described below. Additional special safety topics may be added, as warranted.

Unless otherwise specified, the AESIs will be summarized for all three safety populations during their associated study periods using the baseline and postbaseline definitions described in Sections 6.13.2 and 6.13.4.

Full details of the search terms and rules for deriving AESIs in each of the sections below are described in the compound level safety standards along with information about the types of summaries and listings to be provided.

6.13.8.1. Hepatic Safety

Hepatic laboratory tests include alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin (TBL) and serum alkaline phosphatase (ALP). When criteria are met for hepatic evaluations, investigators will complete a follow-up hepatic safety eCRF.

Analyses will include:

- ALT and AST: The percentages of patients with a measurement greater than or equal to 3 times (3X), 5 times (5X), and 10 times (10X) the Covance upper limit of normal (ULN) during the treatment period for all patients with a postbaseline value and for subsets based on various levels of baseline value.
- TBL and ALP: The percentages of patients with a measurement greater than or equal to 2 times (2X) the Covance ULN during the treatment period will be summarized for all patients with a postbaseline value and for subsets based on various levels of baseline value.
- Plot of maximum postbaseline ALT versus maximum postbaseline total bilirubin (entire safety population).
- A listing of the information collected on the hepatic-safety eCRF.

6.13.8.2. Infections, Including Opportunistic Infections and Serious Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC. Treatment-emergent infections will be analyzed for: all infections (by maximum severity), serious infections and opportunistic infections (OI). The MedDRA terms used to identify infections considered to be OI in patients with immune mediated inflammatory conditions treated with immunomodulatory drugs are based on Winthrop et al. (2015) and are listed in the compound level safety standards. The list contains narrow (more specific) and broad (less specific) PTs with respect to these prospectively defined opportunistic infections.

Analyses will include:

- Infections/Serious Infections: treatment-emergent infections by PT.
- Opportunistic Infections: treatment-emergent OI by narrow terms and broad terms separately.

6.13.8.3. Hypersensitivity

Hypersensitivity reactions is used as an overarching term to describe events that are systemic or localized reactions that likely have an allergic/hypersensitivity etiology. Patients will be evaluated by the investigator for signs and symptoms suggestive of hypersensitivity, and investigators will complete a follow-up eCRF designed to record additional information.

Potential hypersensitivity reactions will be determined using the following SMQs: anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as Immediate (i.e., occurring within 24 hours) and non-immediate (i.e., occurring after the day of study drug administration but prior to subsequent drug administration), based on the timing of the reaction.

Analyses will include:

- For Immediate Hypersensitivity: (1) combined narrow/algorithmic search (i.e. any narrow term from any one of the SMQs, or anaphylaxis algorithm), (2) narrow search (i.e. any narrow term) by SMQ, (3) broad search (i.e. any narrow or broad term) by SMQ, and (4) TEAEs (occurring on the day of study drug administration) by PT not in any of the 3 SMQs
- For Non-Immediate Hypersensitivity: (1) combined narrow search (i.e. any narrow term from any one of the SMQs), (2) narrow search (i.e. any narrow term) by SMQ, and (3) broad search (i.e. any narrow or broad term) by SMQ

CCI [redacted]

6.13.8.5. Cerebro-Cardiovascular Events

The cerebro-cardiovascular events reported in the study will be adjudicated by an independent, external adjudication committee (AC). All confirmed events after adjudication will be used for the analysis of cerebro-cardiovascular events. Categories of events include: Cardiovascular, Neurologic, and Peripheral Vascular Events. As detailed in the compound level safety standards, the categories are further categorized into subcategories.

Analyses will include:

- Treatment-emergent cerebro cardiovascular confirmed events by category, subcategory, and PT.
- By-patient listing for all patients having a TEAE of cerebro-cardiovascular (confirmed event, no event, or insufficient documentation for event determination), at any time.

6.13.8.6. Malignancies

Malignancies will be defined using PTs from the Malignant tumors SMQ. Malignant tumor events will be summarized separately for the categories: Non-Melanoma skin cancer (NMSC) and Malignancies, excluding NMSC.

Analyses will include:

- Treatment-emergent malignancy by category and PT.
- By-patient listing for all patients having a TEAE of malignancy at any time.

6.13.8.7. Suicidal Ideation/Behavior and Depression

During the study, suicidal ideation and behavior, and depression will be assessed prospectively by the investigator via signs and symptoms and through the use of the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR16).

Analyses will include:

- C-SSRS: Only a listing of the C-SSRS will be provided. Additional summaries may be provided if justified by the number of events (further described in the compound level safety standards).
- QIDS-SR16: Shift tables will be provided showing the number and percentage of patients within each baseline category (maximum value) versus each postbaseline category (maximum value) by treatment. Additionally, outcomes such as any increase in depression will be compared between treatments (further described in the compound level safety standards).

CCI [redacted]

[redacted]

6.14.2. Safety Subgroup Analyses

Subgroup analysis for safety related endpoints will be performed within the context of the integrated safety analysis. No safety subgroup analysis will be performed specifically for this study, unless there is a potentially relevant finding during the periodic study safety reviews.

6.15. Analysis for Japan Submission

A subset of the planned efficacy, health outcomes and safety analyses will be reproduced based on patients from Japan sites, in support of the regulatory submission in Japan. The list of tables, listings, and figures for the patients from Japan sites (Japanese population) will be in a separate document.

6.16. Analysis for Australian Submission

In addition to the analysis already specified, efficacy analysis will be conducted to meet the Pharmaceutical Benefits Advisory Commission (PBAC) criteria. The PBAC population is a subset of the patients with a PASI score >15 at baseline in the induction ITT and Re-randomized Maintenance ITT Populations. The sPGA (0,1), sPGA (0), PASI 75, PASI 90 and PASI 100 using the PBAC population will be analyzed.

6.17. 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.

As specified in Table AMAK.6.1, the Induction PPS population is defined as all randomized patients who do not have important protocol deviations excluded from per protocol analysis (IPDPP) in the induction period. A separate document known as the "The AMAK Trial Issues Management Plan" describes the categories and subcategories of important protocol deviations, the action to be taken regarding the exclusion of patients from PPS, and the source of the deviation identified.

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

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

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

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

Week 52 Database Lock: An unblinded analysis will be performed after all patients have completed the Week 52 Visit or discontinued study treatment. This database lock will include all data collected by the cut-off date including follow-up data from patients that have begun Post-Treatment Follow-Up Period. This is the final analysis for the efficacy endpoints up to Week 52. However, the study may be ongoing for the Post-Treatment Follow-Up Period at the time of this database lock.

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

6.19. 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.

6.20. 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

Unblinding details are specified in a separated unblinding plan.

8. References

Agresti A. *Categorical Data Analysis*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2013.

Alosh, M, Bretz, F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33(4):693–713.

Andersen SW, Millen BA. On the practical application of mixed effects models for repeated measures to clinical trial data. *Pharm Stat.* 2013;12(1):7–16.

Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results .*Br J Dermatol*. 2008;159(5):997-1035.

Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes*. 2009;7:36.

Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, Li S, Kimbal AB. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405-417.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28(4):586–604.

Bretz F, Posch M, Glimm E, Kinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J.* 2011;53(6):894-913.

Finlay AY, Khan GK. Dermatology Quality of Life Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216.

Firth D. Bias reduction of maximum likelihood estimates. *Biometrika.* 1993;80(1):27-38.

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

Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, Leonardi CL; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345-356.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125(4):569-664.

Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E, Tsai TF, Wasel N, Tyring S, Salko T, Hampele I, Notter M, Karpov A, Helou S, Papavassilis C; ERASURE Study Group; FIXTURE Study Group.

Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326-338.

Maruish, M.E. (Ed). User's manual for the SF36v2 Health Survey (3rd ed.). Lincoln, RI: Quality Metric Incorporated. 2011.

Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, Menter A, Philipp S, Sofen H, Tyring S, Berner BR, Visvanathan S, Pamulapati C, Bennett N, Flack M, Scholl P, Padula SJ. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N Engl J Med*. 2017;376(16):1551-1560.

PhUSE resources page. PhUSE web site. Available at http://www.phuse.eu/css-deliverables. Accessed September 18, 2017.

PhUSE resouces page. Analyses & Displays Associated with Demographics, Disposition, & Medications in Phase 2-4 Clinical Trials & Integrated Summary Documents. 2018. Available at: https://www.phuse.eu/documents//working-groups/deliverables/analyses-displays-associated-with-demographics-disposition-medications-in-phase-2-4-clinical-trials-version-20-02-mar-18-11808.pdf. Accessed September 6, 2018.

PhUSE resouces page. Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents. 2013. Available at: http://www.phusewiki.org/docs/CSS%20White%20Papers%202016/CSS_WhitePaper_CentralTendency_v1.0.pdf. Accessed September 18, 2017.

PhUSE resources 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_OutliersShifts_v1.0.pdf. Accessed September 18, 2017.

PhUSE resouces page. Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Document. 2017. Available at http://www.phuse.eu/documents//working-groups/cs-whitepaper-adverseevents-v10-4442.pdf. Accessed September 18, 2017.

Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, Li S, Shen YK, Gordon KB. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017;76(3):418-431.

Sato, T. On the variance estimator of the Mantel-Haenszel risk difference. *Biometrics*. 1989;45:1323–1324, letter to the editor.

Swinburn P, Lloyd A, Boye KS, Edson-Heredia E, Bowman L, Janssen B. Development of a disease-specific version of the EQ-5D-5L for use in patients suffering from psoriasis: lesions learned from a feasibility study in the UK. *Value Health*. 2013;16(8):1156-1162.

Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller, T, Polgreen P, Bartalesi F, Lipman M, Mariette X, Lortholary O, Weinblatt ME, Saag M, Smolen J. Opportunistic

infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107-2116.

9. Appendices

Appendix 1. Study Visit Definition for Psoriasis Symptoms Scale (PSS)

Psoriasis Symptoms Scale (PSS) is collected as a daily diary, entries will be mapped to study week by the following:

Week[a]	Start Day[b]	End Day
Baseline	Date of First Injection -7	Date of First Injection-1
Week 1	Max (Baseline Assessment Date, Week 2 Assessment Date – 14)	Week 2 Assessment Date - 8
Week 2	Max (Baseline Assessment Date, Week 2 Assessment Date – 7)	Week 2 Assessment Date - 1
Week 3	Max (Week 2 Assessment Date, Week 4 Assessment Date – 14)	Week 4 Assessment Date -8
Week 4	Max (Week 2 Assessment Date, Week 4 Assessment Date – 7)	Week 4 Assessment Date – 1
Week 5	Max (Week 4 Assessment Date, Week 8 Assessment Date – 28)	Week 8 Assessment Date -22
Week 6	Max (Week 4 Assessment Date, Week 8 Assessment Date – 21)	Week 8 Assessment Date -15
Week 7	Max (Week 4 Assessment Date, Week 8 Assessment Date – 14)	Week 8 Assessment Date -8
Week 8	Max (Week 4 Assessment Date, Week 8 Assessment Date – 7)	Week 8 Assessment Date – 1
Week 9	Max (Week 8 Assessment Date, Week 12 Assessment Date – 28)	Week 12 Assessment Date -22
Week 10	Max (Week 8 Assessment Date, Week 12 Assessment Date – 21)	Week 12 Assessment Date -15
Week 11	Max (Week 8 Assessment Date, Week 12 Assessment Date – 14)	Week 12 Assessment Date -8
Week 12	Max (Week 8 Assessment Date, Week 12 Assessment Date – 7)	Week 12 Assessment Date – 1
Week 13	Max (Week 12 Assessment Date, Week 16 Assessment Date – 28)	Week 16 Assessment Date -22
Week 14	Max (Week 12 Assessment Date, Week 16 Assessment Date – 21)	Week 16 Assessment Date -15
Week 15	Max (Week 12 Assessment Date, Week 16 Assessment Date – 14)	Week 16 Assessment Date -8
Week 16	Max (Week 12 Assessment Date, Week 16 Assessment Date – 7)	Week 16 Assessment Date – 1

Abbreviation: Max = maximum.

[a] If End Day < Start Day, do not assign specified visit week.

[b] Assessment Date is the date of the specified visit week's PASI assessment.

If multiple PSS assessments on a single day are present, use the latest assessment. If more than 7 days are available between assessment dates, use only the last 7 days as the range. If the range contains at least 4 nonmissing daily assessments, calculate the average for the nonmissing daily assessments to get the weekly score. If range contains fewer than 4 nonmissing daily assessments, then the weekly result is missing.

Leo Document ID = f4582dcd-ecee-4563-926b-d744d4903f79

Approver: PPD
Approval Date & Time: 28-Mar-2019 19:37:34 GMT
Signature meaning: Approved