I6T-MC-AMAJ Statistical Analysis Plan Version 2

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis (OASIS-2)

NCT03535194

Date: 25-Nov-2019

1. Statistical Analysis Plan: I6T-MC-AMAJ: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis (OASIS-2)

Mirikizumab (LY3074828)

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[Protocol I6T-MC-AMAJ]
[Phase 3]

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 28 October 2018
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 25-Nov-2019 GMT

2. Table of Contents

Section **Page**

1. Statistical Analysis Plan: I6T-MC-AMAJ: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of Mirikizumab to Secukinumab and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis (OASIS-2) 1
2. Table of Contents 2
3. Revision History 8
4. Study Objectives 10
5. Study Design 14
5.1. Summary of Study Design 14
5.1.1. Screening Period 14
5.1.2. Baseline and Double-Blinded Induction Period (Week 0 to Week 16) 14
5.1.3. Blinded Maintenance Period (Week 16 to Week 52 [36 Weeks]) 14
5.1.4. Posttreatment Follow-Up Period (12 Weeks) 15
5.2. Determination of Sample Size 17
5.3. Method of Assignment to Treatment 18
6. A Priori Statistical Methods 19
6.1. General Considerations 19
6.1.1. Patient Populations for Analysis 19
6.1.1.1. Study Time Intervals 21
6.1.1.2. Definition of Study Baseline 22
6.1.2. Analysis Methods 23
6.2. Adjustments for Covariates 24
6.3. Handling of Dropouts or Missing Data 25
6.3.1. Nonresponder Imputation 25
6.3.2. Mixed-effects Model for Repeated Measures 25
6.3.3. Modified Baseline Observation Carried Forward 25
6.3.4. Tipping Point Analysis 26
6.3.5. As Observed 26
6.4. Multicenter Studies 27
6.5. Multiple Comparisons/Multiplicity 27
6.6. Active-Control Studies Intended to Show Non-inferiority 29
6.7. Patient Disposition 29
6.8. Patient Characteristics 30

6.8.1. Demographics and Baseline Characteristics....30
6.8.2. Historical Illnesses and Preexisting Conditions....33
6.9. Treatment Compliance....34
6.10. Concomitant Therapy....34
6.11. Efficacy Analyses....35
6.11.1. Primary Outcome and Methodology....55
6.11.2. Major Secondary Efficacy Analyses....55
6.11.3. Other Secondary Efficacy Analyses....55
6.11.4. Sensitivity Analyses....55
6.12. Health Outcomes/Quality-of-Life Analyses....55
6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods....55
6.14. Safety Analyses....55
6.14.1. Extent of Exposure....56
6.14.2. Adverse Events....57
6.14.2.1. Common Adverse Events....58
6.14.2.2. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events....58
6.14.3. Clinical Laboratory Evaluation....58
6.14.4. Vital Signs and Other Physical Findings....60
6.14.5. Electrocardiograms....60
6.14.6. Immunogenicity....60
6.14.7. Special Safety Topics including Adverse Events of Special Interest....60
6.14.7.1. Hepatic Safety....61
6.14.7.2. Infections, including opportunistic infections and serious infections....61
6.14.7.3. Hypersensitivity....62
6.14.7.4. Injection Site Reactions (ISR)....62
6.14.7.5. Cerebro-Cardiovascular Events....62
6.14.7.6. Malignancies....63
6.14.7.7. Suicidal Ideation/Behavior and Depression....63
6.15. Subgroup Analyses....63
6.15.1. Efficacy Subgroup Analyses....63
6.15.2. Safety Subgroup Analyses....64
6.16. Analysis for Japan Submission....64
6.17. Analysis for Australian Submission....64
6.18. Protocol Deviations....64
6.19. Interim Analyses and Data Monitoring....65
6.20. Annual Report Analyses....66

6.21. Clinical Trial Registry Analyses 66
7. Unblinding Plan 67
8. References 68
9. Appendices 71
App.2.1. Japan Addendum Design and Objectives 73
App.2.2. Japan Addendum General Considerations 74
App.2.3. Japan Addendum Efficacy/Health Outcome Analyses 75
App.2.4. Japan Addendum Safety Analyses 77

Table of Contents

Table **Page**

Table AMAJ.4.1. Protocol-Defined Objectives and Endpoints 10

Table AMAJ.6.1. Patient Populations for Analysis 20

Table AMAJ.6.2. Treatment Groups and Comparisons for Each Study Period and Analysis Population 20

Table AMAJ.6.3. Definition of Study Period Time Intervals 22

Table AMAJ.6.4. Patient Characteristics (and Variables for Subgroup Analysis) 30

Table AMAJ.6.5. Description and Derivation of Efficacy/Health Outcomes Measures and Endpoints 36

Table AMAJ.6.6. Description of Efficacy/Health Outcomes Analyses 50

Table AMAJ.6.7. Summary Tables Related to Adverse Events 58

Table AMAJ.6.8. Summaries/Displays/Analysis for Clinical Laboratory Evaluations 59

Table of Contents

Figure **Page**

Figure AMAJ.5.1. Illustration of study design for Clinical Protocol I6T-MC-AMAJ. 16

Figure AMAJ.6.1. Graphical approach to control type 1 error rate for Study I6T-MC-AMAJ. 28

Table of Contents

Appendix **Page**

Appendix 1. Study Visit Definition for Psoriasis Symptoms Scale (PSS) 72

Appendix 2. Analysis Plan for Japan Addendum 73

3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to any unblinding.

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

- updated the Study Objectives and Study Design figure per Protocol Amendment A and B
- updated Table AMAJ.6.2 the treatment group descriptions and Table AMAJ.6.3 the Study Period definition
- modified the study baseline definition to be more conclusive
- updated the details for common risk difference, categorical mixed-model repeated measures (MMRM), tipping point analysis, and as-observed analysis
- modified multicenter studies to be subgroup analyses
- updated the section of adjustment for covariates
- updated the figure of the graphical approach per Protocol Amendment B
- updated the prior psoriasis therapy and others in the table of patient characteristics and variables for subgroup analysis
- included the adverse events (AEs) occurring prior to the first dose for preexisting conditions
- changed the population for treatment compliance to Induction Safety Population
- updated the reporting details of concomitant therapy
- updated Table AMAJ.6.5 and Table AMAJ.6.6 with additional details, including:
    - changed the description of consistent maintenance to be a stability analysis
    - added the details for cumulative time with 90% improvement in Psoriasis Area and Severity Index from baseline (PASI 90)
    - revised the analysis for the Patient's Global Assessment of Psoriasis, and facial psoriasis
    - revised Short Form 36-item Health Survey (SF-36) domain score analysis with the Responder Definition
    - added analysis to EuroQol 5 Dimensions (EQ-5D) dimension scores
    - added details for 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16) domain derivation
    - updated the time point and added the period for table of description of the analyses
    - added maintenance of PASI 90/PASI 100 response analysis based on responders at Week 16 and Week 24
- updated the interpretation of p-values for safety sections
- added listing of deaths and clarified some AE reporting by preferred term (PT) instead of nested within System Organ Class (SOC)
- updated the details of hypersensitivity analysis
- modified the subgroup analysis

- added the section of analysis for Japan submission and the Appendix of Analysis Plan for the Japan Addendum
- added the section of analysis for Australian submission
- updated the details of early pharmacokinetics (PK) datalock
- updated Appendix 1 to clarify the week/visit mapping
- made other minor typographical corrections and clarifications not affecting content

4. Study Objectives

Table AMAJ.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 6.11 to provided 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 AMAJ.6.1 and Table AMAJ.6.6.
- The endpoints/variables are listed in Table AMAJ.4.1, Table AMAJ.6.5, and Table AMAJ.6.6.
- The handling of intercurrent events is summarized in Section 6.3 and Table AMAJ.6.6.
- Population summary measures are described in Section 6.10 and Table AMAJ.6.6.

Table AMAJ.4.1. Protocol-Defined Objectives and Endpoints

Objectives	Endpoints
Primary[a,b] To assess whether mirikizumab induction dosing is superior to placebo 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 clinically meaningful response and highest levels of clinical response	At Week 16: • Proportion of patients achieving a 75% improvement in PASI (PASI 75) • Proportion of patients achieving a 100% improvement in PASI from baseline (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

Protocol-Defined Objectives and Endpoints

Objectives	Endpoints
Major Secondary[a,b] To assess whether mirikizumab induction dosing is noninferior to secukinumab with respect to high levels of clinical response To assess whether 250-mg mirikizumab Q8W and 125-mg mirikizumab Q8W maintenance dosing is noninferior to secukinumab with respect to high and highest levels of clinical response To assess whether 250-mg mirikizumab maintenance Q8W and 125-mg mirikizumab Q8W dosing is superior to secukinumab 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 PASI 90 At Week 52: • Proportion of patients achieving sPGA (0,1) • Proportion of patients achieving PASI 90 • Proportion of patients achieving PASI 100 At Week 52: • Proportion of patients achieving sPGA (0,1) • Proportion of patients achieving PASI 90 • Proportion of patients achieving PASI 100
Other Secondary[b] To assess whether mirikizumab induction dosing is superior to placebo with respect to an early, clinically meaningful response 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 4: • Proportion of patients achieving PASI 75 At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90 • Change from baseline in PPASI total score in patients with palmoplantar involvement at baseline • Change in PSSI total score in patients with scalp involvement at baseline • Change from baseline in NAPSI total score in patients with fingernail involvement at baseline • Change from baseline on the SF-36 physical component summary (PCS) and mental component summary (MCS) • Change from baseline on PatGA of disease severity** • Change from baseline for the WPAI PSO scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) • Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1

Protocol-Defined Objectives and Endpoints

Objectives	Endpoints
To compare mirikizumab to secukinumab 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 To assess whether 250-mg mirikizumab Q8W and 125-mg mirikizumab Q8W maintenance dosing is noninferior to secukinumab with respect to high levels of clinical response	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90 At Week 24: • Proportion of patients achieving PASI 90 At Week 52: • Proportion of patients achieving an sPGA (0)
To assess efficacy of 250-mg mirikizumab Q8W and 125-mg mirikizumab Q8W as compared to secukinumab with respect to clinical response	At Week 52 and at various time points during the Maintenance Dosing Period: • Proportion of patients achieving PASI 90 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1
Evaluate the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of mirikizumab	• Clearance and volume of distribution of mirikizumab • Relationship between mirikizumab exposure and efficacy (sPGA and PASI)
Exploratory To evaluate the potential development of antimirikizumab 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

Protocol-Defined Objectives and Endpoints

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = Patient's Global Assessment of Psoriasis; PCS = physical component summary; PPASI = Palmoplantar Psoriasis Severity Index; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; SF-36 = Short Form 36-item Health Survey; sPGA = static Physician's Global Assessment; TE-ADA = treatment-emergent antidrug antibody; TEAE = treatment-emergent adverse event; 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.

* This objective is written as it is in protocol amendment (b), but should be updated to "To assess whether 250-mg mirikizumab maintenance Q8W and 125-mg mirikizumab Q8W dosing is superior to secukinumab with respect to high and highest levels of clinical response."

** This endpoint is written as it is in protocol amendment (b), but should be updated to "Proportion of patients achieving PatGA of disease severity of (0,1) with at least a 2-point improvement from baseline in patients with a baseline PatGA ≥2".

5. Study Design

5.1. Summary of Study Design

Study I6T-MC-AMAJ (AMAJ) is a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, multi-period study in adult patients with moderate-to-severe plaque psoriasis. Approximately 1443 patients will be randomized to treatment groups involving different mirikizumab doses and regimens, placebo, or secukinumab. The study is comprised of 2 treatment periods (Induction and Maintenance), which together last for up to 52 weeks, followed by a 12-week Posttreatment Follow-Up Period.

5.1.1. Screening Period

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

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

At Visit 2 (Week 0; baseline), patients who meet the study eligibility criteria will be randomly assigned to their induction and maintenance treatments with stratification based on previous exposure to biologic therapy (yes/no), body weight (<100 kg or ≥100 kg), and geographic region (North America, Europe, or Other). The treatment groups in the Blinded Induction Period are 250-mg mirikizumab or matching placebo (subcutaneous [SC]) administered at Weeks 0, 4, 8, and 12, and 300-mg secukinumab (SC) administered at Weeks 0, 1, 2, 3, 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 Posttreatment Follow-Up Period.

5.1.3. Blinded Maintenance Period (Week 16 to Week 52 [36 Weeks])

Patients who were randomly assigned at baseline to receive mirikizumab in the Blinded Induction Period were also randomly assigned to receive either 250-mg mirikizumab every 8 weeks (Q8W) SC or 125-mg mirikizumab Q8W SC in the Blinded Maintenance Period, with maintenance dosing starting at Week 16 and ending at Week 48. Patients who were randomized to placebo in the Blinded Induction Period will receive 250-mg mirikizumab SC every 4 weeks (Q4W) for Weeks 16 through 32 and 250-mg mirikizumab Q8W thereafter. Patients who were randomized to 300-mg secukinumab SC in the Blinded Induction Period will continue this treatment with Q4W dosing during the Blinded Maintenance Period, starting at Week 16 and ending at Week 48.

Throughout the study, patients will receive placebo, as appropriate, to maintain the study blind across treatment groups.

A discontinuation criterion has been included for patients in any treatment group who remain at or above their baseline static Physician's Global Assessment (sPGA) score at Week 16 (Visit 9) and Week 24 (Visit 11), or remain at or above their baseline Psoriasis Area and Severity Index

(PASI) score at Week 16 (Visit 9) and Week 24 (Visit 11), to ensure patients who have not shown any benefit from study treatment are offered alternative therapies.

At Week 52, patients have 1 of the following options:

- Enter Study I6T-MC-AMAH (AMAH), a long-term extension study in which patients receive 250-mg mirikizumab Q8W SC or 125-mg mirikizumab Q8W SC, OR
- Discontinue study treatment and complete Study AMAJ's 12-week Posttreatment Follow-Up Period.

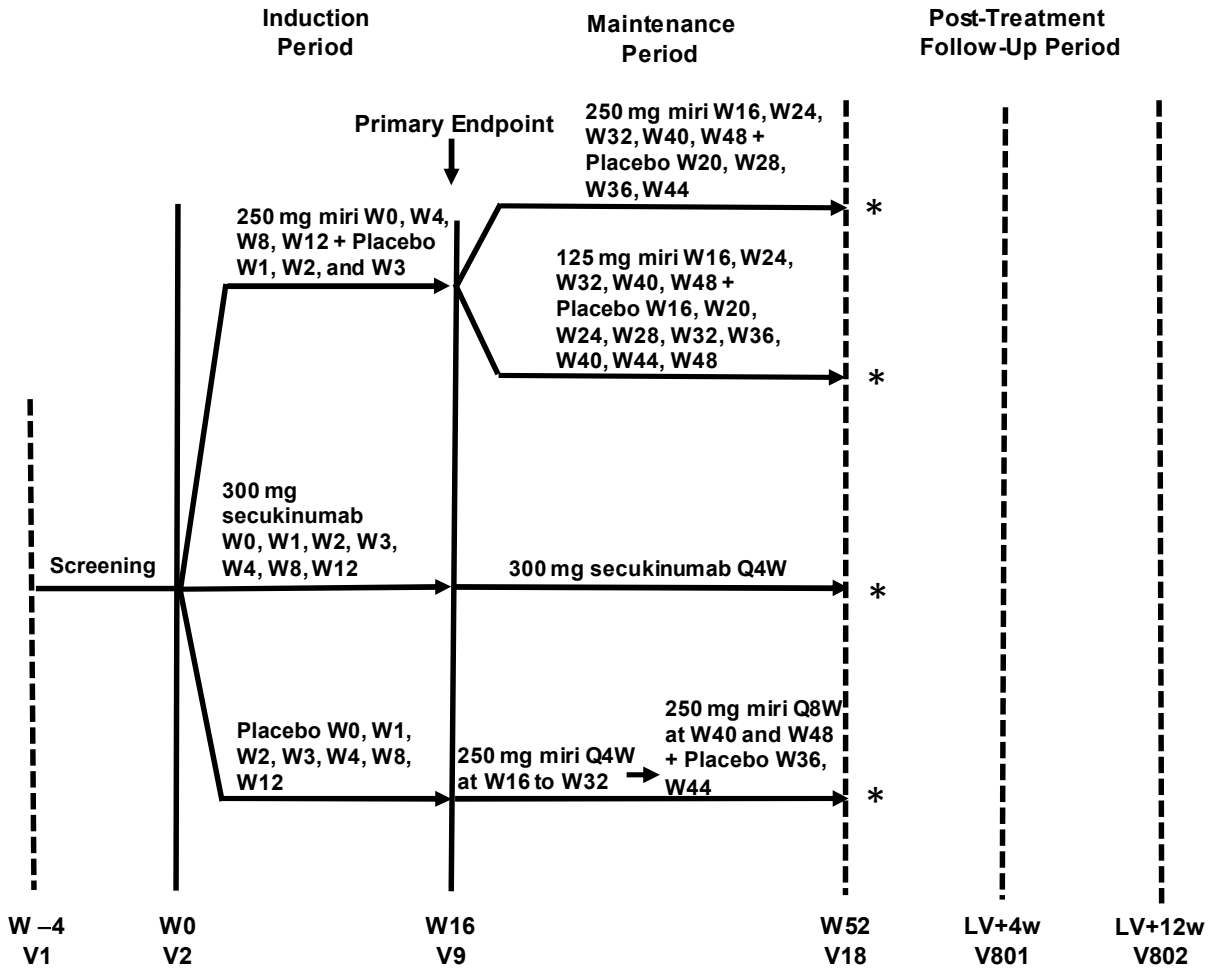
Patients who discontinue early from the study for any reason during this period will stop treatment and continue to the ETV and then the 12-week Posttreatment Follow-Up Period.

5.1.4. Posttreatment Follow-Up Period (12 Weeks)

Patients who do not enroll into Study AMAH or who discontinue early from Study AMAJ will complete the Posttreatment Follow-Up Period (Visit 801 and Visit 802) of Study AMAJ.

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

Figure AMAJ.5.1 illustrates the study design.



Abbreviations: LV = last study visit; miri = mirikizumab; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; V = visit; w = weeks; W = week.
* Option to enter Study I6T-MC-AMAH or to enter the Posttreatment Follow-Up Period.
Note: At Week 0 (V2), patients will be randomized in a 4:4:4:1 ratio to one of the following induction and maintenance period treatments: a) 250-mg miri at Weeks 0, 4, 8, 12 followed by 250-mg miri SC Q8W starting at Week 16; b) 250-mg miri at Weeks 0, 4, 8, 12 followed by 125-mg miri Q8W starting at Week 16; c) 300-mg secukinumab at Weeks 0, 1, 2, 3, 4, followed by 300-mg secukinumab Q4W starting at Week 4; d) placebo at Weeks 0, 4, 8, 12, followed by 250-mg miri Q4W starting at Week 16 through Week 32 followed by Q8W thereafter. Patients will receive placebo to maintain the study blind across treatment groups as shown (patients receiving 125-mg miri will receive 1 placebo injection at weeks they receive miri and 2 placebo injections at other times shown). Dosing is via SC injection for all treatments in all periods.

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

5.2. Determination of Sample Size

This section is based on the original AMAJ Protocol. The section was not changed in Protocol Amendment (b) due to the completion of the enrollment at the time of Amendment (b) approval.

Approximately 1443 patients will be randomized at a 4:4:4:1 ratio in the Blinded Induction Period to receive 250-mg mirikizumab SC at Weeks 0, 4, 8, and 12, then 250-mg mirikizumab SC Q8W, 250-mg mirikizumab SC at Weeks 0, 4, 8, and 12, then 125-mg mirikizumab SC Q8W, 300-mg secukinumab at Weeks 0, 1, 2, 3, and 4, followed by 300-mg secukinumab Q4W, or placebo. 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, Europe, or Other).

There are multiple primary endpoints in this study: the proportion of patients achieving a ≥90% improvement in PASI from baseline (PASI 90) and the proportion of patients with a sPGA (0,1) with at least a 2-point improvement from baseline, comparisons between mirikizumab and placebo (test of superiority), and comparison between mirikizumab and secukinumab (test of non-inferiority). The assumed PASI 90 responses are 70% for the mirikizumab arm, 70% for the secukinumab arm, and 3% for the placebo arm. The assumed sPGA 0 or 1 responses are 70% for the mirikizumab arm, 70% for the secukinumab arm, and 5% for the placebo arm. Both PASI 90 and sPGA (0,1) rates at Week 52 are estimated to be 75% for both mirikizumab dose groups, and 65% for secukinumab group. The assumptions for mirikizumab are based upon the results of the mirikizumab Phase 2 Study I6T-MC-AMAF (Reich et al. 2017b) and review of historical clinical studies in psoriasis (Langley et al. 2014; Gordon et al. 2016; Blauvelt et al. 2017; Papp et al. 2017; Reich et al. 2017a). The assumptions for secukinumab were based upon 2 Phase 3 studies of secukinumab for psoriasis (Langley et al. 2014).

With 888 patients in the mirikizumab group and 111 patients in the placebo group, the estimated power is at least 99% to test superiority of mirikizumab to placebo on PASI 90 at Week 16, and on sPGA (0,1) at Week 16, respectively, at alpha of 0.05 two-sided. With 888 patients in the mirikizumab group and 444 patients in the secukinumab group, the estimated power is at least 90% to test noninferiority of mirikizumab to secukinumab at alpha of 0.025 one-sided with a noninferiority (NI) margin of 10% on PASI 90 at Week 16. Similarly, the estimated power is least 90% to test noninferiority of mirikizumab to secukinumab at alpha of 0.025 one-sided with a NI margin of 10% on sPGA (0,1) at Week 16.

In addition, with 444 patients in the 250-mg mirikizumab Q8W group, 444 patients in 125-mg mirikizumab Q8W group, and 444 patients in the secukinumab group, the study will have an estimated power of 90% to test superiority of 250-mg mirikizumab Q8W compared to secukinumab at alpha of 0.05 two-sided on PASI 90 at Week 52, and sPGA (0,1) at Week 52, respectively, as well as 90% power to test superiority of 125-mg mirikizumab Q8W compared to secukinumab at alpha of 0.05 two-sided on PASI 90 at Week 52, and sPGA (0,1) at Week 52, respectively.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Week 0. Stratified block randomization will be implemented using a computer-generated sequence within an interactive web-response system (IWRS). The 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, Europe, 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 (Lilly). 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 (for example, described in Table AMAJ.4.1 and in Section 4 of AMAJ protocol) are planned to be included in a 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 AMAJ.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 AMAJ.6.2 describes the treatment groups and the comparisons for each study period and the analysis population.

Table AMAJ.6.1. Patient Populations for Analysis

Population	Description
All Entered Patients	All patients who signed informed consent.
Intent-to-Treat (ITT) Population	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 both induction period and combined induction/maintenance periods 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.
All Active Treatment Safety	All randomized patients *who received at least 1 dose of mirikizumab or secukinumab.*
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 referred to as the "The AMAJ Trial Issues Management Plan". These patients will be used to reanalyze the primary endpoints only.
Induction and Maintenance PPS	All randomized patients who do not have IPDPP in the combined induction/maintenance periods. IPDPP are described in a separate document referred to as the "The AMAJ Trial Issues Management Plan." These patients will be used to reanalyze the selected major secondary endpoints of PASI 90 and sPGA (0,1) at Week 52.

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

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

Study Period	Analysis Population	Treatment Groups	Inferential Comparisons
Induction Period	ITT; Induction Safety; Induction PPS	placebo Q4W; 300 secu; 250 miri Q4W	300 secu vs placebo Q4W; 250 miri Q4W vs placebo Q4W; 250 miri Q4W vs 300 secu
Induction and Maintenance Periods*	ITT; Induction and Maintenance PPS	placebo/250 miri; 300 secu; 250 miri Q4W/125 miri Q8W; 250 miri Q4W/250 miri Q8W; Total miri/miri (Note: Total miri represents the combined treatments of 250 miri Q4W/125 miri Q8W and 250 miri Q4W/250 miri Q8W.)	250 miri Q4W/125 miri Q8W vs 300 secu; 250 miri Q4W/250 miri Q8W vs 300 secu (For efficacy/healthoutcome measures, the comparisons will be only conducted from Week 20 to Week 52)
All Active Treatment Periods	All Active Treatments Safety	placebo/250 miri; 300 secu; 250 miri Q4W/125 miri Q8W; 250 miri Q4W/250 miri Q8W; all miri (Note: all miri represents the combined treatments of placebo/250 miri, 250 miri Q4W/125 miri Q8W and 250 miri Q4W/250 miri Q8W.)	250 miri Q4W/125 miri Q8W vs 300 secu; 250 miri Q4W/250 miri Q8W vs 300 secu

Treatment Groups and Comparisons for Each Study Period and Analysis Population

Study Period	Analysis Population	Treatment Groups	Inferential Comparisons
All Active Treatment + Follow-up Periods	All Active Treatment Safety	300 secu + FUP; all miri + FUP (Note: the header with "+ FUP" is used to emphasize that the observations from Follow-up Period are included.)	
All Periods	ITT	For study disposition only: placebo/250 miri; 300 secu; 250 miri Q4W/125 miri Q8W; 250 miri Q4W/250 miri Q8W; Total miri/miri	
	Induction Safety Population	For hepatic plot only: Ever on miri; Never on miri	

Abbreviations: FUP = follow-up; ITT = intent-to-treat; miri = mirikizumab; PPS = per protocol set; Q4W = every 4 weeks; Q8W = every 8 weeks; secu = secukinumab.

* For some analyses based on response status at certain weeks (Week 16 or 24), only maintenance period will be used, and the placebo/250 miri treatment group might not be displayed.

Note: for immunogenicity analysis, 300 secu treatment group will be excluded, thus the comparisons involving 300 secu will not be conducted; also the outputs for the "All Active Treatment Period" and "All Active Treatment + Follow-up Periods" will be combined.

6.1.1.1. Study Time Intervals

Table AMAJ.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:

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

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

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:

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

Table AMAJ.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: All patients who are randomized to the study are considered as entering the Induction Period.	At the first injection following randomization date/time[a]. 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: 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 discontinued or last treatment visit date.
Induction and Maintenance Periods	Use the definition of the start of the Induction Period.	Use the definition of the end of Maintenance Period.
Follow-up Period: 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 as described above, (2) after the end of the Maintenance Period as described above	The last date of the last study visit and study disposition date
All Active Treatment Periods: All patients who are treated with mirikizumab or secukinumab are considered to have entered this period.	For mirikizumab and secukinumab induction treatment groups, use the definition of the start of Induction Period; For placebo/250 miri treatment group, use the definition of the start of Maintenance Period.	The latest of the following dates: (1) the end of the Induction Period, (2) the end of the Maintenance Period
All Periods (Induction + Mainteance + Follow-up Periods)	Induction period start date	The last date of the last study visit and study disposition date

[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.

6.1.1.2. Definition of Study Baseline

For efficacy and health outcomes, study baseline is defined as the last nonmissing assessment (including unscheduled visits) before the first injection, which in most cases will be the measurement 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 randomization date will be used. In cases where baseline measurements are taken on the same day as injection, these measurements will be used as the baseline values for data analysis.

For the Psoriasis Symptoms 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.

6.1.2. 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% two-sided asymptotic (that is, not continuity corrected) confidence intervals (CIs) will be provided.
- The estimated common risk difference along with 95% CIs. The common risk difference 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% two-sided asymptotic (that is, 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 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 secondary analysis, pseudo-likelihood-based MMRM (Categorical MMRM, Agresti 2003) 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 pseudolikelihood with a subject-specific expansion (RSPL) will be used, which is equivalent to the 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 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 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% CI 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 LS means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, p-value, and 95% CI, unless otherwise specified, will also be reported. ANCOVA may also be used as a secondary analysis for 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 analyses 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). Also 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 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, Europe, or Other). 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 6.1.2.

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 AEs, rescue treatment, and loss to follow-up. The missing data methods described below handle intercurrent events in different ways.

6.3.1. Nonresponder Imputation

The nonresponder imputation (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 nonresponders.

Analysis of binary categorical efficacy and health outcome variables will be assessed using an NRI method. Patients will be considered nonresponders 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 without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

6.3.2. Mixed-effects Model for Repeated Measures

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

6.3.3. Modified Baseline Observation Carried Forward

An mBOCF analysis will be performed on continuous efficacy and health outcome endpoints. For patients discontinuing investigational product due to an AE, the baseline observation will be carried forward to the corresponding primary endpoint for evaluation. For patients discontinuing investigational product for any other reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to the corresponding primary endpoint for evaluation. For all patients with sporadically missing observations prior to discontinuation, the last nonmissing 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 AE 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 have received after the event. For other intercurrent events (for example, rescue treatment and discontinuation due to reasons other than an AE) or sporadic missingness, 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. 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 CMH test (Section 6.1.2). 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.

6.3.5. 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 the 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 (postrandomization) 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).

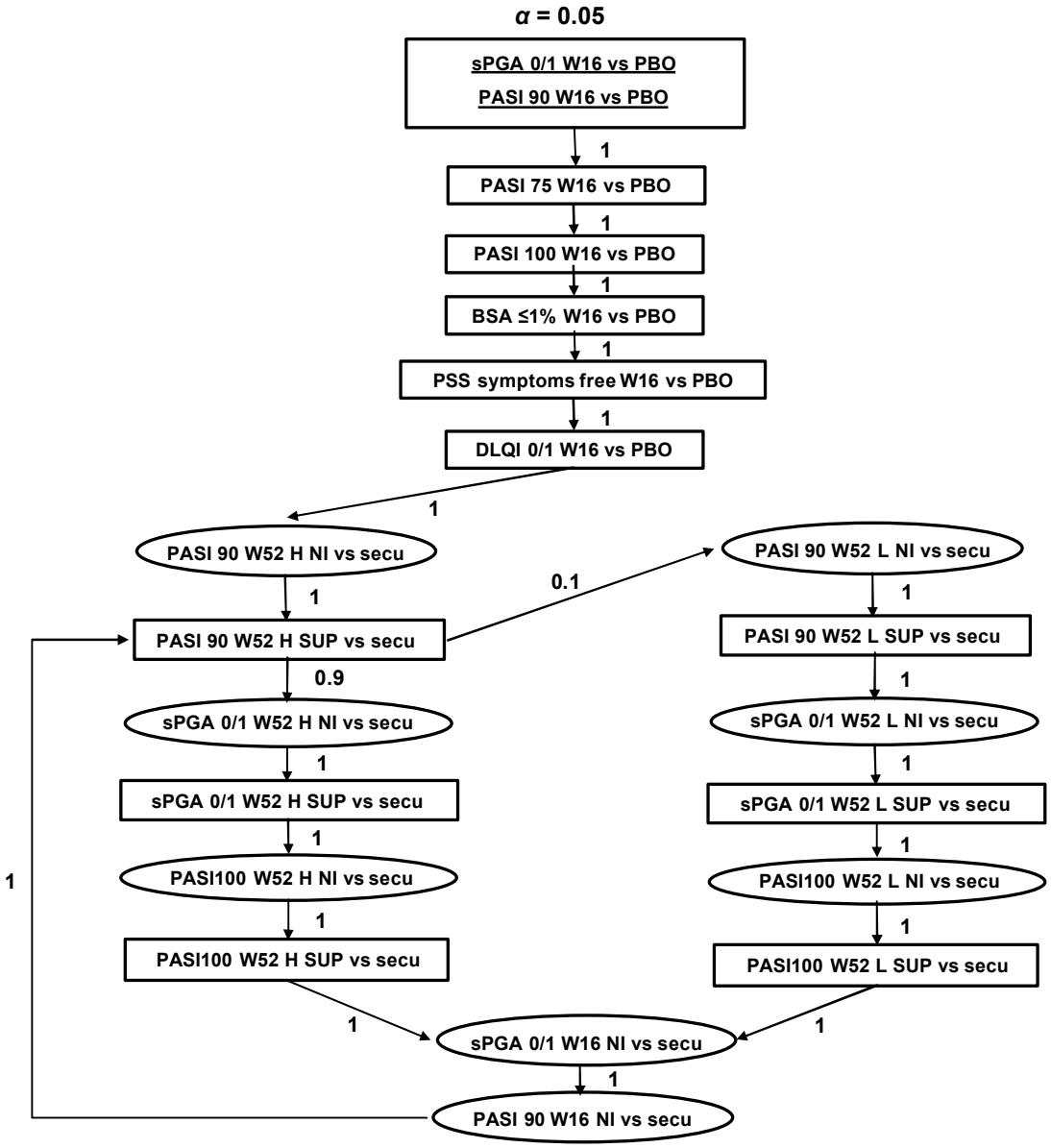
6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites internationally. Typically, a logistic regression with treatment, site, and treatment-by-site may be used to assess the consistence of treatment effect in sites. 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 (Israel, Japan, Korea); North America (Canada, Puerto Rico, United States); Australia (Australia); Central America/South America (Argentina); and Europe (Czech Republic, Germany, France, Hungary, Italy, Poland, Spain, United Kingdom). Subgroup analysis details are provided in Section 6.15.1.

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 (that is, 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. 2011, 2009) will be implemented to control the overall Type I error rate at two-sided alpha of 0.05 and at one-sided alpha of 0.025 for non-inferiority tests, 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. 2011, 2009; 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 AMAJ.6.1 describes the graphical scheme, and all of our alpha will be allocated to the sPGA (0,1) Week16 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; H = mirakizumab high dose in maintenance period (250 mg Q8W); ITT = intent-to-treat; L = mirikizumab low dose in maintenance period (125 mg Q8W); NI = noninferiority tests; PASI = Psoriasis Area and Severity Index; PBO = placebo; PSS = Psoriasis Symptoms Scale; Q8W = every 8 weeks; secu = secukinumab; sPGA = static Physician's Global Assessment; SUP = superiority tests; W16 = Week 16; W52 = Week 52.

Note: Underlined: Primary Endpoints.

Note: PSS Symptoms Free at Week 16 is performed for patients with study baseline PSS symptoms score ≥1 in ITT population; DLQI (0,1) and reduction in DLQI ≥5 at Week 16 is performed for patients with study baseline DLQI ≥5 in ITT population.

Figure AMAJ.6.1. Graphical approach to control type 1 error rate for Study I6T-MC-AMAJ.

6.6. Active-Control Studies Intended to Show Non-inferiority

There is no universally accepted value for what is considered to be a clinically unimportant difference between 2 treatments in sPGA (0,1) or PASI 90 response. Food and Drug Administration (FDA) guidance (2016) states that an appropriate non-inferiority margin should be based on both clinical and statistical grounds.

For active control treatment secukinumab, the treatment difference between secukinumab 300-mg Q4W dosing and placebo on PASI 90 responses at Week 16 in the pivotal Phase 3 studies were around 71.5% and 70% in the FIXTURE and ERASURE studies, respectively (Langley et al. 2014). In these study designs, there were no placebo controls beyond Week 12. As the PASI 90 rates in placebo patients were very low and few fluctuations were observed in the induction phases of these studies, the PASI 90 rates at Week 12 (1.5% and 1.2% in the FIXTURE and ERASURE studies, respectively) were extrapolated to Week 16 to provide estimates of treatment effect with comparisons to placebo at Week 16. The estimated treatment differences for secukinumab 300 mg Q4W (with placebo) were approximately 70% and 69% in the FIXTURE and ERASURE studies. Due to the consistency of treatment effects in pivotal studies of secukinumab, a fixed NI margin is proposed for Study AMAJ, instead of being based on the synthesis method.

The NI margin of 10% on PASI 90 response is considered to be sufficiently small to be a clinically unimportant difference in outcomes between mirikizumab and secukinumab. It represents clinical judgement about the amount of the active control effect that must be retained. Assuming the observed treatment effects for secukinumab and placebo in Study AMAJ is similar to what have been observed in historical studies, for example, 70%, the proposed NI margin of 10% is expected to preserve a substantial fraction (85.7%) of the secukinumab effect.

Similarly, a 10% NI margin will be used for the other primary endpoint sPGA (0,1) and other secondary endpoints with non-inferiority tests comparing mirikizumab and secukinumab. For more details, please refer to Section 10.3.3 in protocol.

The null hypothesis will be rejected if the lower bound of the one-sided 97.5% CI for the difference in proportions of responders on mirikizumab minus secukinumab is greater than the pre-specified NI margin (-10%), meaning mirikizumab will be deemed non-inferior to secukinumab. If the lower bound of the CI exceeds 0 (the corresponding p-value will also be produced), mirikizumab will be deemed superior to secukinumab.

6.7. Patient Disposition

Subject flow will be summarized for the number of patient who: entered, failed screening, were randomized to each treatment, completed induction , and completed the maintenance period. Of the treatment completers, the number who enter Study AMAH, complete the posttreatment follow up, or discontinue the study will be summarized.

More specifically, the following summaries will be produced. The screen failures and reasons for screen failure will be summarized. The *treatment disposition* will be summarized for the intent-to-treat (ITT) population, with patients who entered the Maintenance Period (Table AMAJ.6.3) to be considered to have completed the Induction Period. Summaries will be by treatment group (Table AMAJ.6.2). Summaries will also include reasons for discontinuation from the study tabulated by treatment group. The *study disposition* of all patients who were randomized (that is, ITT population) will be summarized along with the reasons for discontinuation. The completers will be categorized into those completers who entered Study AMAH and those who did not.

All patients who were randomized (that is, in the ITT population) and discontinued from study treatment during any period from the study will be listed, and the timing of discontinuation from 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 the study.

6.8. Patient Characteristics

6.8.1. Demographics and Baseline Characteristics

Patient demographic variables and baseline characteristics will be summarized by dose and overall for the 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 (that is, Age, Sex, Race, Racial subgroup, Ethnicity, Ethnic subgroup, Country, Body, Weight) for the ITT population will be provided.

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

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Week 16	Week 52
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	X
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X	X

Patient Characteristics (and Variables for Subgroup Analysis)

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Week 16	Week 52
Demographic Characteristics				
Geographic Region	No	North America (Canada, Puerto Rico, United States); Europe (Czech Republic, Germany, France, Hungary, Italy, Poland, Spain, United Kingdom); Other (Argentina, Australia, Israel, Japan, Korea)	X	X
	No	By Country	X	X
	No	Asia (Israel, Japan, Korea); North America (Canada, Puerto Rico, United States); Australia (Australia); Central America/South America (Argentina); Europe (Czech Republic, Germany, France, Hungary, Italy, Poland, Spain, United Kingdom)	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/m2), Normal (≥18.5 and <25 kg/m2), Overweight (≥25 and <30 kg/m2), Obese (≥30 and <40 kg/m2), Extreme obese (≥40 kg/m2)	X	X
Alcohol use	No	Never, Current, Former		
Caffeine use	No	Never, Current, Former		
Tobacco use	No	Never, Current, Former	X	X
Prior Psoriasis Therapy				
Prior systemic therapy[d,e]	No	Never used, Ever used	X	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	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	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		
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 only, Topical nonprescription therapy only, Both		
Prior phototherapy	No	Never used, Ever used	X	X
Prior systemic therapy or phototherapy	No	Never used, Ever used	X	X

Patient Characteristics (and Variables for Subgroup Analysis)

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Week 16	Week 52
Prior Psoriasis Therapy				
Prior nonbiologic systemic therapy or phototherapy	No	Never used, Ever used	X	X
Prior biologic inadequate response (among those who had prior biologic therapy)	No	Yes, No	X	X
Prior biologic loss of response (among those who had prior biologic therapy)	No	Yes, No	X	X
Prior biologic intolerance (among those who had prior biologic therapy)	No	Yes, No	X	X
Prior biologic inadequate response, loss of response, or intolerance (among those who had prior biologic therapy)	No	Yes, No	X	X
Prior biologic failure[h] (among those who had prior biologic therapy)	No	Failed, Not failed	X	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	X
Prior failure, contraindication or intolerance to nonbiologic systemic agents or phototherapy	No	Yes, No	X	X
Psoriasis Duration and Age at Onset				
Duration of psoriasis (years) [i]	Yes	<15, ≥15	X	X
Duration of diagnosis (years)[j]	Yes	None		
Age at onset (years)[k]	Yes	<25, ≥25	X	X
Area of Involvement				
Baseline facial involvement	No	Yes, No	X	X
Baseline nail involvement	No	Yes, No	X	X
Baseline scalp involvement	No	Yes, No	X	X
Baseline palmoplantar involvement	No	Palm involvement only, Sole Involvement only, Both, Neither		
		Yes, No	X	X
Baseline psoriatic Arthritis	No	Yes, No	X	X
Baseline Disease Severity				
Baseline PASI score	Yes	<20, ≥20	X	X
		<15, ≥15	X	X
Baseline sPGA score	No	Moderate (3), Severe (4), or Very severe (5)	X	X
Baseline BSA (%)	Yes	<20%, ≥20%	X	X
Baseline PSSI	Yes	None		
Baseline NAPSI	Yes	None		
Baseline PPASI	Yes	None		

Patient Characteristics (and Variables for Subgroup Analysis)

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]	
			Week 16	Week 52
Baseline Disease Severity				
Baseline PSS sign scores	Yes	0, >0 to <1, ≥1		
Baseline PSS symptom score	Yes	0, >0 to <1, ≥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		
Baseline QIDS-SR16 score	Yes	<11, ≥11	X	X
		None (0-5), Mild (6-10), Moderate (11-15), Severe (16-20), Very severe (21-27)		

Abbreviations: BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; IL-17 = interleukin 17; MCS = Mental Component Summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; 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; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; SF-36 = Short Form 36-item Health Survey; sPGA = static Physician's Global Assessment; TNF = tumor necrosis factor; WPAI-PSO = Work Productivity Activity Impairment Questionnaire – Psoriasis.

[a] Subgroup analysis will be used for efficacy endpoints only. See Section 6.15.1 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 date that the patient was randomized.

[c] 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] Nonbiologic 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 6.1.1.1) from the date of psoriasis onset to the date of informed consent.

[j] Length of the interval (see Section 6.1.1.1) 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.

6.8.2. Historical Illnesses and Preexisting Conditions

Historical illness/condition is defined as the condition/event recorded on the Preexisting 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 Preexisting 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 (that is, 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 an Adverse Event eCRF page with the date of worsening as the start date.

The number and percentage of patients with pre-existing conditions will be summarized by treatment group using the MedDRA PT nested within SOC. Also, the number and percentage of patients with historical illnesses will be summarized by treatment using MedDRA PT nested within SOC. Summaries will be performed for the 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 Noninsulin Dependent, Coronary Artery Disease, Stroke, Dyslipidemia, Psoriatic Arthritis, Ulcerative Colitis, Crohn's Disease) by treatment and overall for the ITT Populations.

6.9. Treatment Compliance

Treatment compliance with investigational product will be summarized for patients who have at least one dose (that is, Induction Safety Population) for the Induction Period and for the combined Inducation and Maintenance Periods. Treatment compliance for each subject will be calculated as:

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

- The number of injections prescribed can be derived from the IWRS study drug dispense dataset.
- The total number of injections administered will be derived using the response to the question “Was dose administered?” on the Exposure eCRF page.

A subject will be considered significantly noncompliant if he or 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 will be compared between treatment groups using Fisher’s exact test.

6.10. 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 patient has a new start date.

For the ITT population, prior therapy (reported before randomization) and current concomitant therapy (use during the Induction Period, and combined Induction and Maitenance Periods) will be presented separately in frequency tables. For all summary tables of concomitant medications, preferred names of concomitant medication will be sorted by descending frequency.

The medical monitor for this study will identify the corticosteroids used by the patients from the list of concomitant medication collected during the course of this study. A summary table for the number and percent of patients using corticosteroids during the Induction and combined Induction and Maintenance Periods using the ITT population will be presented by the treatment groups. This will include: (1) topical therapy, (2) topical steroid therapy and (3) systemic corticosteroid therapy. Definition of these 3 classes of interest will be based on compound level safety standards.

6.11. Efficacy Analyses

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

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

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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with 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%	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: $Percent\ improvement\ from\ baseline = 100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$ If a patient has experienced an improvement, this measure will be positive. If a patient has	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	6 = 90% to 100% The various body regions are weighted to reflect their respective proportion of body surface area.		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 Ps; 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 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 for any of Week 16 to each visit up to Week 52. Also missing when patient discontinued study treatment at or before the analysis visit
		Cumulative time with PASI 90 response from Week 16 to Week 52	Area under the curve (AUC) of PASI 90 response over time among PASI 90 responder starting from Week16, 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 from Week 16 to Week 52 Percentages of weeks with PASI 90 response from Week 16 to Week 52	NRI if the observed value is missing
		Cumulative time with PASI 90 response	Area under the curve (AUC) of PASI 90 response over time among PASI90 responder starting from Week 0, using trapezoidal rule (i.e., 100% when patients are PASI 90 responders at the visit and	NRI if the observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		from Week 0 to Week 52	0% when patients are non-PASI 90 responders at the visit) Percentages of scheduled visits with PASI 90 response among all scheduled visits from Week 0 to Week 52 Percentages of weeks with PASI 90 response from Week 0 to Week 52	
		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.
sPGA	sPGA: the physician's global assessment of the patient's psoriasis lesions at a given time point (European Medicines Agency [EMA] 2004). Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	sPGA score	Range from 0-5: 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
		Time to first achieving sPGA (0,1) during Induction	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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		Period		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 eCOA. 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 0-10 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 0-10, are the values of the selected	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 associated 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 score 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 score are missing, the score is missing
		PSS Symptoms Score of 0	Free of itch, pain, stinging, and burning	Missing if PSS Symptoms Score is missing
		PSS Signs Score of 0	Free of redness, scaling, and cracking	Missing if PSS Signs Score is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	numbers indicated by the patient on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0-10 and will be reported as item scores for itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. In addition, a total score ranging from 0 (no psoriasis symptoms) to 80 (worst imaginable psoriasis symptoms) will be reported.	PSS (Signs, Symptoms, items) Score change from baseline	Change from baseline = Observed PSS Score – Baseline PSS Score Here "PSS Score" could refer to the Total, 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 0-72.	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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
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 horizontal and longitudinal lines into quadrants. Each fingernail is given a score for fingernail bed psoriasis (0-4) and fingernail matrix psoriasis (0-4), 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 1 quadrant of nail 2 = present in 2 quadrants of nail 3 = present in 3 quadrants of nail 4 = present in 4 quadrants of nail	NAPSI score change from baseline	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, 0-80), usually indicated as NAPSI score.	For each fingernail, if either bed or matrix score is missing or not done, the score for that finger is missing. If <50% of the finger scores from 10 fingers are missing, the 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 = 0	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	Imputation Approach if with 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 E, I, and D multiplied by a score for the extent of palm and sole area involvement. The range is 0-72. $PPASI = 0.2(E_{rp} + I_{rp} + D_{rp})A_{rp} + 0.2(E_{lp} + I_{lp} + D_{lp})A_{lp} + 0.3(E_{rs} + I_{rs} + D_{rs})A_{rs} + 0.3(E_{ls} + I_{ls} + D_{ls})A_{ls}$ 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
		PPASI 50	At least a 50% improvement in PPASI score from baseline	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		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 0-30 (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 from baseline	Patient is a DLQI (0,1) responder and reduction/decrease of ≥5 points from baseline.	Missing if baseline or the total score is missing
		DLQI total score and domain scores change from baseline	Calculated as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing
		DLQI symptoms and feelings	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been?	If 1 question in a domain is missing, that domain is missing.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
		domain	#2. How embarrassed or self-conscious have you been because of your skin?	
		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.
		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	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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	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 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 nonmissing if patient is unemployed.
SF-36	The SF-36 Version 2 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 0-100, 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).	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 recalibrate 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. This entails exporting the patient data in a CSV or tab-delimited file for import, generation of the SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file for integration into SDTM/ADAM datasets.	Missing data handling offered by SF-36 software will be used. "Maximum Data Recovery" will be selected for Missing Score Estimator in the software.
		SF-36 change from baseline for domain and component	Calculated as: observed SF-36 score – baseline SF-36 score	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	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).	scores		
		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) is a patient-reported, single-item scale on which patients are asked to rank, by selecting a number on a 0-5 NRS, the severity of their psoriasis "today" from 0 (clear), no psoriasis, to 5 (severe).	PatGA (0)	A PatGA assessed as 0	Missing if PatGA 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	The 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.	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 1-5 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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	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 each of the 5 dimensions.	EQ-5D-5L UK population-based index score	Uses the concatenation of the value of each EQ-5D-5L dimension score in the order: item 1; item 2; item 3; item 4; item 5. Derive EQ-5D-5L UK population-based index score according to the link by using the UK algorithm 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 coded as 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 psoriasis patients.	If any of the items is missing or coded as 9, the index score is missing.
		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	TSQM Global Satisfaction	Let "S" be the sum of all nonmissing items 7-9. 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

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	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 Effectiveness	Let "S" be the sum of all nonmissing items 1-3. 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 nonmissing items 4-5. 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.
QIDS-SR16	QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression. A patient is asked to consider each item as it relates to the way they have 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;	QIDS-SR16 Total Score	The QIDS-SR16 total score is the sum of the domain scores below. The total score has a range of 0-27.	The total score will be missing if any domain score is missing.
		Sleep disturbance (initial, middle, and late insomnia or hypersomnia)	The highest score recorded for the 4 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.

Measure	Description	Variable	Derivation/Comment	Imputation Approach if with Missing Components
	(3) decrease/increase in appetite/weight; (4) concentration; (5) self-criticism; (6) suicidal ideation; (7) interest; (8) energy/fatigue; (9) psychomotor agitation/retardation.	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 0-5	If total score is missing, then missing
Facial Psoriasis	Physician-assessed presence or absence of facial psoriasis.	Facial Psoriasis	Response is either Yes or No.	Missing if question is missing

Abbreviations: ADaM = analysis data model; CSV = comma separated values; eCOA = electronic clinical outcomes assessment; EQ-5D = EuroQol 5 Dimensions; EQ-5D-PSO = EuroQol 5 Dimensions – Psoriasis; MCS = Mental Component Score; NRS = Numeric Rating Scale; PCS = Physical Component Score; Q = question; QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology; QoL = quality of life; SDTM = study data tabulation model; SF-36 = Short Form 36-item Health Survey; sPGA = Static Physician Global Assessment; VAS = visual analog scale.

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

Measure	Variable	Analysis Method (Section 6.1.2)	Population (Section 6.1.1)	Time Point and Period
PASI	PASI 90 (Primary and Sensitivity)	CMH analysis with NRI	ITT; Induction PPS	Week 16 and all scheduled visits in Induction Period
			ITT; Induction and Maintenance PPS	Week 52 and all scheduled visits in Induction and Maintenance Periods
		Logistic regression analysis with NRI	ITT	Week 16 and all scheduled visits in Induction Period
		Tipping point analysis	ITT	Week 16
		Categorical MMRM	ITT	Week 16 and all scheduled visits in Induction Period
	PASI 75, PASI 100	CMH analysis with NRI	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	Time to first achieving PASI 100, PASI 90, or PASI 75 (i.e., 3 different analyses)	KM analysis (censoring described in Table AMAJ.6.5)	ITT	All scheduled visits in Induction Period
	Maintenance of PASI 90 response from Week 16 to Week 52	CMH analysis with NRI	ITT - Patients who are PASI 90 Responders at Week 16	Week 52 and all scheduled visits in Maintenance Period
	Maintenance of PASI 90 response from Week 24 to Week 52	CMH analysis with NRI	ITT - Patients who are PASI 90 Responders at Week 24	Week 52 and all scheduled visits in Maintenance Period
	Maintenance of PASI 100 response from Week 16 to Week 52	CMH analysis with NRI	ITT - Patients who are PASI 100 Responders at Week 16	Week 52 and all scheduled visits in Maintenance Period
	Maintenance of PASI 100 response from Week 24 to Week 52	CMH analysis with NRI	ITT - Patients who are PASI 100 Responders at Week 24	Week 52 and all scheduled visits in Maintenance Period
	Stability of PASI 90 up to Week 52 from Week 16	CMH analysis with NRI	ITT	All scheduled visits in Maintenance Period
			ITT - Patients who are PASI 90 Responders at Week 16	All scheduled visits in Maintenance Period
	Stability of PASI 100 up to Week 52 from Week 16	CMH analysis with NRI	ITT	All scheduled visits in Maintenance Period
			ITT - Patients who are PASI 100 Responders at Week 16	All scheduled visits in Maintenance Period

Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.2)	Population (Section 6.1.1)	Time Point and Period
PASI	Cumulative time with PASI 90 response from Week 16 to Week 52: AUCs of PASI 90 response over time; Percentages of scheduled visits with PASI 90 response; Percentages of weeks with PASI 90 response	ANCOVA with factors: treatment, PASI baseline value, biologic therapy, body weight and geographic region	ITT - Patients who are PASI 90 Responders at Week 16	All scheduled visits in Maintenance Period
	Cumulative time with PASI 90 response from Week 0 to Week 52: AUCs of PASI 90 response over time; Percentages of scheduled visits with PASI 90 response; Percentages of weeks with PASI 90 response	ANCOVA with factors: treatment, PASI baseline value, biologic therapy, body weight and geographic region	ITT	All scheduled visits in Induction and Maintenance Periods
	PASI ≤5; PASI ≤3; PASI ≤2; PASI ≤1	CMH analysis with NRI	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	PASI change from baseline	MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	Percentage improvement from baseline	MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
sPGA	sPGA (0,1) (Primary and Sensitivity)	CMH analysis with NRI	ITT; Induction PPS	Week 16 and all scheduled visits in Induction Period
			ITT; Induction and Maintenance PPS	Week 52 and all scheduled visits in Induction and Maintenance Periods
		Logistic regression analysis with NRI	ITT	Week 16 and all scheduled visits in Induction Period
		Categorical MMRM	ITT	Week 16 and all scheduled visits in Induction Period

Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.2)	Population (Section 6.1.1)	Time Point and Period
sPGA		Tipping point analysis	ITT	Week 16
	sPGA (0)	CMH analysis with NRI	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	Time to first achieving sPGA (0,1) or sPGA (0) (i.e., 2 different analyses)	KM product limit curve (censoring described in Table AMAJ.6.5)	ITT	All scheduled visits in Induction Period
BSA	Proportion of patients with ≤1% of BSA with psoriasis involvement	CMH analysis with NRI	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	BSA change from baseline	MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
PSS	PSS Symptoms Score of 0; PSS Signs Score of 0	CMH analysis with NRI	ITT - Patients with Baseline PSS Symptoms Score ≥1 and PSS Signs Score ≥1, respectively	All scheduled weeks in Induction Period; All scheduled weeks/visits in Induction and Maintenance Periods
	Change from baseline for PSS Symptoms Score, Signs Score, and Item Scores	MMRM; ANCOVA with mBOCF	ITT	All scheduled weeks in Induction Period; All scheduled weeks/visits in Induction and Maintenance Periods
PSSI	PSSI change from baseline	MMRM; ANCOVA with mBOCF	ITT - Patients with Scalp Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	PSSI score = 0	CMH analysis with NRI	ITT - Patients with Scalp Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
PPASI	PPASI change from baseline	MMRM; ANCOVA with mBOCF	ITT - Patients with Palmoplanter Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	PPASI 50; PPASI 75; PPASI 100;	CMH analysis with NRI	ITT - Patients with Palmoplanter Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
NAPSI	NAPSI change from baseline	MMRM; ANCOVA with mBOCF	ITT - Patients with Nail Psoriasis Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods

Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.2)	Population (Section 6.1.1)	Time Point and Period
NAPSI	NAPSI score = 0	CMH analysis with NRI	ITT - Patients with Nail Psoriasis Involvement at Baseline	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
DLQI	DLQI (0,1) and ≥5-point reduction from baseline	CMH analysis with NRI	ITT - Patients with Baseline DLQI ≥5	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	DLQI (0,1)	CMH analysis with NRI	ITT - Patients with Baseline DLQI >1	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	DLQI total score ≥5-point reduction from baseline	CMH analysis with NRI	ITT - Patients with Baseline DLQI ≥5	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	DLQI total score and domain scores change from baseline	MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
SF-36	SF-36 change from baseline for PCS and MCS Component Scores and Domain Scores	ANCOVA with mBOCF	ITT	Last visit in Induction Period
		MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction and Maintenance Periods
	SF-36 PCS Responder Definition; SF-36 MCS Responder Definition; SF-36 Domain score Responder Definition;	CMH analysis with NRI	ITT	Last visit in Induction Period; All scheduled visits in Induction and Maintenance Periods
PatGA	PatGA(0)	CMH analysis with NRI	ITT - Patients with Baseline PatGA >0	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	PatGA (0,1) and ≥2-point improvement from baseline	CMH analysis with NRI	ITT - Patients with Baseline PatGA ≥2	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
WPAI-PSO	Change from baseline in WPAI-PSO Scores (Absenteeism, Presenteeism, Work Productivity, Activity Impairment)	ANCOVA with mBOCF	ITT - Patients with Baseline Employment Status of Yes	Last visit in Induction Period
		MMRM; ANCOVA with mBOCF	ITT - Patients with Baseline Employment Status of Yes	All scheduled visits in Induction and Maintenance Periods

Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Section 6.1.2)	Population (Section 6.1.1)	Time Point and Period
TSQM	Mean Effectiveness, Convenience, and Global Satisfaction	ANCOVA with mBOCF	ITT	Last visit in Induction Period
		MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction and Maintenance Periods
EQ-5D-5L + Bolt On	Change from baseline of EQ-5D VAS and Index scores	MMRM; ANCOVA with mBOCF	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
	EQ-5D Dimension Scores with no problems	CMH analysis with NRI	ITT	All scheduled visits in Induction Period; All scheduled visits in Induction and Maintenance Periods
QIDS-SR16	QIDS-SR16 Response; QIDS-SR16 Remission	CMH analysis with NRI	ITT - Patients with Baseline Value ≥11	Last visit in Induction Period; All scheduled visits in Induction and Maintenance Periods
Facial Psoriasis	Facial Psoriasis	Summary statistics; Shift table	ITT	Last visit in Induction Period; All scheduled visits in Induction and Maintenance Periods
	Absence of Facial Psoriasis	CMH analysis with NRI	ITT - Patients with Baseline Facial Psoriasis	Last visit in Induction Period; All scheduled visits in Induction and Maintenance Periods

Abbreviations: AUC = area under the curve; ANCOVA = analysis of covariance; BSA = body surface area; CMH = Cochran-Mantel-Haenszel; DLQI = Global Assessment Dermatology Life Quality Index; E5-5D = EuroQoL 5 Dimensions; EQ-5D-5L = EuroQoL–5 Dimensions–5 Level; ITT = intent-to-treat; KM = Kaplan-Meier; mBOCF = modified baseline observation carried forward; MCS = Mental Component Score; MMRM = mixed model repeating measures; NAPSI = Nail Psoriasis Severity Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; 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 = a self-administered, 16-item instrument to assess symptoms of depression; SF-36 = a 36-item, patient-completed measure designed to assess health; sPGA = Static Physician Global Assessment; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI-PSO = Work Productivity and Activity Impairment - Psoriasis.

6.11.1. Primary Outcome and Methodology

Primary outcome PASI 90 and sPGA (0,1) and their analysis are described in Table AMAJ.6.5 and Table AMAJ.6.6.

6.11.2. Major Secondary Efficacy Analyses

Major secondary outcomes and their analyses are described in Table AMAJ.6.5 and Table AMAJ.6.6.

6.11.3. Other Secondary Efficacy Analyses

Other secondary outcomes and their analyses are described in Table AMAJ.6.5 and Table AMAJ.6.6.

6.11.4. Sensitivity Analyses

Sensitivity analyses for both primary and secondary endpoints are described in Table AMAJ.6.5 and Table AMAJ.6.6.

6.12. Health Outcomes/Quality-of-Life Analyses

Analyses of PSS, Global Assessment Dermatology Life Quality Index (DLQI), Patients Global Assessment of Psoriasis (PatGA), Work Productivity and Activity Impairment-Psoriasis (WPAI-PSO), TSQM, EQ-5D-5L + Bolt on, QIDS-SR16 and SF-36 health outcomesare described in Table AMAJ.6.5 and Table AMAJ.6.6.

6.13. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

6.14. Safety Analyses

The planned analyses of safety data will be performed with an intent to maintain consistency with compound level standard safety analyses. These standards are based on internal standards which were informed by Clinical Data Interchange Standards Consortium (CDISC) standards, regulatory guidance (for example, FDA Clinical Review Template), and cross-industry standardization efforts (for example, 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]).

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

- Induction Safety Population
- All Active Treatment Safety Population

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

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 or secukinumab as the denominator.

Treatment differences in mean change for continuous measurements will be assessed using an 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 LS mean 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.

6.14.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for each of the 2 safety analysis populations (that is, Induction Safety and All Active Treatment 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 6.1.1.1) with start and end dates described in Table AMAJ.6.3. The following periods will be used for calculations:

- For the Induction Safety Population, the Induction Period Interval will be used.
- For the All Active Treatment Safety Population, 1) for patients randomized to mirikizumab and secukinumab, the Induction and Maintenance Period Interval will be used; 2) for patients randomized to placebo and entering the Maintenance Period, the Maintenance Period Interval will be used.

Total patient-years (PY) of exposure will be reported for both safety analysis populations by treatment group (see Table AMAJ.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, ≥48 weeks
- >0 to <4 weeks, ≥4 weeks to <8 weeks, ≥8 weeks to <12 weeks, ≥12 weeks to <16 weeks, …, ≥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.

6.14.2. 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 posttreatment. 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 AMAJ.6.7 will be presented for the 2 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. For document writing purposes, tests with 2-sided p-values less than 0.05 will be referred to as "having strong evidence for a treatment difference", unless otherwise noted. However, p-values should not be over interpreted for these safety analyses. Except for prespecified hypotheses, they correspond to data-driven hypotheses and hence are only useful as a flagging mechanism.

For the 2 safety populations, the baseline period and postbaseline will be defined as follows:

- *Induction Safety Population*: The baseline period is the Screening Period. The postbaseline period will be the Induction Period.
- *All Active Treatment Safety Population*: The baseline period for patients randomized to mirikizumab and secukinumab during induction is the Screening Period. For patients randomized to placebo, the baseline events are those events which are ongoing at the time of the first injection with mirikizumab (that is, the baseline period is a moment in time). Two different postbaseline periods will be used:
  - For "all miri" and "all secu", the All Active Treatment Periods will be used.
  - For "all miri + follow-up" and "all secu + follow-up", the All Active Treatment and Follow-Up Periods will be used.

Table AMAJ.6.7. Summary Tables Related to Adverse Events

Analysis	Population
Overview of AEs	I, A
Summary of TEAE PTs by decreasing frequency	I, A
Summary of TEAE PTs occurring in ≥1% of patients by decreasing frequency	I, A
Summary of TEAE PTs by decreasing frequency within SOC	I, A
Summary of TEAE PTs by maximum severity by decreasing frequency	I, A
Summary of SAE PTs by decreasing frequency	I, A
Summary of AEs leading to treatment discontinuation	I, A
Listing of SAEs	ITT
Listing of Deaths	All Entered Patients

Abbreviations: A = All Active Treatment Safety; AE = adverse event; I = Induction Safety; ITT = Intent-to-Treat; PT = preferred term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

6.14.2.1. Common Adverse Events

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

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

The number and percentage of patients reported with an SAE during the treatment period will be summarized by treatment using MedDRA PT. Events will be ordered by decreasing frequency in the all treatment group. This analysis will be conducted for the 2 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. Events will be ordered by decreasing frequency in the all treatment groups. This analysis will be conducted for the 2 safety populations.

6.14.3. 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 AMAJ.6.8.

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

Analysis	Population
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 box plot along with a p-value using the ANCOVA model described in Section 6.14.	I, A[a]
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 lab values (i.e., patients shifting from normal/high minimum baseline value to a low minimum postbaseline value)	I, A
Scatter plot of maximum (minimum) postbaseline value vs maximum (minimum) baseline value	I, A
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, A

Abbreviations: A = All Active Treatment Safety; ANCOVA = analysis of covariance; I = Induction Safety.

[a] Excluding placebo/250 miri treatment group for all active treatment safety population.

For these displays, the postbaseline periods will be identical to those described in Section 6.14.2. Postbaseline measurement for continuous analysis (for example, boxplots) will include *only* scheduled measurements, while postbaseline categorical analysis (for example, 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 nonmissing measurement recorded during the Screening Period.
  - For analyses of categorical measurements: all scheduled or unscheduled nonmissing measurements recorded during the Screening Period.
- *All Active Treatment Safety Population:*
  - For analyses of continuous measurements: (1) the last scheduled or unscheduled nonmissing measurement recorded during the Screening Period for the patients randomized to mirikizumab and secukinumab, (2) the last scheduled or unscheduled nonmissing measurement recorded before first miri treatment for patients randomized to placebo.
  - For analyses of categorical measurements: (1) all scheduled or unscheduled nonmissing measurements recorded during the Screening Period for the patients randomized to mirikizumab and secukinumab, (2) the last scheduled or unscheduled nonmissing measurement recorded before first miri treatment for patients randomized to placebo.

For any lab 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 lab was pre-

versus postbaseline. If time for the lab is missing, it will be assumed to be in the baseline period (that is, we assume the protocol defined order of procedures was followed). Following the compound level safety standards, for some labs a safety concern may exist for only high (or only low) values. For these labs, displays with only maximum (or minimum) values will be used and shift tables will be presented accordingly.

6.14.4. 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 6.14.4). For vital signs, the low and high limits are based on a combination of a specified value and a change or percentage change as defined in the compound level safety standards. In this case, the PhUSE white paper recommends providing scatter plots and shifts to low/high. Boxplots will also be presented.

6.14.5. Electrocardiograms

Complete electrocardiogram (ECG) data will not be part of the clinical database. 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 as an AE via eCRF. Aside from standard AE summary tables no additional analysis of ECG data will be performed.

6.14.6. Immunogenicity

An individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample antidrug antibodies (ADA) assay result and potentially a sample neutralizing antidrug antibodies (NAb) assay result. A patient has treatment-emergent antidrug antibodies (TE-ADA) when ADAs are induced or boosted by exposure to study drug; that is, when at least 1 postbaseline ADA sample has a 4-fold increase in titer compared to baseline (if ADAs were present at baseline) or has a titer 2-fold greater than the minimum required dilution of 1:10 (if no ADAs 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 the 2 safety populations, where the postbaseline period for reporting is the same as described for AEs in Section 6.14.2. The subgroup analysis of efficacy by TE-ADA status (positive, negative) is described in the Section 6.15. 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.

6.14.7. 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 version of MedDRA, 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 the 2 safety populations during their associated study periods using the baseline and postbaseline definitions described in Sections 6.14.2 and 6.14.3.

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.

6.14.7.1. Hepatic Safety

Hepatic labs include alanine aminotransferase (ALT) and aspartate transaminase (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 TBL (Induction Safety Population for All Periods: ever on miri and never on miri).
- A listing of the information collected on the Hepatic-Safety eCRF.

6.14.7.2. 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 OIs.

Analyses will include:

- treatment-emergent infections by PT
- serious infections by PT
- OI: treatment-emergent OI by narrow terms and broad terms separately

6.14.7.3. 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 (that is, occurring within 24 hours) and non-immediate (that is, 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 (that is, any narrow term from any one of the SMQs, or anaphylaxis algorithm); (2) narrow search (that is, any narrow term) by SMQ; (3) broad search (that is, 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 nonimmediate hypersensitivity: (1) combined narrow search (that is, any narrow term from any one of the SMQs); (2) narrow search (that is, any narrow term) by SMQ; and (3) broad search (that is, any narrow or broad term) by SMQ

6.14.7.4. Injection Site Reactions (ISR)

Injection site reactions (ISRs) are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related ISRs will be through the unsolicited reporting of ISR TEAEs and through the use of an Injection Site Reaction Follow-up Form completed by the investigator for each ISR reported.

Injection site reactions will be defined using the MedDRA High Level Term (HLT) of Injection Site Reaction, excluding certain PTs (for example, those PTs related to injections into a joint).

Analyses will include:

- TE ISRs by PT.
- The additional data collected on the ISR follow-up form will be summarized in 2 distinct ways: at the patient level and at the event level. A by-patient listing of these data will be provided.

6.14.7.5. 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, Cerebrovascular and Peripheral Vascular Events. As detailed in the compound level safety standards, the categories are further categorized into subcategories.

Analyses will include:

- TE 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.

6.14.7.6. 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:

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

6.14.7.7. 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 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).

6.15. Subgroup Analyses

6.15.1. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoints of Week 16 PASI 90 and sPGA (0,1) proportion in the ITT Population. Also, subgroup analysis for the Week 52 PASI 90 and sPGA (0,1) proportion in the ITT population will be performed. The subgroups to be analyzed are listed in Table AMAJ.6.4 along with the demographic characteristics. Some additional subgroup analyses may be performed to meet regulatory requirements in specific countries. Additional subgroup analyses, which are not based on baseline/demographic characteristics in Table AMAJ.6.4 are:

- concomitant topical steroid product use: yes, no.
- concomitant systemic corticosteroid use: yes, no
- treatment-emergent antimirikizumab antibody status: positive, negative

The analysis of additional subgroups will not require an amendment to the SAP. Missing outcome data will be imputed using NRI. Within each subgroup category the proportion of responders by treatment, treatment differences and 95% CIs will be displayed. Also, p-values using Fisher's exact test for treatment comparison will be provided. If the number of patients in any subgroup category is <10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing). Forest plots will be generated to display the odds ratios and 95% CIs for the efficacy subgroup analyses.

A logistic regression model with treatment, subgroup, and the interaction of subgroup by treatment will be used. The subgroup-by-treatment interaction will be tested using the Firth correction (Firth 1993) at the significance level of 0.10.

6.15.2. 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.

6.16. 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.

Protocol Addendum I6T-MC-AMAJ (1.1) is performed in Japan to enable the inclusion of patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) to fufill the needs for Japan submission. Appendix 2 provides the details of the Analysis Plan for the Japan Addendum.

6.17. Analysis for Australian Submission

In addition to the analysis already specified, a subset of planned efficacy analyses 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 ITT Population. The sPGA (0,1), sPGA (0), PASI 75, PASI 90 and PASI 100 using the PBAC population will be analyzed for Induction Period, and combined Induction and Maintenance Periods.

6.18. 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.

The major protocol deviations, which are the subset of the important protocol deviations, are the protocol deviations that might have impact on the efficacy and/or safety results. The impact of

major protocol deviations on the efficacy results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population, both by including and excluding the data potentially affected by major protocol deviations.

A separate document known as the "The AMAJ Trial Issues Management Plan" describes the categories and subcategories of important protocol deviations, whether or not these deviations are major protocol violations, 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 ITT population in the Induction Period and the combined Induction and Maintenance Periods.

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

6.19. Interim Analyses and Data Monitoring

Data Monitoring Committee: One DMC consisting of members external to Lilly will be established for interim safety monitoring across Studies I6T-MC-AMAK, AMAJ, and 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 52 Database lock (DBL): An unblinded analysis will be performed after all patients have completed the Week 52 Visit or discontinued study treatment. This DBL will include all data collected by the cut-off date including follow-up data from patients that have begun the Posttreatment Follow-Up Period. This is the final analysis for the efficacy endpoints up to Week 52. However, the study may be ongoing for the Posttreatment Follow-Up Period at the time of this DBL.

Final DBL: A final DBL will occur after the Posttreatment Follow-Up Period is completed.

Pharmacokinetics Analysis: In addition, a limited number of preidentified internal Lilly personnel that are not in contact with clinical sites may gain access to unblinded data including PK, as specified in the unblinding plan, after all patients have completed Week 40 visit or discontinued study treatment, in order to initiate the population PK model development processes. The unblinded data will be restricted and will NOT be shared with anyone outside this preidentified group until after the Week 52 DBL. Unblinding details will be provided in the unblinding plan.

6.20. 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.

6.21. 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 Serious Adverse Events (SAEs) and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- 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.

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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[c] - 7	Date of First Injection-1
Week 1	Max(Date of First Injection, 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

[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 the PASI assessment date is missing, the first date from the following order will be selected: (1) date of dosing if injection was given, (2) office visit date if available, or (3) schedule date of visit from the protocol for that visit.

[c] If date of first injection is missing, the randomization date will be used.

If multiple PSS assessments on a single day are present, use the latest assessment. If more than 7 days is 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.

Appendix 2. Analysis Plan for Japan Addendum

App.2.1. Japan Addendum Design and Objectives

The main protocol for Study I6T-MC-AMAJ (AMAJ) enrolls patients with plaque psoriasis (Cohort 1). In parallel, the AMAJ(1) addendum will enroll Japanese patients who are diagnosed as generalized pustular psoriasis (GPP) by the Japanese Dermatological Association or erythrodermic psoriasis (EP) who have ≥80% body surface area (BSA) involvement (with inflammatory erythema) (Cohort 2). Approximately 8 patients with GPP and 8 patients with EP will be enrolled in Cohort 2 in Japan. During the Induction Period, GPP and EP patients will receive 250-mg mirikizumab subcutaneously (SC) at Weeks 0, 4, 8, and 12. During the Maintenance Period, starting at Week 16, GPP and EP patients will receive 250-mg mirikizumab every 8 weeks (Q8W) SC for up to a total of 52 weeks. Placebo control is not required for the GPP and EP patient arms because placebo-controlled studies are not ethical for patients with these severe conditions. The enrollment period of Cohort 2 will begin in parallel with the enrollment period of Cohort 1, but Cohort 2 enrollment may continue for a longer period of time if necessary to achieve the numbers planned for Cohort 2.

Eight patients with GPP and 8 patients with EP will be enrolled in Cohort 2 in Japan. The number of patients with GPP and EP is based on the population size of these patients being very small in Japan (Umezawa et al. 2003, Rosenbach et al. 2010).

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

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

Exploratory To assess the efficacy of mirikizumab in patients with GPP	**GPP ONLY** Time course of response to treatment as measured by the following measures: • global improvement score • assessment of dermal symptoms for GPP* • change from baseline in PASI • change from baseline in DLQI total score At Week 16 and Week 52: • change from baseline in global improvement score** • change from baseline in assessment of dermal symptoms for GPP • change from baseline in PASI • change from baseline in DLQI total score
To assess the efficacy of mirikizumab in patients with EP	**EP ONLY** Time course of response to treatment as measured by the following measures: • global improvement score • change from baseline in PASI • change from baseline in DLQI total score At Week 16 and Week 52: • global improvement score • change from baseline in PASI • change from baseline in DLQI total score

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

* This endpoint is written as it is in Japan Addenda (1.1), but should be updated to "change from baseline in assessment of dermal symptoms for GPP".

** This endpoint is written as it is in Japan Addenda (1.1), but should be updated to "global improvement score".

App.2.2. Japan Addendum General Considerations

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

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

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

The Japan Addendum Safety Population – Patients with GPP or EP is defined as all GPP and EP patients who enrolled in the Japan addendum and received at least 1 dose of study treatment. Safety analyses for the combined Induction and Maintenance Periods (which are similar to the All Active Treatment Periods for the 250-mg mirikizumab Q4W/250-mg mirikizumab Q8W in the main SAP) will be conducted on this population. Generalized pustular psoriasis and EP patients will be reported separately.

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

Due to small sample size in the Japan Addendum, no formal inferencial statistics will be performed. Data will be summarized for GPP and EP patients separately. The methods of summary are the same as in the main SAP

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

- patient disposition including treatment disposition and study disposition
- patient demographics and other baseline characteristics
    - Add baseline GPP dermal symptom total score
- preexisting conditions
- prespecified medical history
- previous psoriasis therapy and the corresponding reason for discontinuation
- prior medications and concomitant medications
- study treatment exposure
- listing of randomization/treatment assignment
- important protocol deviations
- treatment compliance

App.2.3. Japan Addendum Efficacy/Health Outcome Analyses

Table AMAJ.App.3 includes the description and derivation of the additional efficacy measures and endpoints that are collected in the Japan Addendum

Table AMAJ.App.4 provides the detailed analyses for efficacy/health outcomes analyses in the Japan Addendum.

Table AMAJ.App.3. Description and Derivation of Additional Efficacy/Health Outcomes Measures and Endpoints for Japan Addendum

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

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

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

Table AMAJ.App.4. Description of Efficacy/Health Outcomes Analyses for Japan Addendum

Measure	Variable	Analysis Method	Population	Time Point and Period
Global Improvement Score	Global improvement score	Descriptive statistics for each grade based on observed	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits in Induction and Maintenance Periods
GPP dermal symptom total score	GPP dermal symptom total score change from baseline	Descriptive statistics based on observed and mBOCF	Japan Addendum Intent-to-Treat Population – Patients with GPP	All scheduled visits in Induction and Maintenance Periods
PASI	PASI change from baseline	Descriptive statistics based on observed and mBOCF	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits in Induction and Maintenance Periods
DLQI	DLQI total score change from baseline	Descriptive statistics based on observed and mBOCF	Japan Addendum Intent-to-Treat Population – Patients with GPP or EP	All scheduled visits in Induction and Maintenance Periods

Abbreviations: DLQI = Dermatology Life Quality Index; EP = erythrodermic psoriasis; GPP = generalized pustular psoriasis; mBOCF = modified baseline observation carried forward; PASI = Psoriasis Area and Severity Index.

App.2.4. Japan Addendum Safety Analyses

The following safety summaries will be provided for the Japan Addendum Safety Population – Patients with GPP or EP, for the Induction and Maintenance Periods:

- overview of adverse events (AEs)
- treatment-emergent adverse event (TEAE) by Preferred Terms (PTs)
- TEAE by PTs within System Organ Class
- TEAE maximum severity by PTs
- serious adverse event (SAE) by PTs
- AEs leading to treatment discontinuation
- listings of SAEs
- laboratory tests: box plot of change from baseline by visit
- vital signs: box plot of change from baseline by visit
- immunogenicity: incidence of antidrug antibodies

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Leo Document ID = c15f678f-bc2f-477e-97e6-dac29bfb1635

Approver: PPD

Approval Date & Time: 25-Nov-2019 17:34:55 GMT

Signature meaning: Approved