To assess whether mirikizumab induction dosing is superior to placebo with respect to patient-reported outcomes	At Week 16: • Proportion of patients with a PSS symptoms score of 0 (free of itch, pain, stinging, and burning) in those with a PSS symptoms score ≥1 at baseline • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5
To assess whether mirikizumab induction dosing is noninferior 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
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	At Week 52: • Proportion of patients achieving sPGA (0,1) • Proportion of patients achieving PASI 90 • Proportion of patients achieving PASI 100
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 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	At Week 4: • Proportion of patients achieving PASI 75
To compare mirikizumab to placebo with respect to clinical response and time to clinical response during the induction dosing period, and with respect to patient-reported outcomes during the induction dosing period	At Week 16 and various time points over the first 16 weeks of dosing: • Proportion of patients achieving PASI 90 • Change 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)

Table AMAJ.1. Schedule of Activities

Procedure[a]	Screening Period	Baseline	Induction Period						Maintenance Period									
Visit Number	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18
Week	-4	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Day with Visit Tolerance Interval	≤28 days from V2	1	8 ± 3	15 ± 3	22 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5
Informed Consent	X																	
Demographics	X																	
Height	X																	
Physical Exam[c]	X	X							X									X
Weight	X	X							X									X
Inclusion/Exclusion Criteria	X	X																
Complete Medical/Surgical History & Habits	X																	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting Conditions	X																	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, temperature, and pulse)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest Radiography for TB Screening	X[e]																	
PPD/QuantiFERON-TB Gold/ T-SPOT.TB® (per local guidelines)	X[f]																	
ECG	X																	

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 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
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)

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 sPGA score at Week 16 (Visit 9) and Week 24 (Visit 11), or remain at or above their baseline 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 (see Section 8.2).

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

1. 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

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

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

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

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

Figure AMAJ.1 illustrates the study design.

placebo demonstrated by the active control (FDA 2016). The duration of the 16-week primary evaluation is sufficiently short that patients will receive placebo without lasting adverse effects.

The efficacy of mirikizumab in treating psoriasis will be measured by the sPGA and PASI response scales, with the primary efficacy endpoint at Week 16. These measures and the 16-week endpoint are in alignment with efficacy endpoints for currently approved psoriasis therapies and with regulatory guidance (EMA 2004). Steady-state exposure is expected to be reached within the 16-week time period (median half-life [$t_{½}$] of mirikizumab is 10.5 days), and it is anticipated that a significant clinical effect will be observed within this timeframe based on previous studies with mirikizumab in patients with psoriasis.

The Maintenance Dosing Period (Period 3) is designed to evaluate the maintenance of response with 2 different dose regimens of mirikizumab (250 mg and 125 mg, Q8W) as compared to the comparator (300 mg secukinumab, Q4W), as well as assessment of safety data following at least 1 year of treatment with mirikizumab.

The Post-Treatment Follow-Up Period (Period 4) is included for safety monitoring following the last study visit for patients who do not enroll in Study AMAH or discontinue early from Study AMAJ.

5.5. Justification for Dose

The dose levels and regimens selected for this study were based primarily on analyses of interim PK, safety, and efficacy data from the Phase 2 Study AMAF, safety data from other clinical studies evaluating mirikizumab, and nonclinical safety data.

Safety Considerations

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

The margin of safety for the 250 mg Q4W SC induction dose regimen proposed for this study relative to the NOAEL level in the 6-month nonclinical toxicology study in cynomolgus monkeys is 22, based on area under the plasma concentration versus time curve.

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

for signs or symptoms that could result from such events, educated on the signs or symptoms of these types of events, and instructed to contact the study site immediately if any of the symptoms are experienced following an injection. If a patient experiences an acute hypersensitivity event after an injection of investigational product, he or she should be managed appropriately and given instructions to receive relevant supportive care.

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

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

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

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

See also Section 9.4.4.

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

9.1.2.2. Psoriasis Area and Severity Index

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

9.1.2.3. Body Surface Area

Percent BSA will be evaluated as the percent involvement of psoriasis on each subject's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation 2016).

9.1.2.4. Nail Psoriasis Severity Index

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

9.1.2.5. Psoriasis Scalp Severity Index

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

9.1.2.6. Palmoplantar Psoriasis Severity Index

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

9.1.2.7. Health Outcomes Assessments

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

9.1.2.7.1. Dermatology Life Quality Index

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

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

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

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

9.1.2.7.3. Work Productivity and Activity Impairment Questionnaire: Psoriasis

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

9.1.2.7.4. Psoriasis Symptoms Scale

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

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

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- When a condition related to the prefilled syringes necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

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

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

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Adverse Event Monitoring with a Systematic Questionnaire

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at every visit with the administration of the C-SSRS and the Self-Harm Supplement Form. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the Self-Harm Follow-Up Form. The Self-Harm Follow-Up form is a series of questions that provides a more detailed description of the behavior cases.

The QIDS-SR16 instrument (for description, see Section 9.1.2.7.6) will be used to collect patient-reported data on signs and symptoms related to depression.

9.2.3. Adverse Events of Special Interest

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

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

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

Infections, Including Opportunistic Infections

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

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

Hypersensitivity Events

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

Cerebro-Cardiovascular Adjudication

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

9.2.4. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

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

9.3. Treatment of Overdose

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

Refer to the Product Label of secukinumab for advice on overdose.

9.4. Safety

9.4.1. Electrocardiograms

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

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

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

9.4.5.2. Tuberculosis Screening

Screening:

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

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

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

Monitoring:

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

Interpretation of Screening Tests for LTBI

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

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

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

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

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

10.3.8. Interim Analyses

One DMC consisting of members external to Lilly will be established for interim safety monitoring across all Phase 3 trials in patients with psoriasis. This committee will consist of a minimum of 3 members including a physician with expertise in dermatology, a statistician, and an additional clinician(s). 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. The study team will not have access to the unblinded data. The purpose of the DMC is to advise Lilly regarding continuing patient safety; however, the DMC may request key efficacy data to put safety observations into context and to confirm a reasonable benefit/risk profile for ongoing patients in the study. 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.

To support regulatory submission, an analysis including the primary and major secondary endpoints will be conducted after all patients complete Week 52 or discontinue early. If all patients have entered the long-term extension Study I6T-MC-AMAH, or discontinued the study early, this analysis is deemed as the final analysis. Otherwise, this analysis will be an interim analysis for the primary outcome; the final analysis will be conducted after all patients have entered the long-term extension Study I6T-MC-AMAH, or have completed the follow-up period of Study AMAJ, or discontinued the study early.

In addition, a limited number of pre-identified internal Lilly personnel that are not in contact with clinical sites may gain access to unblinded PK/PD data, as specified in the unblinding plan, prior to the Week 52 database lock, in order to initiate the final population PK/PD model development processes. Unblinding details will be provided in the unblinding plan.

Procedure[a]	Screening Period	Baseline	Induction Period						Maintenance Period									
Visit Number	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18
Week	-4	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Day with Visit Tolerance Interval	≤28 days from V2	1	8 ± 3	15 ± 3	22 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Suppl Form[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QIDS-SR16 (patient completed)		X							X			X			X			X
IP Dosed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Investigator Completed Clinical Efficacy Scales																		
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Facial Psoriasis		X							X									X
PSSI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPASI[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Completed Health Outcomes Scales[j]																		
PSS	|----------Daily Electronic Diary[k]----------|											X			X			X
DLQI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36		X							X									X
PatGA		X	X	X	X	X	X	X	X			X			X			X
WPAI-PSO		X							X			X			X			X

10.3.4. Safety Analyses

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

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

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

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

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

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

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

5.2. Number of Participants

Approximately 1872 participants will be screened to achieve 1443 randomized participants for an estimated total of 888 participants randomized to mirikizumab, 444 randomized to secukinumab, and 111 randomized to placebo.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will examine the effect of mirikizumab versus placebo and versus an active comparator (secukinumab) in patients with moderate-to-severe plaque psoriasis. Secukinumab was chosen as the active-comparator as it:

- is a biologic inhibitor of IL-17, which has been shown to be a primary effector molecule in the pathogenesis of plaque psoriasis. Currently, IL-17 inhibitors are the most effective biologic systemic therapies approved for the treatment of moderate-to-severe psoriasis.
- has demonstrated effectiveness in the treatment of moderate-to-severe psoriasis and is approved for the treatment of adults with moderate-to-severe plaque psoriasis.
- has an established safety profile

Thus, secukinumab has been selected as an appropriate active comparator for a direct comparison of efficacy of mirikizumab against a well-established biologic standard of care during a 52-week treatment period.

The 300-mg secukinumab dose administered at Weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks is the approved dose regimen for adult patients with moderate-to-severe psoriasis (Cosentyx® Summary of Product Characteristics 2017; Cosentyx® [secukinumab] package insert 2018).

During the Induction Dosing Period (Period 2), 250 mg mirikizumab will be compared to 300 mg secukinumab and placebo. During the Maintenance Dosing Period (Period 3), 2 dose regimens, 250 mg and 125 mg, of mirikizumab will be compared to 300 mg secukinumab. All treatment groups are detailed in Section 7.1, with the dose justification outlined in Section 5.5.

The study will not use a placebo-to-match for secukinumab. The study blind will be maintained as described in Section 7.3 using designated Unblinded Site Personnel to administer study injections, and by using physical means of shielding the investigational product from the patients' view as detailed in Section 7.1.

The Induction Dosing Period (Period 2) is designed to compare efficacy and safety of mirikizumab versus secukinumab and versus placebo in patients with psoriasis. The selection of placebo as a comparator is justified on the basis that the most robust evaluation of efficacy can be made versus placebo treatment, to provide clear evidence on assay sensitivity, and to conclude non-inferiority of the test treatment to the active control by showing that the test treatment preserves a certain predetermined percentage of effect over placebo relative to the effect over

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

	• Change from baseline in QIDS-SR16 total score in those with a baseline QIDS-SR16 total score ≥11 • Proportion of patients achieving a DLQI total score of (0,1) with at least a 5-point improvement (reduction) from baseline in patients with a baseline DLQI total score ≥5 • Proportion of patients achieving DLQI (0,1) with DLQI baseline score >1
To 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 To assess efficacy of 250 mg mirikizumab Q8W and 125 mg mirikizumab Q8W as compared to secukinumab with respect to 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) 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)

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; 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; 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.

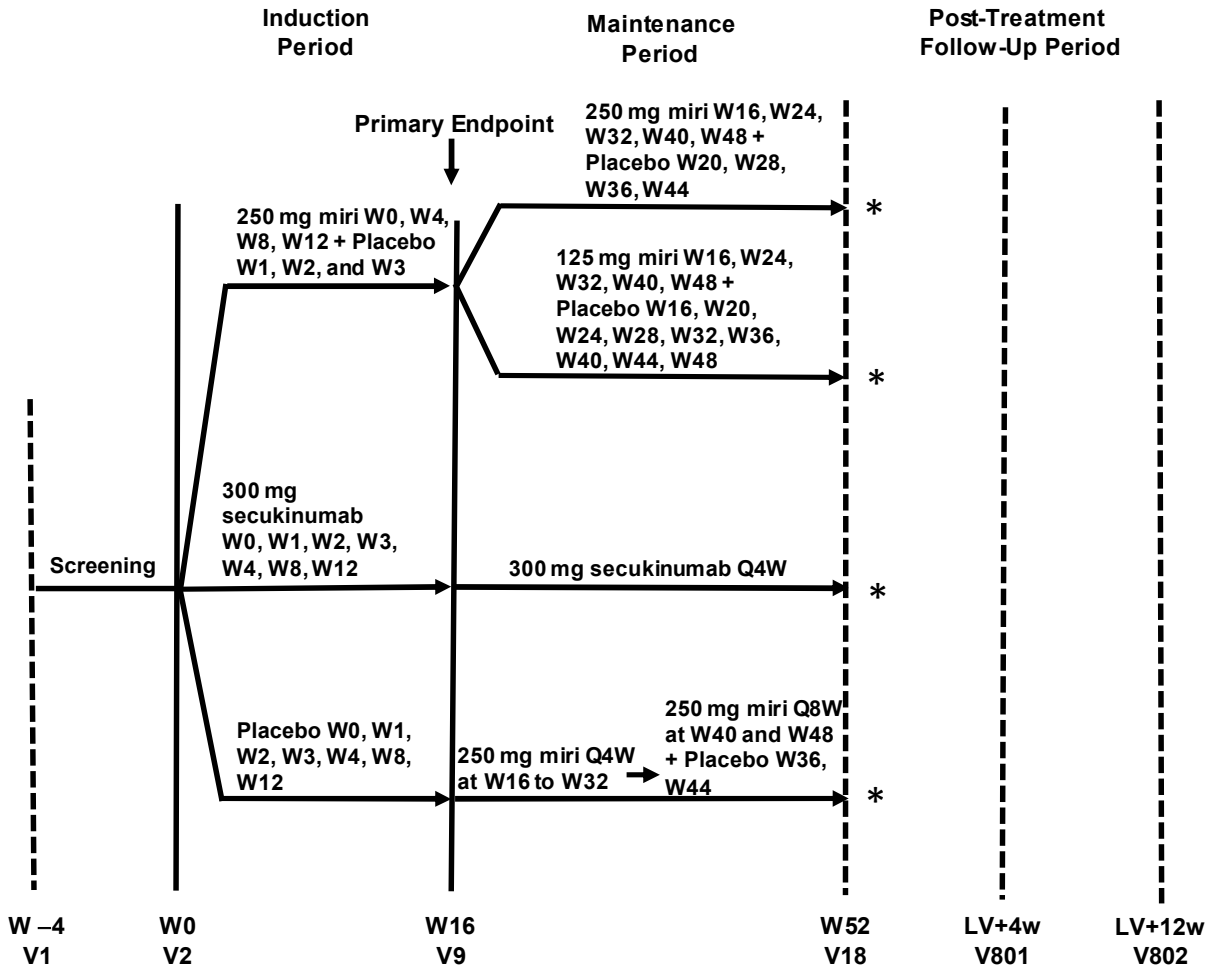
[b] Note: A "clinically meaningful" response is a PASI 75 response, which represents at least a 75% decrease (improvement) from the baseline PASI score. A "high level" of clinical response is a PASI 90 response, which represents at least a 90% decrease (improvement) from baseline in PASI score, or sPGA (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.

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 anti-mirikizumab antibodies and their potential relationship with efficacy, TEAEs, and mirikizumab exposure	At Week 16 and Week 52: • Relationship between TE-ADA and efficacy (sPGA and PASI) • Relationship between TE-ADA and TEAEs • Relationship between TE-ADA and mirikizumab pharmacokinetics

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; MCS = mental component summary; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = ≥75%/≥90%/≥100% improvement in PASI from baseline; PatGA = patient's global assessment; 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 anti-drug 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.



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 AMAH or to enter the Post-Treatment 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.1. Illustration of study design for Clinical Protocol I6T-MC-AMAJ.

Efficacy Considerations

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

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

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

Formulation Considerations

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

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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

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

8.1.2. Temporary Interruption (Withholding) of Study Treatment

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

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

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

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

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

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

The QIDS-SR16 is a self-administered, 16-item instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) (American Psychiatric Association 2013). A patient is asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation.

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

9.1.2.7.7. Treatment Satisfaction Questionnaire for Medication

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

9.4.2. Vital Signs

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

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

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

9.4.2.1. Hypertension

Patients who experience changes in BP (systolic BP at ≥160 mm Hg plus ≥20 mm Hg increase from baseline [Week 0; Visit 2]; and/or diastolic BP at ≥100 mm Hg plus ≥10 mm Hg increase from baseline) on 2 consecutive visits are to receive intervention for the management of hypertension. Intervention may begin with lifestyle changes and could lead to the maximal intervention of withholding the dose of investigational product (see Section 8.1.2) and/or the introduction of antihypertensive agent(s) as medically appropriate.

9.4.3. Laboratory Tests

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

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

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

9.4.3.1. Pregnancy Testing

Pregnancy testing is to be performed only on women of child-bearing potential.

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

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

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

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

Re-Testing and Confirmatory Testing

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

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

Diagnosis of LTBI During Study

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

Prior Treatment for LTBI or TB

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

Active TB

Patients diagnosed with active TB at screening will be excluded.

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

9.4.5.3. Chest Radiography

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

11. References

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

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing. 2013.

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

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

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

Boniface K, Guignouard E, Pedretti N, Garcia M, Delwail A, Bernard FX, Nau F, Guillet G, Dagregorio G, Yssel H, Lecron JC, Morel F. A role for T cell-derived interleukin 22 in psoriatic skin inflammation. *Clin Exp Immunol*. 2007;150(3):407–415.

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

Caruso R, Botti E, Sarra M, Esposito M, Stolfi C, Diluvio L, Giustizieri ML, Pacciani V, Mazzotta A, Campione E, Macdonald TT, Chimenti S, Pallone F, Costanzo A, Monteleone G. Involvement of interleukin-21 in the epidermal hyperplasia of psoriasis. *Nat Med*. 2009;15(9):1013–1015.

Cosentyx® (secukinumab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, Inc; January 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125504s001s002lbl.pdf. Accessed February 22, 2018.

Cosentyx® (secukinumab) [Summary of Product Characteristics]. Camberley, UK: Novartis Europharm Limited; August 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf. Accessed February 07, 2018.

Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol.* 2009;129(6):1339–1350.

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 2004. Available at:

Procedure[a]	Screening Period	Baseline	Induction Period						Maintenance Period									
Visit Number	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18
Week	-4	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
Day with Visit Tolerance Interval	≤28 days from V2	1	8 ± 3	15 ± 3	22 ± 3	29 ± 3	57 ± 5	85 ± 5	113 ± 5	141 ± 5	169 ± 5	197 ± 5	225 ± 5	253 ± 5	281 ± 5	309 ± 5	337 ± 5	365 ± 5
EQ-5D-5L-PSO		X					X		X			X			X			X
TSQM		X							X			X			X			X
Laboratory Tests																		
Hematology[l]	X	X	X	X	X	X	X		X		X		X		X		X	X
Clinical Serum Chemistry[l]	X	X	X	X	X	X	X		X		X		X		X		X	X
Lipid Panel (fasting)[m]		X							X									X
Urinalysis	X	X							X									
hsCRP		X				X	X		X		X		X		X			X
HBsAg, HBcAb, HBsAb	X[n]																	
HBV DNA testing[n]	X							X			X			X			X	
Hepatitis C Antibody	X																	
HCV RNA testing	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
HIV	X																	
Immunogenicity for miri[p]		X		X		X	X		X	X	X		X		X			X
Serum for miri Concentrations (PK)[q]		X		X		X	X		X	X	X		X		X			X
Serum Pregnancy Test (WCBP only)	X																	

CCI [redacted]

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

10.3.6. Evaluation of Immunogenicity

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

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

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

Subgroup analyses will be conducted for sPGA (0,1) and PASI 90 at Week 16 (NRI) using the Induction ITT population.

Subgroups to be evaluated will include the following:

- Patient Demographics and Characteristics Subgroups
  - Gender, age, body weight, BMI, race/ethnicity, age at onset of psoriasis
- Geographic Regions
- Baseline Severity of Disease Subgroups, including:
  - Disease duration, sPGA, and PASI
- Previous Psoriasis Therapy Subgroups, including:
  - Naïve to conventional systemic and biologic therapies
  - Previous use of systemic or phototherapies
  - Previous use biologic psoriasis therapies
  - Prior failure of biologic psoriasis therapies
  - Prior failure of systemic agent or contraindication
- Psoriasis Involvement Subgroups
- Concomitant Medications Subgroups
- Anti-Mirikizumab Antibody Status

A detailed description of the subgroup variables will be provided in the SAP. Additional subgroups and analyses may be performed as deemed appropriate and necessary.

10.3.7.2. Psoriasis Symptoms Scale Psychometric Analysis

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

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