Statistical Analysis Plan I6T-MC-AMAF (Version 2)

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate-to-Severe Plaque Psoriasis

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Approval Date: 28-Jun-2017

1. Statistical Analysis Plan: I6T-MC-AMAF: A Phase 2, Multicenter, Randomized, Parallel-arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate to Severe Plaque Psoriasis

IL-23 Antibody II (LY3074828) Psoriasis

Study I6T-MC-AMAF is a Phase 2, multicenter, randomized, double-blind, placebo controlled study of LY3074828 in subjects with moderate to severe plaque psoriasis. The study consists of a 16-week Induction Period where subjects will receive 1 of 4 treatment arms (LY3074828 300 mg, 100 mg, 30 mg, or placebo) every 8 weeks, an 88-week Maintenance Period to explore as needed (PRN) dosing, and a 16-week Follow-Up Period.

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Protocol I6T-MC-AMAF
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly:
09 February 2017
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly
on date provided below.

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first internal Trial Level Safety Review (TLSR).

SAP Version 2 was approved prior to the primary snapshot.

4. Study Objectives

4.1. Primary Objective

To test the hypothesis that treatment with LY3074828 is superior to placebo in inducing PASI 90 response at Week 16 in subjects with moderate-to-severe plaque psoriasis

4.2. Secondary Objectives

- To evaluate the safety and tolerability of treatment with LY3074828
- To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing PASI 100 and PASI 75 at Week 16
- To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing sPGA 0 (clear) and sPGA 0/1 at Week 16
- To evaluate the effect of LY3074828 on patient reported outcome measures: Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Week 16
- To characterize the long-term efficacy of LY3074828 on the PASI 100, PASI 90, and PASI 75 responses at Week 52, 104, and 120
- To characterize the long-term efficacy of LY3074828 on patient reported outcome measures Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Weeks 52, 104, and 120
- To characterize the PK of LY3074828.

4.3. Exploratory Objectives

- To characterize the loss of response during the Maintenance Period (if applicable) for subjects who achieve PASI 100 at Week 16
- To characterize the loss of response during the Maintenance Period (if applicable) for subjects who achieve PASI 90 at Week 16
- To characterize the ability of retreatment (if applicable) with LY3074828 to regain PASI 100 for subjects who achieve PASI 100 response at Week 16 and experience loss of response during the Maintenance Period
- To characterize the ability of retreatment (if applicable) with LY3074828 to regain PASI 90 for subjects who achieve PASI 90 response at Week 16 and experience loss of response during the Maintenance Period
- To evaluate the efficacy of treatment with LY3074828 in inducing PASI 100, PASI 90, PASI 75, and mean PASI improvements at all time points evaluated
- To evaluate the efficacy of treatment with LY3074828 in inducing mean BSA improvements at all time points evaluated
- To evaluate the efficacy of treatment with LY3074828 in inducing sPGA 0 and sPGA 0/1 at all time points evaluated

- To evaluate the efficacy of treatment with LY3074828 in PSSI at all time points evaluated
- To evaluate the efficacy of LY3074828 on patient reported outcome measures: Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at all time points evaluated
- To evaluate the psychometric properties of the Psoriasis Symptom Scale including validity, reliability, and responder definition
- To evaluate the relationships between LY3074828 exposure, biomarkers, and efficacy
- To evaluate the development of anti-drug antibodies for LY3074828.

5. Study Design

5.1. Summary of Study Design

Study AMAF is a multicenter, randomized, parallel-arm, placebo-controlled trial with 4 study periods in subjects with moderate-to-severe plaque psoriasis.

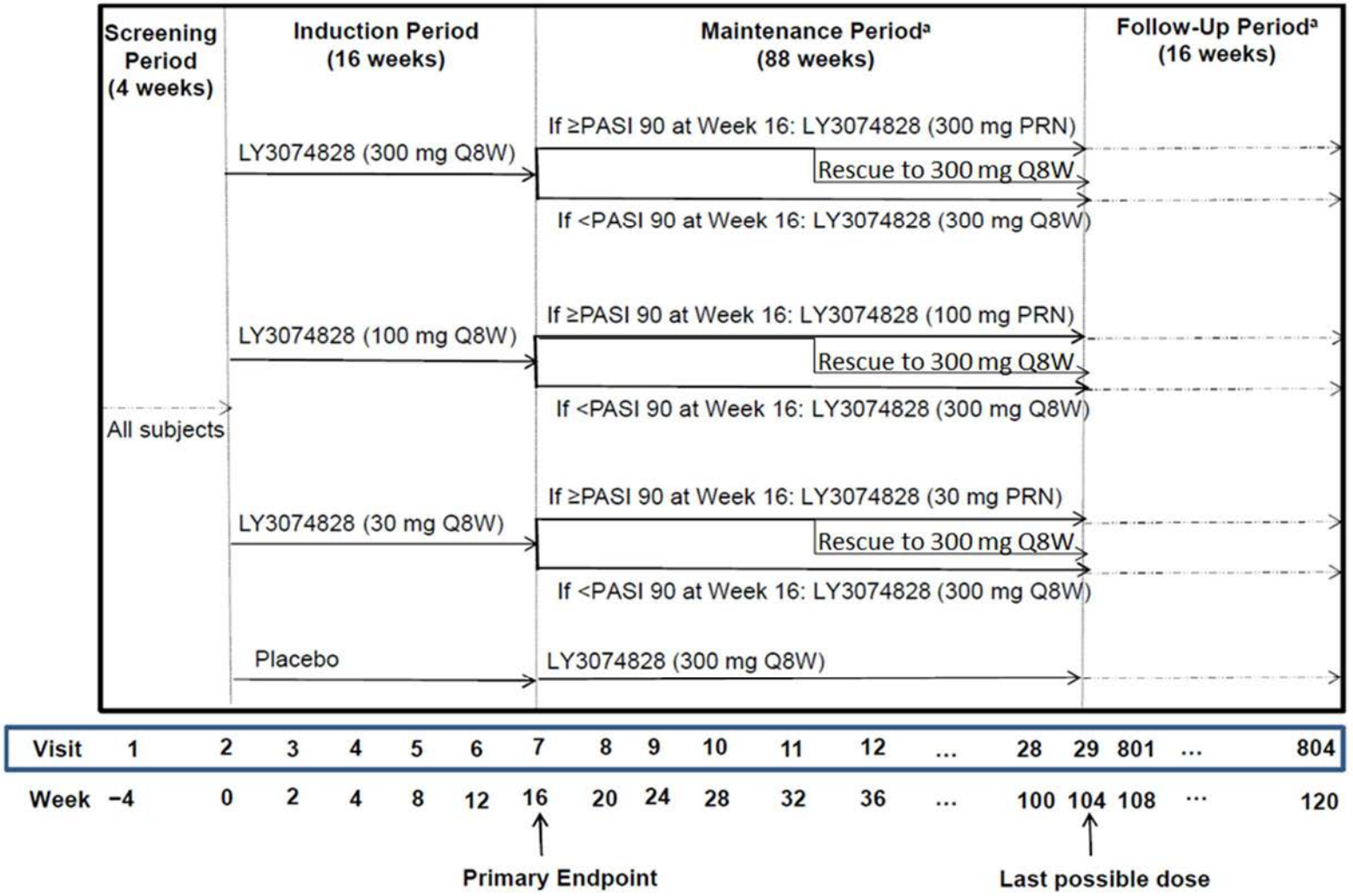
Screening Period (≤4 weeks): Subjects will be evaluated for study eligibility ≤28 days before the baseline visit (Visit 2/Week 0). At the baseline visit (Visit 2), subjects who fulfill the eligibility criteria will be randomized to 1 of 4 induction treatment arms.

Induction Period (16 weeks): A double-blind, 16-week Induction Period is designed to establish the efficacy and safety of LY3074828 administered at Visit 2 (Week 0) and Visit 5 (Week 8). Subjects will be randomized to 1 of 4 induction treatment arms (LY3074828 30 mg SC, LY3074828 100 mg SC, LY3074828 300 mg SC, and placebo every 8 weeks [Q8W]) stratified on the basis of previous exposure to biologic therapy for treatment of psoriasis.

Maintenance Period (88 weeks): The Maintenance Period consists of 88 weeks of treatment. At the end of the Induction Period (Week 16), subjects will continue treatment in the Maintenance Period which is intended to explore 1 of 2 treatment strategies through Week 104. All placebo subjects and subjects assigned to treatment with LY3074828 who have a <90% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 90) at Week 16 will receive LY3074828 300 mg SC Q8W during the entire Maintenance Period. Subjects with ≥PASI 90 PRN dosing group) at Week 16 will only be dosed with LY3074828 at the baseline dose level assignment no more frequently than Q8W when disease activity level is <PASI 90, and this will continue until ≥PASI 90 is regained.

Follow-up Period (16 weeks): The Follow-up Period will include a visit every 4 weeks for a total of 16 weeks following Visit 29 to assess subject safety and study drug efficacy.

Figure 5.1 illustrates the study design.



[a] Visits will occur every 4 weeks in the Maintenance and Follow-up Periods.

Abbreviations: PASI = Psoriasis Area and Severity Index; PRN = as needed; Q8W = every 8 weeks.

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

5.2. Determination of Sample Size

Approximately 200 subjects will be randomized at a 1:1:1:1 ratio in the blinded induction dosing period to LY3074828 30 mg, 100 mg, 300 mg, and placebo (50 subjects per dosing regimen, respectively). Randomization will be stratified by prior exposure to biologic therapy for psoriasis (yes/no).

Assuming 60% and 3% PASI 90 response rates at 16 weeks for LY3074828 and placebo, respectively, pairwise comparisons to placebo have over 99% power using a 2-sided Fisher's exact test at the 0.05 significance level, with no adjustment for multiple comparisons.

As results for PRN dose arms in the Maintenance Period will support the maintenance dosing strategy in Phase 3 planning, a reasonable total number of subjects who completed 1-3 visits in the Maintenance Period (Week 20 to Week 28) will be needed. Based on study simulations under the treatment effect scenario outlined above, approximately 49 subjects (9 on 30 mg, 18 on 100 mg, 22 on 300 mg PRN arms) will have completed the Week 20 visit at the time of the primary endpoint datalock.

5.3. Method of Assignment to Treatment

This study involves a comparison of SC administration of LY3074828 versus placebo during a 16-week Induction Period followed by a Maintenance Period designed to explore PRN maintenance treatment based upon disease activity at the end of the Induction Period. A Rescue Period is also available for subjects who received PRN treatment. Table 5.1 shows the treatment regimens.

Table 5.1. Treatment Regimens in Induction, Maintenance and Rescue Periods

Treatment Group	*Description*		
	Induction Period	**Maintenance Period**	**Rescue Period**
LY Dose Arm 1	30 mg LY SC Q8W	If <PASI 90 at Week 16: 300 mg LY given SC Q8W	
		If ≥PASI 90 at Week 16: 30 mg LY given SC PRN	30 mg LY SC PRN to 300 mg LY SC Q8W
LY Dose Arm 2	100 mg LY SC Q8W	If <PASI 90 at Week 16: 300 mg LY given SC Q8W	
		If ≥PASI 90 at Week 16: 100 mg LY given SC PRN	100 mg LY SC PRN to 300 mg LY SC Q8W
LY Dose Arm 3	300 mg LY SC Q8W	If <PASI 90 at Week 16: 300 mg LY given SC Q8W	
		If ≥PASI 90 at Week 16: 300 mg LY given SC PRN	300 mg LY SC PRN to 300 mg LY SC Q8W
Placebo	Placebo SC Q8W	300 mg LY given SC Q8W	

Abbreviations: LY = LY3074828; PASI = Psoriasis Area and Severity Index; PASI 90 = 90% improvement in PASI from baseline; PRN = as needed; Q8W = every 8 weeks; SC = subcutaneous.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (hereafter Lilly). The statistical analyses will be performed using SAS® Version 9.4 or higher.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), minimum, median, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to 1 more decimal place than the raw data recorded in the database. The SD will be reported to 2 more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be 4 for any summary statistic.

Categorical data will be summarized in terms of the number of patients in the analysis population, the number of patients providing data at the relevant time point, frequency counts, and the percentages corresponding to the appropriate method. Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts.

All confidence intervals (CIs) and statistical tests will be 2-sided unless otherwise specified. P-values which are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to 1 more decimal place than the raw data.

6.1.1. Subject Populations for Analyses

For purposes of analysis, populations for analyses are described in Table 6.1.

Table 6.1. Subject Populations for Analyses

Population	Description
Intent-to-treat (ITT) (Induction Period Efficacy)	All randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol: • Unless otherwise noted, efficacy and health outcomes analyses for the Induction Period will be conducted on this population. • Subjects will be analyzed according to the treatment to which they were assigned.
Induction Period Safety	All randomized subjects who received at least 1 dose of study treatment: • Unless otherwise noted, safety analyses for the Induction Period will be conducted on this population. • Subjects will be analyzed according to the treatment to which they were assigned.
Maintenance Period Efficacy	All randomized subjects who have entered the Maintenance Period (see definition of entering Maintenance Period in Section 6.1.2.1): • Unless otherwise noted, efficacy, and health outcomes for the Maintenance Period will be conducted on this population. • Subjects will be analyzed according to the treatment to which they were assigned in Maintenance Period.

Population	Description
Maintenance Period Safety	All randomized subjects received at least 1 dose of study treatment who have entered the Maintenance Period (see definition of entering Maintenance Period in Section 6.1.2.1): • Unless otherwise noted, safety analyses for the Maintenance Period will be conducted on this population. • Subjects will be analyzed according to the treatment to which they were assigned in Maintenance Period, with all LY3074828 300 mg Q8W arms combined, that is, there will be 4 treatment groups in the Maintenance Period: o LY 300 mg PRN o LY 100 mg PRN o LY 30 mg PRN o LY 300 mg Q8W (including subjects from 4 Induction Period treatment groups)
Rescue Period (Efficacy and Safety)	All PRN subjects who received at least 1 dose of rescue treatment: • For subjects who didn't qualify for rescue treatment but get the rescue dose by mistake, they will still be included in the Rescue Period analysis population. • Unless otherwise noted, efficacy, health outcomes and safety endpoints for the Rescue Period will be analyzed on this population.
All Periods Safety	All subjects who received at least 1 dose of LY3074828 treatment • Safety analysis will be analyzed for all subjects who were exposed to at least 1 dose of LY3074828 treatment • All LY3074828-exposed subjects will combined in the All Periods safety analysis

Abbreviation: ITT = intent-to-treat; PRN = as needed.

6.1.2. Definitions

6.1.2.1. Study Time Intervals

Induction Period

All subjects who were randomized to the study are considered as entering the Induction Period.

The start of the Induction Period is defined as the date of first injection following randomization. For subjects who were randomized but not dosed, the Induction Period starts at the randomization date.

The end of the Induction Period is defined as the date of PASI measurement at Week 16, or the early termination date if subjects discontinued from study prior to or at Week 16, or Day 117, whichever comes first.

Maintenance Period

All subjects who had Week 16 visit with PASI measurement (except the ones discontinued the study at Week 16) are considered to have entered the Maintenance Period.

The start of the Maintenance Period is defined as the same date as end of the Induction Period, which is the date of PASI measurement at Week 16.

The end of the Maintenance Period is defined as the visit date at Week 104, or the date when the subjects received rescue treatment, or the early termination date if subjects discontinued from study prior to or at Week 104, whichever comes first.

Rescue Period

All subjects in PRN groups who received at least 1 dose of rescue treatment are considered to have entered the Rescue Period, and will be included in the Rescue Period analysis population.

The start of the Rescue Period is defined as the date the patient received the first dose of rescue treatment.

The end of the Rescue Period is defined as the visit date at Week 104, or early termination date if subjects discontinued from study prior to or at Week 104, whichever comes first.

Follow-up Period

All subjects who had Visit 29 are considered to have entered the Follow-up Period, and will be included in the Follow-up Period analysis population.

6.1.2.2. Definition of Study Baseline

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

For PSS, the weekly average of at least 4 days of the consecutive 7 days prior to the first injection will be the study baseline score.

In cases where baseline measurements are taken on the same day as injection and no times are recorded, it will be assumed that these measurements are taken prior to the injection.

6.1.3. Analysis Methods

The analysis method for comparisons of each Induction Period LY3074828 dose regimen (300 mg, 100 mg, 30 mg) and placebo for categorical binary efficacy and health outcome variables will be a logistic regression analysis with treatment, geographic region (United States/Outside United States [US/OUS]), and previous biologic therapy (yes/no) using SAS PROC Logistic. Note although geographic region is not a stratification factor, due to its potential impact on outcome, unless otherwise specified, it is included in all logistic regression models. In addition, sensitivity analysis with other covariates for primary endpoint will be conducted using logistic regression (Section 6.2.1).

Logistic regression with a Firth penalized likelihood will be used (see Appendix 1 for simulation study). 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, linear trend tests will be performed for dose-response analysis using all 4 doses (placebo, LY3074828 30 mg, 100 mg and 300 mg). For the first test, all 4 doses will be used and the lower 3 doses will be used for the second test, and the lowest 2 doses will be used for the third test. Under the assumption of monotonic treatment response, the conclusion of trend implies that the highest dose in the test is efficacious.

1. Hypothesis 1: There is no treatment difference in PASI 90 response at Week 16 between LY 300 mg and placebo group
2. Test if there is a monotonic linear trend between the 4 doses
3. Hypothesis 2: There is no treatment difference in PASI 90 response at Week 16 between LY 100 mg and placebo group
4. Test if there is a monotonic linear trend between the 3 doses (LY 100 mg, 30 mg, and placebo)
5. Hypothesis 3: There is no treatment difference in PASI 90 response at Week 16 between LY 30 mg and placebo group.

The analysis method for comparisons of each Induction Period LY3074828 dose regimen (300 mg, 100 mg, 30 mg) and placebo for the continuous efficacy and health outcome variables will be a Mixed effect Model Repeat Measurement (MMRM) analysis when the endpoint is collected at multiple postbaseline visits during a study period, or analysis of covariance (ANCOVA) when the endpoint is collected at one postbaseline visit during a study period, or for sensitivity analyses. When the MMRM model is used, the model will include treatment, geographic region (US/OUS), previous therapy (yes/no), baseline value, visit, and the interaction of treatment-by-visit as fixed factors. When the ANCOVA model is used, the model will include baseline value as a continuous covariate and treatment, geographic region (US/OUS), and previous therapy (yes/no) as fixed factors. For both models, the covariance structure to model the within-patient errors will be unstructured. The Restricted Maximum Likelihood (REML) will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure. Type III tests for the least squares (LS) means will be used for the statistical comparison; the 95% CI will be reported. Dosing regimen comparisons at Week 16 (Visit 7) and all other postbaseline visits in the Induction Period will be reported.

Proportions and 95% confidence intervals will be summarized for binary outcomes observed in the Maintenance Period. Mean change from baseline and 95% confidence intervals will be summarized for continuous outcomes observed in the Maintenance Period.

The Kaplan-Meier product limit method will be used to estimate the survival curves for post induction (includes Maintenance and Follow-up Periods) time-to-event variables (time to loss of response, time to response recapture after loss of response); median times will be summarized by treatment.

Time to First Loss of Response in the Maintenance Period for PRN Patients

Time to first loss of response (PASI 90 or PASI 100) in the Maintenance Period includes only those subjects who achieved the respective response at Week 16 and is defined in weeks as:

(First study day when response is lower than the specified level – First study day when response is greater than or equal to the specified level + 1) / 7

If a patient does not lose response by completion or early discontinuation of the Maintenance Period, the patient will be censored with the censored date defined as the earliest date between the data cutoff for an interim analysis, the study discontinuation date, Maintenance Period end date for non-rescued patients, or the rescue start date.

Time to Recapture of Response in the Maintenance Period After PRN Dosing

Time to recapture of response (for example, PASI 90 or PASI 100) in the Maintenance Period includes only those subjects who lost the specified level of response during the Maintenance Period and is defined in weeks as:

(First study day when response is recaptured at the specified level – First study day when response is lower than the specified level +1) / 7

If a patient does not recapture response by completion or early discontinuation of the Maintenance Period, the patient will be censored with the censored date defined as the earliest date between the data cutoff for an interim analysis, the study discontinuation date, Maintenance Period end date for non-rescued patients, or the rescue start date.

Time to Recapture of Response in the Rescue Period

Time to recapture of response (PASI 50, PASI 90, or PASI 100) in the Rescue Period includes only those subjects who lost the specified level of response during the Maintenance Period and is defined in weeks as:

(First study day when response is recaptured at the specified level – First study day when response is lower than the specified level +1) / 7

If a patient does not recapture response by completion or early discontinuation of the Rescue Period, the patient will be censored with the censored date defined as the earliest date between the data cutoff for an interim analysis, the study discontinuation date, Rescue Period end date, and the start date of the Follow-up Period.

For variables that are not collected at each postbaseline visit, data may exist at visits where the variable was not scheduled to be collected, due to early discontinuation visits. 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). However, the data will still be used in other analyses, including shift analyses, change from baseline to mBOCF endpoint analyses, and other categorical analyses.

Fisher's exact test will be used for all adverse events (AEs). The continuous baseline characteristics will be analyzed using an analysis of variance (ANOVA) model with dosing regimen as a factor. Continuous vital sign data and laboratory values will be analyzed by an ANCOVA with dosing regimen and baseline value in the model.

6.2. Adjustments for Covariates

6.2.1. Logistic Regression

The randomization is stratified by previous biologic therapy (yes/no). Unless otherwise specified, categorical efficacy variables will be analyzed using a logistic regression analysis with treatment, geographic region (US/OUS), and previous biologic therapy (yes/no) in the model. Logistic regression details are provided in Section 6.1.3.

For primary endpoint PASI 90 at Week 16, additional covariates will be added to the logistic regression as sensitivity analysis, including baseline PASI score, treatment by previous biologic use interaction, and treatment by geographic region interaction.

6.2.2. MMRM

Analysis of continuous efficacy and health outcome variables collected at multiple postbaseline visits during a study period will be made using MMRM analysis using a model that includes treatment, geographic region (US/OUS), previous therapy (yes/no), baseline value, visit, and the interaction of treatment-by-visit as fixed factors. MMRM details are provided in Section 6.1.3.

6.2.3. ANCOVA

Analysis of continuous efficacy and health outcome variables collected at one postbaseline visit during a study period and for sensitivity analyses will be made using ANCOVA using a model that includes baseline value as a continuous covariate and treatment, geographic region (US/OUS), and previous therapy (yes/no) as fixed factors. ANCOVA details are provided in Section 6.1.3.

6.3. Handling of Dropouts or Missing Data

6.3.1. Non-Responder Imputation (NRI)

Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. Subjects will be considered a non-responder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized subjects without at least 1 postbaseline observation will also be defined as non-responders for the NRI analysis.

Due to the design, PRN subjects who got rescued will get a different treatment (300 mg LY SC Q8W), therefore the subsequent visits following the first dose of rescue treatment will be defined as non-responders in the analysis for the Maintenance Period.

6.3.2. MMRM

MMRM will be the primary analysis method for longitudinal continuous measurements. It 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. MMRM model details are provided in Section 6.1.3.

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

6.3.3. mBOCF

An mBOCF analysis will be performed on key continuous efficacy endpoints in the Induction Period only, including PASI, BSA, PSSI, and PSS.

The above is proposed as a sensitivity analysis. 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. 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.

6.3.4. As Observed

In the Rescue Period, the efficacy endpoints will be summarized as observed. Only descriptive statistics will be reported. No comparisons will be done in this period.

6.4. Multiple Comparisons/Multiplicity

No multiplicity adjustment is planned for this Phase 2 study.

6.5. Subject Disposition

Subject flow will be summarized from entered to randomized to completion, and analysis populations will be listed and summarized by treatment group and visit.

Subject allocation by geographic region, country, and center will be summarized with number of subjects who entered the study, number of intent-to-treat (ITT) subjects for each treatment group, number of subjects discontinued from study treatment, number of subjects discontinued from study, and reasons for discontinuation.

Subject disposition will be summarized for each treatment period by visit. Reasons for discontinuation from the study will be tabulated by treatment randomized.

All subjects who are included in the ITT population and discontinue from the study will be listed, and the extent of their participation in the study will be reported for Induction Period, Maintenance Period, and Posttreatment Follow-up Period. If known, a reason for their discontinuation will be given.

6.6. Subject Characteristics

Subject characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include gender, age, age category, body weight, race, geographic region (US/OUS), baseline disease severity, duration of disease, prior exposure to biologic therapy (yes/no), previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical measurements will include PASI total score, sPGA score, BSA, PSSI for subjects with scalp psoriasis involvement at baseline or who developed scalp psoriasis postbaseline, PSS total score and item score, PatGA, DLQI total score, SF-36 Physical Component Score (PCS), and SF-36 Mental Component Score (MCS).

No inferential analysis for the comparability of baseline covariates across treatment groups will be performed.

Subject demographic variables and baseline characteristics will be summarized by dose and overall for ITT population with the baseline values defined for the Induction Period. The continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, minimum, Q1, median, Q3, and maximum) and the categorical variables will be summarized using frequency counts and percentages.

For the Maintenance and Follow-up populations, subject demographic variables and baseline characteristics will be summarized using the baseline as defined in Section 6.1.2.

The following demographic variables and baseline characteristics will be summarized:

- Age (in years): calculated using an imputed date of birth of July 1st in the year of birth collected in the electronic case report form (eCRF). Age will be calculated as:
  - Age = floor((intck('month', brthdtc, rfstdtc) - (day(rfstdtc) < day(brthdtc)))/12)
  - where brthdtc = Imputed date of birth, and rfstdtc = subject reference start date (that is, the date when subject is first exposed to study treatment)
- Age group: <65 years, ≥65 years
- Age group: <40 years, ≥40 years
- Gender
- Age groups within gender
- Race
- Ethnicity

- Geographic region: United States (US), Other (Non-US): Canada, Germany, Japan, Poland
- Height (cm): measured at Visit 1
- Weight (kg): measured at Visit 2
- Weight category:
  - <80 kg, ≥80 kg
  - <100 kg, ≥100 kg
- Body mass index (BMI) (kg/m2): BMI will be calculated as:
  - $BMI\ (kg\ /\ m^2) = \frac{Weight\ (kg)}{(Height\ (m))^2}$
  - BMI category: 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)
- Alcohol use: never, current, former
- Caffeine use: never, current, former
- Tobacco use: never, current, former
- Previous psoriasis therapy:
  - Previous systemic therapy: never used, non-biologic only, biologic only, biologic and non-biologic.
  - Previous non-biologic systemic therapy: never used, ever used
  - Previous biologic therapy: never used, ever used
  - Previous topical therapy: never used, topical prescription therapy, topical non-prescription therapy
  - Previous phototherapy (ultraviolet B [UVB] or PUVA): never used, ever used

    where

    - Non-biologics include: methotrexate, cyclosporine, corticosteroids, acitretin, fumaric acid derivatives, apremilast, other
    - Biologics include: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, secukinumab, ixekizumab, other
- Duration of psoriasis (in years): Will be calculated using the date of psoriasis onset (as recorded on the Prespecified Medical History - Indication eCRF page) as follows:

$$Duration\ of\ psoriasis\ (years) = \frac{Date\ of\ informed\ consent - Date\ of\ psoriasis\ onset}{365.25}$$

- Duration of psoriasis diagnosis (in years): Will be calculated using the date of psoriasis diagnosis (as recorded on the Prespecified Medical History - Indication eCRF page) as follows:

$$Duration\ of\ psoriasis\ diagnosis\ (years) = \frac{Date\ of\ \text{informed consent} - Date\ of\ psoriasis\ diagnosis}{365.25}$$

- Baseline PASI score
- Baseline PASI category: <20, ≥20
- Baseline PASI category: <15, ≥15
- Baseline sPGA
- Baseline sPGA category: 0, 1, 2, 3, 4, 5
- Scalp psoriasis: yes, no (reported on Psoriasis Involvement eCRF form)
- Baseline PSSI score
- Baseline PSS score
- Baseline BSA (%)
- Baseline BSA category: <20%, ≥20%
- Baseline DLQI total score
- Baseline DLQI total category: <10, ≥10
- Baseline DLQI total category: <5, ≥5
- Baseline DLQI total category: 0 or 1, >1
- Baseline SF-36 physical functioning score
- Baseline SF-36 role-physical score
- Baseline SF-36 role-emotional score
- Baseline SF-36 bodily pain score
- Baseline SF-36 vitality score
- Baseline SF-36 social functioning score
- Baseline SF-36 mental health score
- Baseline SF-36 general health score
- Baseline SF-36 physical component score

- Baseline SF-36 mental component score.

By-subject listings of demographic and baseline characteristics, respectively, for the ITT population will be provided.

6.7. Treatment Compliance

Treatment compliance with investigational product will be summarized for subjects who enter the Induction 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 subjects who demonstrate overall compliance during the Induction Period will be compared between treatment groups using Fisher's exact test.

Subject treatment compliance will be summarized for the ITT and Maintenance populations. A by-subject listing of study treatment administration and compliance for the ITT and Maintenance populations will be provided.

6.8. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary.

Medication start and stop dates will be compared to the date of first dose of treatment in 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.

Prior therapy (reported before randomization) and current concomitant therapy (reported after randomization) will be presented separately in frequency tables by drug name for all randomized patients.

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 Period will be presented by the treatment groups. This table will also include a summary on the quantity of corticosteroid used by the patients, if an imbalance is observed between dosing groups. Corticosteroid use may also be summarized in conjunction with efficacy.

6.9. Efficacy Analyses

Table 6.2 includes the description and derivation of the efficacy/health outcomes measures and endpoints.

Table 6.3 provides the detailed analyses including analysis type, method and imputation, population, time point, and dosing regimen comparisons for efficacy/health outcomes analyses.

Table 6.2. 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% 6 = 90% to 100%	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: $Percent\ improvement\ from\ baseline\ =$ $100 \times \frac{Baseline\ PASI - Observed\ PASI}{Baseline\ PASI}$	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	The various body regions are weighted to reflect their respective proportion of body surface area.		If a patient has experienced an improvement, this measure will be positive. If a patient has experienced a worsening in the condition, this measure will be negative.	
		PASI 75	A clinically meaningful response; at least a 75% improvement in PASI score from baseline	Missing if baseline or observed value is missing
		PASI 90 (Primary)	Higher level of clearance; at least a 90% improvement in PASI score from baseline	Missing if baseline or observed value is missing
		PASI 100	Complete resolution of plaque Ps; a 100% improvement in PASI score from baseline	Missing if baseline or observed value is missing
sPGA	Static Physician Global Assessment (sPGA): the physician's global assessment of the patient's psoriasis (Ps) 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 to 5: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).	Single item, missing if missing
		sPGA (0,1)	An sPGA assessed as either 0 or 1, which represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque Ps.	Missing if sPGA is missing
		sPGA (0)	An sPGA assessed as 0, which represents a clinically important endpoint indicating complete resolution of plaque Ps.	Missing if sPGA is missing
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 change from baseline	Calculated as: observed BSA – baseline BSA	Missing if baseline or observed value is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
PSSI	Psoriasis Scalp Severity Index (PSSI): will be used if the patient has scalp psoriasis at baseline. The scalp will be assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows: Erythema, Induration and Desquamation: 0 = Absent 1 = Slight 2 = Moderate 3 = Severe 4 = Severest Possible Percent of Scalp Involved: 0 = none 1 = <10% 2 = 10 – 29% 3 = 30 – 49% 4 = 50 – 69% 5 = 70 – 89% 6 = 90 – 100%	PSSI score	The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 to 72.	If any individual score is missing, the PSSI score will not be calculated, hence missing.
		PSSI improvement from baseline and percent change from baseline (for subjects with baseline scalp psoriasis involvement only)	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
DLQI	Dermatology Life Quality Index (DLQI): is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related quality of life. 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:	DLQI symptoms and feelings domain	Sum of responses of questions #1 and #2: #1. How itchy, sore, painful or stinging has your skin been? #2. How embarrassed or self-conscious have you been because of your skin?	If 1 question in a domain is missing, that domain is missing.
		DLQI daily activities domain	Sum of responses of questions #3 and #4: #3. How much has your skin interfered with you going shopping or looking after your home or garden? #4. How much has your skin influenced the clothes you wear?	If 1 question in a domain is missing, that domain is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0	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.
		DLQI total score	A DLQI total score is calculated by summing all 10 question responses, and has a range of 0 to 30 (less to more impairment) (Finlay and Khan 1994; Basra et al. 2008).	If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		DLQI (0,1)	A DLQI (0,1) response is defined as a post-baseline DLQI total score of 0 or 1. A DLQI total score of 0	Missing if DLQI total score is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
			to 1 is considered as having no effect on a patient's HRQoL (Khilji et al. 2002; Hongbo et al. 2005).	
		DLQI (0)	A DLQI (0) response is defined as a postbaseline DLQI total score of 0.	Missing if DLQI total score is missing
		DLQI total score ≥5	A DLQI total score ≥5 response is defined as a postbaseline DLQI total score ≥5.	Missing if DLQI 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
SF-36	The SF-36 is a 36-item, patient-completed measure designed to be a short, multipurpose assessment of health (The SF Community – SF-36 Health Survey Update). The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. Items are answered on Likert scales of varying lengths. The SF-36 comprises 8 domain scores and 2 overarching component scores. The SF-36 acute version will be used, which has a 1 week recall period. Minimal Clinically Important Difference (MCID) cut-offs were determined in Strand et al. 2013.	SF-36 Domain scores: Physical functioning, Role-physical, Role-emotional, bodily pain, vitality, social functioning, mental health, general health	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software 4.5 will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will re-calibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (t-scores) using the 1-week recall period. No missing-imputation method will be used. Both, raw and domain scores without missing-data imputation will be recorded in the SDTM dataset, however only the domain scores will be used for analyses specified in this SAP.	Missing data handling offered by SF-36 software will be used.
		SF-36 Component Scores: PCS and MCS		

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
		SF-36 change from baseline for domain and component scores	Calculated as: observed SF-36 domain score – baseline SF-36 domain score	Missing if baseline or observed value is missing
		SF-36 Physical Component response (PCS)	PCS component score (change from baseline) ≥2.5	Missing if baseline or observed value is missing
		SF-36 Mental Component response (MCS)	MCS component score (change from baseline) ≥2.5	Missing if baseline or observed value is missing
PSS	The Psoriasis Symptoms Scale (PSS) is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms. The overall severity for each individual symptom from patient's psoriasis is indicated by selecting the number from an NRS of 0 to 10 that best describes the worst level of each symptom in the area in the past 24 hours, where 0 (= no severity) and 10 (worst imaginable severity). The symptom severity scores, ranging from 0 to 10, are the values of the selected numbers indicated by the patient on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, discomfort,	PSS total score	The PSS total score will be calculated by summing the individual item scores as follows: PSS = itch NRS + pain NRS + discomfort NRS + stinging NRS + burning NRS + redness NRS + scaling NRS + cracking NRS	If any item score are missing, the PSS total score is missing
		PSS change from baseline	Change from baseline = Observed PSS Total Score – Baseline PSS Total Score A negative change indicates improvement and a positive change indicates deterioration of the condition.	Missing if either observed or baseline PSS total score is missing
		PSS item scores	The PSS score for each item as reported in daily diaries from visit1 up to visit 7, then on the tablet device at visits 7, 11, 16 and 28 (see Appendix 2).	Missing if the PSS score for the item is missing
		Change from baseline for item scores	Change from baseline = Observed PSS Item Score – Baseline PSS Item Score A negative change indicates improvement and a positive change indicates deterioration of the condition.	Missing if either observed or baseline item PSS score is missing

Measure	Description	Variable	Derivation / Comment	Imputation Approach if with Missing Components
	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.			
PatGA	The Patient's Global Assessment of Psoriasis (PatGA) is a patient reported, single item scale on which subjects are asked to rank, by selecting a number on a 0-to-5 NRS, the severity of their psoriasis "today" from 0 (clear), no psoriasis, to 5 (severe).	Change from baseline	Change from baseline = Observed Item PatGA score – Baseline Item PatGA score	Missing if baseline or observed value is missing

Abbreviations: BSA = body surface area; DLQI = Global Assessment Dermatology Life Quality Index; EMA = European Medicines Agency; HRQoL = health-related quality of life; MCS = Mental Component Score; MCID = Minimal Clinically Important Difference; NRS = Numeric Rating Scales; PASI = Psoriasis Area and Severity Index; PatGA = Patients Global Assessment of Psoriasis; PCS = Physical Component Score; Ps = psoriasis; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; sPGA = Static Physician Global Assessment

Table 6.3. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Analysis Method (Sections 6.1.3)	Population (Section 6.1.1)	Time Point
PASI	PASI 90 (Primary)	Logistic regression analysis with NRI	ITT Population	Week 16: All pairwise comparisons against placebo (primary analysis), and linear trend tests (supportive analysis)
	PASI 75, PASI 90, PASI 100	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		Summary statistics with NRI	Maintenance Period Efficacy Population	All visits in Maintenance Period
		Summary statistics (As observed) or individual trajectory line plot if total number of subjects is too small	Rescue Period Efficacy Population	All visits in Rescue Period
	PASI <5; PASI <3; PASI <1	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
	PASI change from baseline, percent improvement from baseline	MMRM; mBOCF ANCOVA	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		MMRM	Maintenance Period Efficacy Population	All visits in Maintenance Period
		Summary statistics (As observed) or individual trajectory line plot if total number of subjects is too small	Rescue Period Efficacy Population	All visits in Rescue Period
	Time to first loss of response (PASI 90, PASI 100) for PRN subjects	KM product limit curve; time to loss of response	Maintenance Period Efficacy Population	Maintenance Period

Measure	Variable	Analysis Method (Sections 6.1.3)	Population (Section 6.1.1)	Time Point
	Time to recapture of response (PASI 90, PASI 100) after first loss of response for PRN subjects	KM product limit curve; time to response recapture after first loss of response	Maintenance Period Efficacy Population	Maintenance Period
	Time to recapture of response (PASI 50, PASI 90) after loss of response for rescued subjects	KM product limit curve; time to response recapture after first loss of response	Rescue Period Efficacy Population	Rescue Period
sPGA	sPGA (0,1); sPGA (0)	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		Summary statistics with NRI	Maintenance Period Efficacy Population	All visits in Maintenance Period
		Summary statistics (As observed) or individual trajectory line plot if total number of subjects is too small	Rescue Period Efficacy Population	All visits in Rescue Period
BSA	BSA change from baseline	MMRM; mBOCF ANCOVA	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		MMRM	Maintenance Period Efficacy Population	All visits in Maintenance Period
PSSI	PSSI percent improvement from baseline (for subjects with scalp psoriasis involvement only); PSSI score (for all subjects)	MMRM; mBOCF ANCOVA	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		MMRM	Maintenance Period Efficacy Population	All visits in Maintenance Period
	PSSI score = 0 (for all subjects)	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		Summary statistics with NRI	Maintenance Period Efficacy Population	All visits in Maintenance Period

Measure	Variable	Analysis Method (Sections 6.1.3)	Population (Section 6.1.1)	Time Point
DLQI	DLQI (0,1), DLQI (0)	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		Summary statistics with NRI	Maintenance Period Efficacy Population	All visits in Maintenance Period
	DLQI total score and domain scores change from baseline	MMRM;	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		ANCOVA	Maintenance Period Efficacy Population	All visits in Maintenance Period
SF-36	SF-36 change from baseline for Domain Scores and Component Scores	ANCOVA	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		ANCOVA	Maintenance Period Efficacy Population	All visits in Maintenance Period
	SF-36 Physical Component (PCS) and Mental Component (MCS) Response	Logistic regression analysis with NRI	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		Summary statistics with NRI	Maintenance Period Efficacy Population	All visits in Maintenance Period
PatGA	Change from baseline	MMRM	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		ANCOVA	Maintenance Period Efficacy Population	All visits in Maintenance Period
PSS	PSS total score and item scores change from baseline	MMRM; mBOCF ANCOVA	ITT Population	All pairwise comparisons against placebo at all postbaseline visits in Induction Period
		ANCOVA	Maintenance Period Efficacy Population	All visits in Maintenance Period

Measure	Variable	Analysis Method (Sections 6.1.3)	Population (Section 6.1.1)	Time Point
		Summary statistics (As observed) or individual trajectory line plot if total number of subjects is too small	Rescue Period Efficacy Population	All visits in Rescue Period

Abbreviations: ANCOVA = analysis of covariance; BSA = body surface area; DLQI = Global Assessment Dermatology Life Quality Index; ITT = intent-to-treat; KM = Kaplan-Meier; mBOCF = modified baseline observation carried forward; MCS = Mental Component Score; MMRM = mixed model repeating measures; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PatGA = Patients Global Assessment of Psoriasis; PCS = Physical Component Score; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; sPGA = Static Physician Global Assessment.

6.9.1. Primary Outcome and Methodology

Primary outcome Psoriasis Area and Severity Index (PASI) 90 and its analysis are described in Table 6.2 and Table 6.3.

6.9.2. Secondary Efficacy Analyses

Analyses of PASI and Static Physician Global Assessment (sPGA) secondary outcomes are described in Table 6.2 and Table 6.3.

6.9.3. Exploratory Analyses

Analyses of body surface area (BSA) and Psoriasis Scalp Severity Index (PSSI) exploratory outcomes are described in Table 6.2 and Table 6.3.

The Kaplan-Meier product limit method will be used to estimate the survival curves for the Maintenance and Rescue Period time-to-event variables (time to loss of response for subjects in as needed (PRN) arm, time to response recapture after loss of response for subjects who lost response in PRN arm). Time to event analyses will be summarized by PRN treatment arms.

Summary of PRN doses, including total number of PRN doses given and week of first PRN dose given after loss of response, will be summarized by PRN treatment arms.

6.10. Health Outcomes/Quality-of-Life Analyses

Analyses of Psoriasis Symptoms Scales (PSS), Global Assessment Dermatology Life Quality Index (DLQI), Patients Global Assessment of Psoriasis (PatGA), and SF-36 health outcomes are described in Table 6.2 and Table 6.3.

6.11. Pharmacokinetic/Pharmacodynamic Methods

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

6.12. Safety Analyses

All safety evaluations will be based upon the Safety Population as defined in Section 6.1.1.

Safety and tolerability will be evaluated in terms of adverse events (AEs), treatment-emergent AEs (TEAEs), discontinuations due to AEs, deaths, other SAEs, permanent discontinuations and interruptions of study drug, laboratory analyses including neutrophil counts and immunogenicity, Columbia Suicide Severity Rating Scale (C-SSRS), vital signs, echocardiogram (ECG) findings, and concomitant medications.

The Induction Period safety analyses will summarize each LY3074828 dose regimen (300 mg, 100 mg, and 30 mg) and compare the pooled LY3074828 dose regimens to placebo. Treatment group comparisons will be analyzed using the methods described in Section 6.1.3.

For the Maintenance Period, safety will be summarized by treatment (each PRN arm and 300 mg Q8W). No comparisons will be conducted. Only events occurred in the Maintenance Period will be included in this analysis, that is, no events in the Rescue Period will be included. Only a

smaller set of safety analyses (for example, TEAE, serious adverse events (SAE), AE leading to study treatment discontinuation, TE high/low labs, TE high/low vitals) will be needed for the Maintenance Period.

In addition, an overall summary of safety for all LY3074828 exposed subjects, will be provided by presenting all LY3074528 arms pooled including the Induction, Maintenance, and Rescue Periods; Follow-Up Period separately (if there are meaningful number of subjects); and All Periods + Follow-up Period. Only a smaller set of safety analyses (for example, TEAE, SAE, AE leading to study treatment discontinuation, TE high/low labs, TE high/low vitals) will be needed for the overall safety summary.

Safety event occurring on the same day of the end of a period and the start of next period will be counted towards the next period, for example, if a safety event occurred on the date of PASI measurement at Week 16, the event will be allocated to the Maintenance Period.

Change from baseline analyses will use baseline definition provided in Section 6.1.2.

6.12.1. Extent of Exposure

6.12.1.1. Duration of Exposure

Duration of exposure to study treatment (defined as time since first injection of study treatment in days) will be summarized by treatment group during the Induction Period, the Maintenance Period, and the combined Induction Period, Maintenance Period, and Rescue Period.

Duration of exposure during the Induction Period will be calculated as:

(Date of last study visit in the Induction Period– Date of first injection of study treatment + 1)

Duration of exposure during the Maintenance Period will be calculated as:

(Date of last study visit in Maintenance Period- Date of last study visit in the Induction Period+1)

Duration of exposure during the Rescue Period will be calculated as:

(Date of last study visit in Rescue Period- Date of First Rescue Treatment+1)

Duration of exposure to LY3074828 for the combined Induction Period, Maintenance Period, and Rescue Period will be calculated as:

(Date of last study visit in the Maintenance Period – Date of first injection of LY3074828 + 1) for subjects without rescue and

(Date of last study visit in the Rescue Period– Date of first injection of LY3074828 + 1) for subjects with rescue

For the combined Induction Period, Maintenance Period, and Rescue Period summaries, exposure will be summarized for all LY3074828 dosing regimens pooled.

Descriptive statistics will be provided for patient days of exposure and the frequency of patients falling into the following different exposure ranges (that is, only the exposure ranges that fall within the treatment period will be presented) will be summarized:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, ≥120 days, ≥183 days, ≥365 days, ≥548 days.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <183 days, ≥183 to <365 days, ≥365 days to <548 days, and ≥548 days.

Additional exposure ranges may be considered if necessary.

A by-patient listing of exposure duration will be provided.

No inferential analysis for comparison between treatment arms will be performed.

6.12.1.2. Total Dose of active study treatment

The total number of active injections of LY3074828 will be summarized by LY3074828 treatment group.

Mean and median total dose will be reported for all the treatment groups.

Total dose of active study treatment during the Induction Period, the Maintenance Period, and the combined Induction Period, Maintenance Period, and Rescue Period will be summarized by active treatment group using descriptive statistics. The total dose (mg) will be calculated as:

Total Dose =
Sum over all injections received of [dose of LY3074828 (mg) prescribed per injection]

The injections received during the treatment periods will be identified using the response to the question "Was study drug administered to patient?" on the Study administration eCRF page. The total dose of LY3074828 will then be calculated for each treatment group based on the injection schedule in the study protocol.

No inferential analysis for comparison between treatment arms will be performed.

6.12.2. Adverse Events

Adverse events will be classified based upon the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be recorded at every study visit. Conditions starting on or after the date of informed consent will be considered an AE. Preexisting conditions which worsens in severity on or after the date of informed consent will be considered and recorded as an AE on the AE electronic case report form (eCRF) page from the date of worsening onwards.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline as defined in Section 6.1.2. Both the date/time of the event and the date/time of the dose (that is, injection) are considered when determining TEAEs. TEAE will be assigned to the study period to which it's considered treatment-emergent:

- The MedDRA lowest level term (LLT) will be used when classifying AEs as treatment-emergent.
- The maximum severity recorded for each LLT prior to the first dose date/time in the Induction Period will be used as the pretreatment severity for that LLT. If an event during the baseline period has missing severity, and the event persists during the treatment period, then it will be considered as treatment-emergent, regardless of the postbaseline level of severity. Events with a missing severity during the treatment period will be considered treatment-emergent.
- AEs with a particular LLT will be classified as treatment-emergent if they first start on or after the first dose date/time in the treatment period (that is, a patient has no preexisting conditions with that lowest level term), or if the severity is greater than the pretreatment severity for that lowest level term. If a partial AE start date/time is present, the date/time will be compared as far as possible to the treatment start date/time in order to determine whether the event is treatment-emergent or not. If there is any doubt, the event will be flagged as treatment-emergent.

A follow-up emergent adverse event is defined as an event that first occurred or worsened in severity after the date of Visit 29 or early termination visit (ETV):

- The MedDRA LLT will be used when classifying AEs as follow-up emergent.
- For AEs that are ongoing at the date of Visit 29 or ETV, the maximum severity recorded for each LLT on or prior to the date of Visit 29 or ETV will be used as the follow-up baseline severity for that LLT.
- If a partial AE start date is present, the date will be compared as far as possible to the date of Visit 29 or ETV in order to determine whether the event is follow-up emergent or not. If there is any doubt, the event will be flagged as follow-up emergent, unless the same event was already counted as treatment-emergent during the Induction Period.

Adverse events and TEAEs will be summarized and analyzed for the safety population for the Induction Period. Treatment comparisons between all Induction Period LY3074828 dose regimens (300 mg, 100 mg, 30 mg) combined and placebo will be conducted using Fisher's exact test. Resulting p-values will be used to help identify potential adverse drug reactions. Significant p-values will need to be interpreted with caution due to the fact that multiplicity is not controlled in this study.

Maintenance Period adverse events and TEAEs will be summarized by treatment. Follow-up emergent adverse events and TEAEs during the Rescue Period will be summarized in the All Periods safety analyses.

Additionally,

- An overall summary of AEs including the number and percentage of patients who experienced TEAE, TEAE by maximum severity, death, SAE, discontinuations from the treatment due to an AE, and TEAEs of special interest.
- TEAE by system organ class (SOC) and PT.
- TEAEs related to study treatment by SOC and PT
- TEAE by maximum severity, SOC, and PT.

If a safety event occurred on the same date of the last date of Induction and the first date of the Maintenance Period, the event will be allocated to the Maintenance Period only.

If a safety event occurred on the same date of the last date of Maintenance and the first date of Rescue, compare the event onset time with rescue dose time to allocate the event to the Maintenance Period or Rescue Period accordingly; if either time is missing, the event will be allocated to the Rescue Period only.

If a safety event occurred on the same date of the last date of Maintenance or Rescue and the first date of the Follow-up Period, the event will be allocated to the previous period (Maintenance or Rescue) only.

In general, for all AE related summaries, the number and percentage of patients experiencing the events will be presented by dosing regimen. The events will be ordered by decreasing frequency in the total LY3074828 group, followed in the order of 300 mg, 100 mg, 30 mg, within SOC and/or PT for sorting. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender.

A by-patient listing of all AEs will be provided.

6.12.2.1. Common Adverse Events

The percentages of patients with TEAEs will be summarized by treatment using MedDRA Preferred Term for the common TEAEs (occurred in ≥5% before rounding of treated patients). Events will be ordered by decreasing frequency within System Organ Class.

The percentages of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA Preferred Term nested within System Organ Class for the common TEAEs. For each subject and TEAE, the maximum severity for the MedDRA level being displayed (Preferred Term, High Level Term, or System Organ Class) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level. These summary tables will be provided for the Induction Period.

In the event differential dropout rates are seen or to further investigate events of interest, summary tables comparing exposure-adjusted incidence rate (that is, person-time-adjusted incidence rates) over the entire time period will be generated for the Induction and Maintenance Periods.

6.12.2.2. Hypersensitivity, Immediate and Non-Immediate

Two main analyses are performed in support of assessment of potential immediate hypersensitivity, including anaphylaxis, and well as potential non-immediate hypersensitivity. These analyses will be conducted for the Summaries of Clinical Safety for the Induction and Maintenance Periods.

Time Period A, of potential immediate hypersensitivity, includes all TEAEs occurring on the day of study drug administration.

Time Period B, of potential non-immediate hypersensitivity, includes all TEAEs occurring strictly after the day of study drug administration (but prior to subsequent drug administration).

Analyses for both time periods use the current standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) to search for relevant events. TEAEs are characterized as follows:

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per MSSO SMQ guide, and broad). Algorithm terms apply only for Time Period A.
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad).

The number and percentage of patients who experienced a TEAE for the following will be analyzed for each of the 2 time periods:

- Any narrow or algorithmic term from any 1 of the 3 SMQs indicated above (that is, combined search across narrow and algorithmic portions of all 3 SMQs). Algorithm terms apply only for Time Period A.
- Any narrow scope term within each SMQ, separately (that is, narrow SMQ search)
- Any term within each SMQ, separately (that is, broad SMQ search).

Within query, individual PTs that satisfy the queries will be summarized.

The Anaphylactic reaction SMQ algorithm will be run only for Time Period A. The SMQ defines a category (A, B, C, D) for each SMQ PT. All Narrow terms have category A, and the occurrence of a Narrow term satisfies the algorithm. Additionally, a pair of PTs *from the same drug administration* satisfies the algorithm if the 2 events are from different categories (that is, B&C, or B&D, or C&D). Both contributing events must begin within Time Period A. Tables will summarize (the number of patients experiencing) each PT that contributes to such an algorithmic pair, and include such terms in the combined narrow and algorithmic search. Broad events that do not contribute to the algorithm will be summarized in a distinct portion of the table.

For Time Period A only, the number and percentage of each PT that is not in any of the 3 SMQs will be summarized overall and by individual PT. Only PTs that occur in at least 3 patients receiving LY3074828 will be displayed in this portion of the table.

The PT and LLT are listed for summary in decreasing order of incidence for LY-treated patients. Note that an individual patient may contribute multiple events. Also, a single event may satisfy multiple SMQ, in which case the event contributes to every applicable SMQ.

6.12.2.3. Injection Site Reactions

A summary will be provided for the Induction and Maintenance Periods, by treatment group, of the number of patients with reported events that map to any 1 of the following:

- MedDRA High Level Term (HLT) of Injection site reaction
- HLT of Administration site reaction.

The number and percentage of patients who experienced a TEAE for the following will be analyzed:

- Any term from either of the HLTs indicated above (that is, a combined query of these HLTs)
- Any term within each HLT separately.

Within HLT, individual PTs that satisfy the queries will be summarized.

The PT will be listed for summary with each category in decreasing order of incidence for LY-treated patients.

Injection site reactions occurring during the Rescue Period will be listed.

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

The number and percentage of patients who experienced a serious adverse event during the treatment period will be summarized by treatment using MedDRA Preferred Term nested within System Organ Class. Events will be ordered by decreasing frequency within System Organ Class.

These summary tables will be generated for the Induction and Maintenance Periods and for All Periods.

In the event differential dropout rates are seen or to further investigate serious events of interest, summary tables comparing exposure-adjusted incidence rate (that is, person-time-adjusted incidence rates) over the entire time period will be generated for the Induction and Maintenance Periods.

A listing of deaths will be provided. All deaths will be included, regardless of the Investigator's or the Sponsor's judgment about causality, including (1) any deaths occurring during participation of the study, (2) any deaths occurring after a patient leaves (that is, discontinued from the study or completes the study if the death is the result of a process initiated during the study, regardless of when it actually occurs. Each listing will include investigator ID, patient ID, treatment group, baseline age, sex, associated AE, whether or not the death and Lilly's assessment of whether the process leading to death (NOT the death itself) began:

a) "On study": during study or within the 24-hour day after date of discontinuation or completion.

b) "Shortly after study": from the end of the time period in a) to 4 weeks after date of discontinuation or completion or

c) "Long after study": more than 4 weeks (or longer, as specified in b) after the date of discontinuation or completion.

6.12.4. Clinical Laboratory Evaluation

Laboratory evaluations will be summarized and analyzed for the Induction Period only except where noted.

Laboratory tests include all planned analytes as defined in the protocol, excluding those collected in a reflex manner (only collected under certain circumstances).

Values at each visit (starting at randomization) and change from baseline to each visit for laboratory tests will be displayed in box plots (notched box for each treatment with outliers displayed) for patients who have both a baseline and a result for the specified visit. Individual measurements outside of reference limits will also be displayed using distinct symbols overlaying the box plot. Baseline will be the last non-missing observation in the baseline period. Original-scale data will be used for the display. Unplanned measurements will be excluded. Displays using both SI and U.S. conventional units will be provided (when different). The following summary statistics will be included in a table below the box plot: N, mean, standard deviation, minimum, Q1, median, Q3, and maximum. P-values and confidence limits will not be included in the summary statistics at the bottom of the box plot. Box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

Change from baseline to last observation will also be summarized within the box plot of changes (rightmost column) for patients who have both baseline and at least 1 postbaseline result. Baseline will be the last nonmissing observation in the baseline period. The last nonmissing observation in the treatment period will be used as the last observation. Original-scale data will be used. Unplanned measurements will be excluded.

For quantitative laboratory analyte measurements, 3-panel displays that include a scatterplot, a shift table, and a shift to high/low table will be created. Specifically, for each measurement, both a 3-panel display assessing low values and a 3-panel display assessing high values will be created.

In the 3-panel display to assess low values, the scatterplot will plot the minimum value during the baseline period versus the minimum value during the treatment period. Lines indicating the reference limits are included. In cases where limits vary across demographic characteristics, lines indicating the most common limit will be displayed. The shift table will include the number and percentage of patients within each baseline category (minimum value is low, normal, high, or missing) versus each treatment category (minimum value is low, normal, or high) by treatment. Patients with at least 1 result in the treatment period will be included in the

shift table. The shift from normal/high to low table will include the number and percentage of patients by treatment whose minimum baseline result is normal or high and whose minimum treatment result is low. Patients whose minimum baseline result is normal or high and have at least 1 result during the treatment period are included. The Fisher's exact test will be used to compare percentages of patients who shift from normal/high to low between treatments.

The 3-panel display to assess high values will be created similarly. The scatterplot will plot the maximum value during the baseline period versus the maximum value during the treatment period. The shift table will include the number and percentage of patients within each baseline category (maximum value is low, normal, high, or missing) versus each treatment category (maximum value is low, normal, or high) by treatment. The shift from normal/low to high table will include the number and percentage of patients by treatment whose maximum baseline result is normal or low and whose maximum treatment result is high. Patients whose maximum baseline result is normal or low and have at least 1 result during the treatment period are included. The Fisher's exact test will be used to compare percentages of patients who shift from normal/low to high between treatments.

The low/high displays will be created for the Maintenance Period as well, but no statistical comparisons are planned and only summaries will be produced.

For laboratory analyte measurements collected qualitatively, a listing of abnormal findings will be created. The listing will include patient ID, treatment group, laboratory collection date, analyte name, and analyte finding.

6.12.4.1. Hepatic Laboratory Examinations

Analyses for change from baseline to last observation, change from the minimum value during the baseline period to the minimum value during the treatment period, change from the maximum value during the baseline period to the maximum value during the treatment period, and treatment-emergent high or low laboratory results at any time are described in Section 6.12.4. This section describes additional analyses for the topic.

The percentages of patients with the following elevations in hepatic laboratory tests at any time will be summarized between treatment groups:

- The percentages of with a alanine aminotransferase (ALT) 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 will be summarized for all patients with a postbaseline value and for subsets based on various levels of baseline.
    - The analysis of 3X ULN will contain 4 subsets:
        - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
        - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,

        - patients whose maximum baseline value is greater than or equal 3X ULN, and
        - patients whose baseline values are missing.
    - The analysis of 5X ULN will be contain 5 subsets:
        - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
        - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,
        - patients whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN,
        - patients whose maximum baseline value is greater than or equal to 5X ULN, and
        - patients whose baseline values are missing.
    - The analysis of 10X ULN will contain 6 subsets:
        - patients whose non-missing maximum baseline value is less than or equal to 1X ULN,
        - patients whose maximum baseline is greater than 1X ULN but less than 3X ULN,
        - patients whose maximum baseline is greater than or equal to 3X ULN but less than 5X ULN,
        - patients whose maximum baseline is greater than or equal to 5X ULN but less than 10X ULN,
        - patients whose maximum baseline value is greater than or equal to 10X ULN, and
        - patients whose baseline values are missing.
- The percentages of patients with an AST 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 will be summarized for all patients with a postbaseline value and for subsets based on various levels of baseline. Analyses will be constructed as described above for ALT.
- The percentages of patients with a total bilirubin measurement greater than or equal to 2 times (2X) the Covance upper limit of normal (ULN) during the treatment period will be summarized for all patients with a postbaseline value, and subset into 4 subsets:
    - patients whose nonmissing maximum baseline value is less than or equal to 1X ULN,

- patients whose maximum baseline is greater than 1X ULN but less than 2X ULN,
- patients whose maximum baseline value is greater than or equal to 2X ULN, and
- patients whose baseline values are missing.

Maximum baseline will be the maximum nonmissing observation in the baseline period. The maximum value will be the maximum nonmissing value from the treatment period. Planned and unplanned measurements will be included.

In addition, the percentages of patients with treatment-emergent potentially drug-related hepatic disorders will be summarized by treatment by using the MedDRA preferred terms contained in any of the following SMQs:

- Broad and narrow terms in the Liver related investigations, signs and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015).

The percentage of patients with any 1 of the terms will be summarized in addition to the percentages for each MedDRA preferred term. The percentages of patients with potentially drug-related hepatic disorders that led to study medication discontinuation will be summarized similarly.

Individual graphic patient profiles will be prepared for patients with an ALT or AST measurement greater than or equal to 5X ULN or with an alkaline phosphatase measurement greater than or equal to 2X ULN. The graphical profile will be created for any patient meeting the criteria from the safety population (any phase, any medication) The graphical patient profile will include demographics, disposition, and a display of study drug exposure, adverse events, medications, and the liver-related measurements over time. The review for these patients includes an assessment of the proximity of any ALT or AST elevation to any total bilirubin elevation, alkaline phosphatase levels, gamma-glutamyl transpeptidase (GGT) levels, other potential causes, and the temporal association with events such as nausea, vomiting, anorexia, abdominal pain, or fatigue.

6.12.5. Vital Signs and Other Physical Characteristics

Vital signs include systolic blood pressure, diastolic blood pressure, pulse, and temperature. Physical characteristics include weight and body mass index (BMI).

Vital signs and physical characteristics will be summarized and analyzed for the Induction Period only, except where noted.

Other periods may be summarized if appropriate.

Vital sign and physical characteristic results will be provided in a by-patient listing.

BMI will be calculated using the following formula:

BMI (kg/m2) = weight (kg) divided by the square of the height (m).

Values at each visit (starting at randomization) and change from baseline to each visit for vital signs and physical characteristics will be displayed in box plots (notched box for each treatment with outliers displayed) for patients who have both a baseline and a result for the specified visit. Individual measurements outside of reference limits will also be displayed using distinct symbols overlaying the box plot. Baseline will be the last nonmissing observation in the baseline period. Original-scale data will be used for the display. Unplanned measurements will be excluded. The following summary statistics will be included in a table below the box plot: N, mean, standard deviation, minimum, Q1, median, Q3, and maximum. P-values and confidence limits will not be included in the summary statistics at the bottom of the box plot. Box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

Change from baseline to last observation will also be summarized within the box plot of changes (rightmost column) for patients who have both baseline and at least 1 postbaseline result. Baseline will be the last nonmissing observation in the baseline period. The last nonmissing observation in the treatment period will be used as the last observation. Original-scale data will be used. Unplanned measurements will be excluded. No statistical comparisons are planned and only summaries will be produced.

The percentages of patients with treatment-emergent high or low vital signs and physical characteristics results at any time will be summarized. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time that meets the specified change criteria during the treatment period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time that meets the specified change criteria during the treatment period. To assess increases, change from the maximum value during the baseline period to the maximum value during the treatment period will be used. To assess decreases, change from the minimum value during the baseline period to the minimum value during the treatment period will be used. Table 6.4 will be used to define the low and high limits and change thresholds. The low/high displays will be created for the Maintenance Period as well, but no statistical comparisons are planned and only summaries will be produced.

Additionally, values at each visit (starting at randomization) and change from baseline to each visit for vital signs and physical characteristics will be displayed in box plots (with outliers displayed) for patients who have both a baseline and a result for the specified visit. Baseline will

be the last non-missing observation in the baseline period. Original-scale data will be used for the display. Unplanned measurements will be excluded. Reference limits will not be displayed. The following summary statistics will be included in a table below the box plot: N, mean, standard deviation, minimum, Q1, median, Q3, and maximum. P-values and confidence limits will not be included in the summary statistics at the bottom of the box plot. Box plots will be used to evaluate trends over time and to assess a potential impact of outliers on central tendency summaries.

Table 6.4. Categorical Criteria for Abnormal Treatment-Emergent Blood Pressure and Pulse Measurement, and Categorical Criteria for Weight and Temperature Changes for Adults

Parameter	Low mmHg	High mmHg
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15
Weight (kg) (Consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease ≥7%	(Gain) increase ≥7%
Temperature	<96 degrees F and decrease ≥2 degrees F	≥101 degrees F and increase ≥2 degrees F

Abbreviations: BP = blood pressure; bpm = beats per minute

6.12.6. Electrocardiograms

Electrocardiogram results will be provided in a by-patient listing.

Complete ECG data will not be part of the clinical database for this study. According to protocol instructions, clinically significant ECG measurements as determined by the investigator should be reported and recorded as an AE. ECG data will not be analyzed.

6.12.7. C-SSRS

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the C-SSRS, will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (that is, if a patient answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point then all their ideation and behavior will be displayed, even if not positive.

6.13. Immunogenicity

Figure 6.1 provides an overview of the immunogenicity assay process.

At a high level, an individual sample is potentially examined multiple times in a hierarchical procedure to produce a sample Anti-Drug Antibodies (ADA) assay result and potentially a sample neutralizing antibody (NAb) assay result. The cut points used, the drug tolerance of an assay, and the possible values of titers are operating characteristics of the assay.

It can be the case that the presence of high concentrations of LY will affect the measurements of the presence of ADA or NAb, and conversely high levels of ADA or NAb may affect the measurement of LY concentration. Thus an LY drug concentration, assessed from a sample drawn at the same time as the ADA sample, plays a key role in clinical interpretation of a sample when the laboratory result is Not Detected, as shown in Figure 6.1.

The rest of this section defines the component concepts of Figure 6.1 in greater detail.

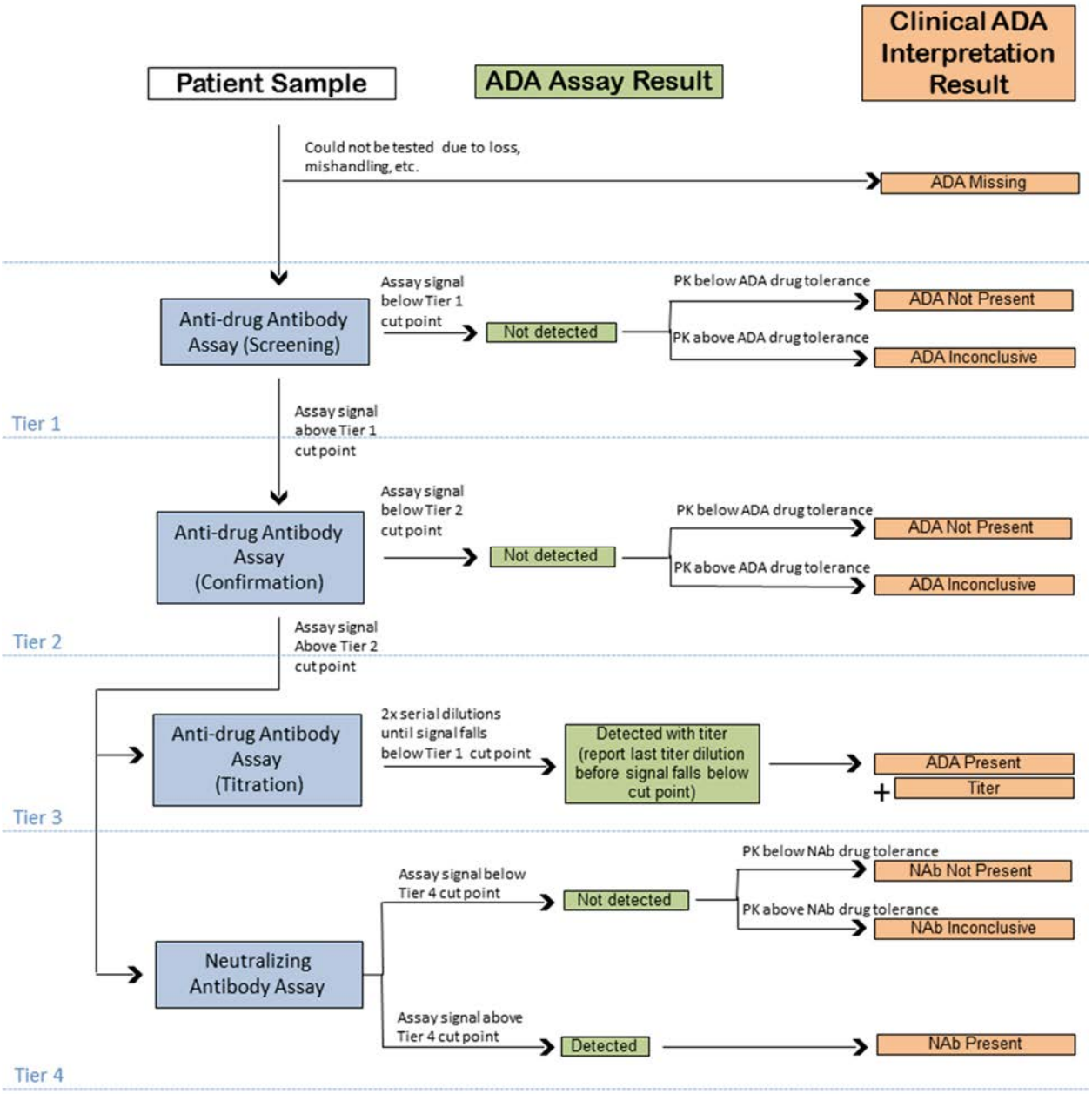


Figure 6.1. Flow chart of ADA sample assessment with clinical interpretation.

6.13.1. Definitions of Sample ADA Status

Table 6.5. Sample ADA Assay Results

Sample Laboratory Result	Explanation
Detected	ADA are detected and confirmed.
Not Detected	The raw result as reported from the laboratory indicates not detected. The clinical interpretation of such results depends on other factors (see below).
NO TEST, QNS, etc.	Sample exists but was unevaluable by the assay

Abbreviations: ADA = anti-drug antibodies; QNS = quantity not sufficient

Table 6.6. Sample Clinical ADA Interpretation Results

Sample Clinical Interpretation	Explanation
ADA Present	ADA assay result is Detected
ADA Not Present	ADA assay result is Not Detected and simultaneous drug concentration is at a level that has been demonstrated to not interfere in the ADA detection method (that is, drug concentration is below the assay's drug tolerance level). For patients receiving placebo, drug concentration is not assessed and is assumed to be below the assay's drug tolerance level. If drug concentration was planned but is not available for a treatment-period sample, a Not Detected sample will be declared ADA Not Present, on the basis of prior knowledge that the drug tolerance level of the ADA assay is high relative to peak PK levels.
ADA Inconclusive	ADA assay result is Not Detected but drug concentration in the sample is at a level that can cause interference in the ADA detection method, or drug concentration is planned per protocol but is not available.
ADA Missing	ADA sample not drawn, QNS, not tested, etc., causing there to be no laboratory result reported or the result is reported as "no test".

Abbreviations: ADA = anti-drug antibodies; PK = pharmacokinetic; QNS = quantity not sufficient.

Parallel terminology applies for NAb Detected, NAb Not Detected, NAb Present, NAb Not Present, NAb Inconclusive, and NAb Missing. ADA and NAb are distinct assays and have different assay operating characteristics.

6.13.2. Definitions of Immunogenicity Assessment Periods

Immunogenicity Baseline Observations: Baseline period for immunogenicity assessment for each patient includes all observations on or prior to the date of the first administration of study drug. In instances where multiple baseline observations are collected, to determine patient ADA status, the last non-missing immunogenicity assessment prior to first administration of study drug is used to determine ADA treatment-emergent status (see below). In this context, 'missing' includes explicit 'ADA Missing' results, as defined in Table 6.6.

Immunogenicity Postbaseline Period Observations: Postbaseline period observations for each patient include all observations after the first administration of study drug.

6.13.3. Definitions of Patient ADA Status

Patient evaluable for treatment-emergent ADA: A patient is evaluable for treatment-emergent ADA if the patient has a non-missing baseline ADA result, and at least 1 non-missing postbaseline ADA result.

Treatment-emergent ADA positive (TE ADA+) patient: A patient who is evaluable for treatment-emergent ADA is TE ADA+ if either of the following holds:

a. The patient has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer $\geq 2 *$ MRD, where the MRD is the minimum required dilution of the ADA assay.
b. The patient has baseline and postbaseline status of ADA Present, with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer. That is, the patient has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P, with P/B ≥ 4.

Treatment-emergent ADA Inconclusive patient: A patient who is evaluable for TE ADA is TE ADA Inconclusive if $\geq 20\%$ of the patient's postbaseline samples, drawn predose, are ADA Inconclusive and all remaining postbaseline samples are ADA Not Present.

Treatment-emergent ADA negative (TE ADA-) patient: A patient who is evaluable for TE ADA is TE ADA- when the patient is not TE ADA+ and the patient is not TE ADA Inconclusive.

6.13.4. Analyses to be Performed

A listing will be provided of all immunogenicity assessments for those patients who at any time had ADA Present. This includes the laboratory ADA assay result (Detected or Not Detected), LY concentration from a simultaneous PK sample, and the clinical interpretation result that combines these (ADA present, ADA Not Present, ADA Inconclusive, Missing). When Detected, a titer will be included, and TE ADA+ observations will be flagged. Also included will be the laboratory NAb assay result (Detected or Not Detected) and the NAb clinical interpretation result (NAb Present, NAb Not Present, NAb Inconclusive, Missing) when the NAb assay was performed (see Table 6.5).

For the remainder of this section, "ADA result" will refer to the clinical interpretation result. "NAb result" will be handled similarly.

The number and proportion of patients who are TE ADA+ will be tabulated by treatment group, where proportions are relative to the number of patients who are TE ADA evaluable, as defined above. The tabulation will include all postbaseline observations, the number and proportion of patients with ADA Present at baseline, and the number and proportion of TE ADA+ patients exhibiting NAb+.

For each TE ADA+ patient, a plot will be constructed of titer values from individual samples over time. Samples that are ADA Not Present are ADA Inconclusive will also be indicated.

A summary will be provided of the number and percentage of LY-treated patients experiencing specific TEAEs (see Table 6.7) by patient TE ADA status (TE ADA+, TE ADA-, TE ADA Inconclusive). The PT will be ordered by decreasing incidence in TE ADA+ status group. For event terms not occurring in any TE ADA+ or TE ADA Inconclusive patient, a summary will be provided of the number of distinct terms reported, but individual PTs will not be summarized.

A listing will be provided of all TEAEs alongside ADA data, for any patient who had ADA Present at any time (including baseline) or had any specific TEAE (see Table 6.7). This listing includes a time course of ADA (clinical interpretation result plus flags for samples meeting TE ADA+ criteria and for NAb+ samples) along with the TEAE.

Table 6.7. TEAE for Analysis with ADA / NAb Results

Events satisfying Anaphylaxis SMQ (narrow or broad)
Events satisfying Hypersensitivity SMQ (narrow or broad)
Events satisfying Angioedema SMQ (narrow or broad)
Events mapping to High Level Term (HLT) of Injection site reaction
Events mapping to High Level Term (HLT) of Administration site reaction

Abbreviations: ADA = anti-drug antibody; HLT = high level term; NAb = neutralizing antibody; SMQ = standardized Medical Dictionary for Regulatory Activities (MedDRA) query.

6.14. Histopathology

Biopsies will not be summarized for this study.

6.15. Subgroup Analyses

The following subgroups will be analyzed:

- Demographic subgroups:
  - Gender: M, F
  - Age group: <65 years, ≥65 years
  - Weight category:
  - <80 kg, ≥80 kg
  - <100 kg, ≥100 kg
  - Body mass index (BMI) category: 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)
- Geographic region subgroups: United States (US); Other (Non-US): Canada, Germany, Japan, Poland
- Baseline severity subgroups:
  - Baseline sPGA category: 3, 4, 5
  - Baseline sPGA category: 3, combined 4 or 5

  - Baseline PASI category: <20, ≥20
  - Baseline BSA category: <20%, ≥20%
- Previous psoriasis therapy subgroups:
  - Previous systemic therapy: never used, non-biologic only, biologic only, biologic and non-biologic.
  - Previous non-biologic systemic therapy: never used, ever used
  - Previous biologic therapy: never used, ever used
  - Where
    - Non-biologics include: methotrexate, cyclosporine, retinoids, corticosteroids, acitretin, fumaric acid derivatives, apremilast, PUVA, other
    - Biologics include: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, secukinumab, ixekizumab, other
- Concomitant topical steroid product use: yes, no.

6.15.1. Efficacy Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint of proportion of patients achieving a PASI 90 at Week 16 (NRI) using the ITT population for the Induction Period. Subgroup analyses for the secondary efficacy endpoints, the proportion of patients achieving PASI 75, and PASI 100, will also be conducted at Week 16 (NRI) using the ITT population.

A logistic regression model with dosing regimen, subgroup, and the interaction of subgroup-by-dosing regimen, and previous biologic use (yes/no) included as factors will be used. The subgroup-by-dosing regimen interaction will be tested at the significance level of 0.10. Missing data will be imputed using NRI. If any treatment group within the subgroup has ≤5 subjects, only summaries of the efficacy data will be provided (that is, no inferential testing is planned).

Forest plots will be generated for efficacy subgroup analyses for pairwise comparisons between LY3074828 groups vs. placebo group.

6.15.2. Safety Subgroup Analyses

Safety subgroup analysis for common TEAEs may be summarized by treatment and overall, for the safety population during the Induction and Maintenance Periods.

6.16. Protocol Violations

Review of all major and minor protocol violations will be performed on an ongoing basis during the conduct of the study. All protocol exemptions/violations identified from the following sources will be tracked:

- During clinical monitoring visits

- During data validation process.

No patient will be excluded from the ITT population due to any protocol violations.

There is no Per-Protocol Population in this plan.

All protocol exemptions and violations that require medical review will be listed.

6.17. Interim Analyses and Data Monitoring

Two interim analyses will be conducted according to the specifications set forth in the protocol.

- Interim Analysis 1 (Primary Analysis): Once all patients complete the 16-week Induction Period or discontinue prior to Week 16
- Interim Analysis 2 (Post-Primary Interim Analysis): Once all patients on PRN dosing complete 16 weeks in the Maintenance Period or discontinue during the Maintenance Period.

This is a double-blind study during the Induction Period. Baseline dose cohort assignment will remain blinded throughout the study; however, during the Maintenance Period, dosing strategy (PRN or Q8W) will be open label. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

To minimize any bias being introduced into the analysis of the study results, the SAP and PK/PD analysis plan will be finalized and approved before the efficacy interim analysis begins. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

The interim analyses will be conducted for internal decision for future development. Interim analyses will not impact the current study design or implementation. The study may not be stopped for positive efficacy. Hence, there will be no alpha adjustment for the interim analysis.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will be continued throughout the study using blinded data. Reviewing details are specified in the TLSR plan or a separate document.

6.18. 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 adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).

- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE 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 subjects/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.

7. Unblinding Plan

This is a double-blind study during the Induction Period. Induction dose cohort assignment will remain blinded throughout the study; however, during the Maintenance Period, dosing strategy (PRN or Q8W) will be open label. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

To minimize any bias being introduced into the analysis of the study results, the SAP and PK/PD analysis plan will be finalized and approved before the Interim Analysis 1 (Primary Analysis) is implemented. A limited number of pre-identified individuals at Lilly may gain access to the unblinded data as part of the prespecified interim analysis (see Section 6.17 and the Study AMAF Blinding and Unblinding Plan). Information that may potentially unblind the study during the analyses will not be shared with study sites until the entire study has been unblinded.

A study blinding and unblinding plan will be finalized prior to first unblinded data transfer.

8. References

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Appendix 1. Simulation for Logistic Regression with Firth Correction

When PBO response rate is small and there are zero cell values, logistic regression will over estimate variance resulting in larger *p*-values and reduced power. Logistic regression with a Firth correction adjusts for small sample sizes and zero cell values. We used simulation to investigate a "two-step" approach. If there is

- "Small" number of PBO responders, then use logistic regression with Firth correction
- "Not Small" number of PBO responders, then use logistic regression without correction

LY Response Rate	Treatment Effect (LY-PBO)	Single Analysis Power		"Two-Step" Approach Power			
		Logistic Regression	**Logistic Regression w/ Firth Correction**	**≤1 PBO Responder**	**≤2 PBO Responder**	**≤3 PBO Responder**	**≤4 PBO Responder**
0.03	0.00	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
0.05	0.02	0.002	0.002	0.002	0.002	0.002	0.002
0.10	0.07	0.063	0.075	0.075	0.075	0.075	0.075
0.15	0.12	0.277	0.363	0.372	0.369	0.363	0.363
0.20	0.17	0.535	0.683	0.695	0.694	0.684	0.683
0.25	0.22	0.709	0.892	0.901	0.899	0.893	0.893
0.30	0.27	0.783	0.981	0.984	0.984	0.982	0.982
0.35	0.32	0.793	0.993	0.994	0.994	0.993	0.993
0.40	0.37	0.798	0.999	0.999	0.999	0.999	0.999
0.45	0.42	0.798	0.999	0.999	0.999	0.999	0.999
0.50	0.47	0.799	>0.999	>0.999	>0.999	>0.999	>0.999
0.55	0.52	0.799	>0.999	>0.999	>0.999	>0.999	>0.999
0.60	0.57	0.799	>0.999	>0.999	>0.999	>0.999	>0.999

Results showed that logistic regression with Firth correction increased the power by ~10% compared to the ones without Firth correction when the treatment difference is >7%. Therefore, it is suggested to apply Firth correction in the logistic regression models in Study AMAF.

Appendix 2. 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	-7	-1
Week 1	Max(Baseline Assessment Date, Week 2 Assessment Date – 14)	Week 2 Assessment Date - 8
Week 2	Max(Baseline Assessment Date, Week 2 Assessment Date – 7)	Week 2 Assessment Date - 1
Week 3	Max(Week 2 Assessment Date, Week 4 Assessment Date – 14)	Week 4 Assessment Date -8
Week 4	Max(Week 2 Assessment Date, Week 4 Assessment Date – 7)	Week 4 Assessment Date – 1
Week 5	Max(Week 4 Assessment Date, Week 8 Assessment Date – 28)	Week 8 Assessment Date -22
Week 6	Max(Week 4 Assessment Date, Week 8 Assessment Date – 21)	Week 8 Assessment Date -15
Week 7	Max(Week 4 Assessment Date, Week 8 Assessment Date – 14)	Week 8 Assessment Date -8
Week 8	Max(Week 4 Assessment Date, Week 8 Assessment Date – 7)	Week 8 Assessment Date – 1
Week 9	Max(Week 8 Assessment Date, Week 12 Assessment Date – 28)	Week 12 Assessment Date -22
Week 10	Max(Week 8 Assessment Date, Week 12 Assessment Date – 21)	Week 12 Assessment Date -15
Week 11	Max(Week 8 Assessment Date, Week 12 Assessment Date – 14)	Week 12 Assessment Date -8
Week 12	Max(Week 8 Assessment Date, Week 12 Assessment Date – 7)	Week 12 Assessment Date – 1
Week 13	Max(Week 12 Assessment Date, Week 16 Assessment Date – 28)	Week 16 Assessment Date -22
Week 14	Max(Week 12 Assessment Date, Week 16 Assessment Date – 21)	Week 16 Assessment Date -15
Week 15	Max(Week 12 Assessment Date, Week 16 Assessment Date – 14)	Week 16 Assessment Date -8
Week 16	Max(Week 12 Assessment Date, Week 16 Assessment Date – 7)	Week 16 Assessment Date – 1
Week 32	211	238
Week 52	351	378
Week 104	715	742

[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 range is at least 4 days and contains at least 4 daily entries, calculate the visit week assessment.

If more than 7 days is available between assessment dates, use only the last 7 days.

If multiple PSS assessments on a single day are present, use the latest assessment.

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