LYCERA

Statistical Analysis Plan (SAP)

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE EFFICACY AND SAFETY OF LYC-30937-EC IN SUBJECTS WITH MODERATE CHRONIC PLAQUE-TYPE PSORIASIS

Protocol LYC-30937-2003
SAP Version 1.0 (Final)

Statistical Analysis Plan Signature Page

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATP	adenosine triphosphate
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CFBL	change from baseline
CPK	creatine phosphokinase
CRF	case report form
CRO	Clinical Research Organization
EC	enteric coated
ECG	electrocardiogram
FAS	Full Analysis Set
FSH	follicle stimulating hormone
hCG	human chorionic gonadotropin
HBsAg	surface antigen of the hepatitis B virus
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	high sensitivity C-reactive protein
IGA	Investigator's Global Assessment
INR	international normalized ratio
LDL	low density lipoprotein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events

PASI	Psoriasis Area and Severity Index
PE	physical examination
PI	principal investigator
PK	pharmacokinetics
q.d.	*quaque die*, once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
RR	respiratory rate
SAP	statistical analysis plan
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO Drug	World Health Organization Drug dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan is to describe in detail the procedures and statistical methods required for completing the statistical analysis for Protocol LYC-30937-2003 dated 30 Aug 2016.

2 STUDY OVERVIEW

2.1 Study Design and Population

This is a phase 2a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety and tolerability of LYC-30937-EC treatment in subjects with chronic plaque-type psoriasis.

A total of approximately 30 subjects who meet the eligibility criteria will be randomized into the study at a 2:1 randomization ratio of LYC-30937-EC 25 mg or placebo daily.

After signing an informed consent, all eligible subjects will be followed for approximately 16 weeks. The screening visit will take place up to 2 weeks prior to randomization and subject's first dose of LYC-30937-EC (or matching placebo). Subjects will be randomized on the same day (Visit 2) and just prior to the subject's first dose of study drug, which will be taken while in the clinic under medical supervision. The treatment (LYC-30937-EC or placebo) will be administered orally once daily (q.d.) from Study Day 1 through the end of the double-blind treatment phase (Visit 6/Week 12) for a total of 84 days of treatment. A Follow-Up visit will be performed 2 weeks after the end of treatment phase (Week 14).

The assessments to be conducted at each scheduled visit are displayed in Appendix 1.

2.2 Study Drug Administration

The treatment (LYC-30937-EC or placebo) will be administered orally q.d. from Study Day 1 through the end of the double-blind treatment phase (Visit 6/Week 12) for a total of 84 days of treatment.

2.3 Efficacy Assessments

2.4 Psoriasis Area and Severity Index (PASI)

The PASI is an index widely used to express the severity of chronic plaque-type psoriasis through a quantitative rating score measuring the severity of psoriatic lesions based on area coverage and plaque appearance. This assessment will be done at Screening, Randomization, Week 4, Week 8, and Week 12.

The index combines the assessment of severity of the lesions (erythema, induration/thickness, and desquamation/scaling) and percentage of affected area into a single score. PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis (no disease), up to a theoretic maximum of 72.0 (maximal disease). The investigator is only responsible for collecting the components or scoring signs and total regional area. These components will be entered into the case report form eCRF where the PASI score will be calculated.

The final PASI is calculated in eCRF as follows:

- The subject's body is divided into 4 regions (head, upper extremities, trunk, and lower extremities). Each of these 4 regions is first scored by itself and then all 4 scores are combined into the final PASI.
- For each region, the percent of area of skin involved (0 to 100% body surface area [BSA]), is estimated using the palm (including fingers).
- The % BSA in each of the 4 body regions is then transformed into an area score from 0 (0%) to 6 (90-100%) for the PASI calculation.
- Within each of the 4 body regions, the severity of chronic plaque-type psoriasis is estimated by the evaluation of 3 clinical signs: erythema (redness), induration (thickness), and desquamation (scaling). Severity parameters are measured on a scale of 0 (none) to 4 (very severe).
- The sum of all 3 severity parameters within each region of skin is then multiplied by the area score for that region and multiplied by a different factor for each region (0.1 for head, 0.2 for upper extremities, 0.3 for trunk and 0.4 for lower extremities).
- The products from each of the regions are then added to get the final PASI

The PASI scoring system is described further in Appendix 2.

2.5 Total % Body Surface Area (% BSA)

The total % BSA affected by plaque-type psoriasis will be recorded on the eCRF by the investigator. This assessment will be done at Screening, Randomization, Week 4, Week 8, and Week 12.

2.6 Static Investigator's Global Assessment (static IGA)

The static IGA is used to measure psoriasis severity in clinical trials. The static IGA used in this trial will be a 6-point scale and will be evaluated at Screening, Randomization, Week 4, Week 8, and Week 12. The scoring is based on response to treatment measured by lesion erythema, induration, and scale. The static IGA scoring and descriptors are as follows:

Score	Short Descriptor	Detailed descriptor
0	Cleared	No plaque elevation, erythema or scaling; hyperpigmentation may be present
1	Minimal	Minimal plaque elevation (=0.25mm); faint erythema; minimal scaling, with occasional fine scale over < 5% of lesion
2	Mild	Mild plaque elevation (=0.5mm); light red coloration; fine scale predominates
3	Moderate	Moderate plaque elevation (=0.75mm); moderate red coloration; coarse scale predominates
4	Marked	Moderate plaque elevation (=1mm); bright red coloration; thick, non-tenacious scale predominates
5	Severe	Severe plaque elevation (≥1.25mm); dusky to deep red coloration; very thick, tenacious scale predominates

2.7 Safety Assessments

All subjects who are randomized will be monitored for adverse events (AEs) until they leave the study.

Additional safety assessments include:

- physical examinations (PE)
- vital sign measurements including systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature
- 12-lead electrocardiogram (ECG)
- laboratory assessments including chemistry, hematology, and urinalysis

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to assess the efficacy, safety, and tolerability of LYC-30937-EC compared to placebo in subjects with chronic plaque-type psoriasis.

3.2 Primary Objective

The primary objective will be to assess the efficacy of LYC-30937-EC in inducing a reduction from baseline in PASI compared with placebo in subjects with chronic plaque-type psoriasis over the treatment duration of 12 weeks.

3.3 Secondary Objective

The secondary objectives will be to evaluate the overall efficacy, safety and tolerability of LYC-30937-EC compared with placebo in subjects with chronic plaque-type psoriasis.

3.4 Exploratory Objectives

The exploratory objectives will be to assess concentration of LYC-30937 in plasma and in skin tissue. Skin biopsies are optional and will be collected in a subset of approximately 6 consenting study subjects to assess LYC-30937 concentrations in skin.

3.5 Study Endpoints

3.6 Efficacy Endpoint

The primary efficacy endpoint of the study will be the mean percent change from baseline at Week 12 in PASI.

The secondary efficacy endpoints of the study will be:

- The proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI at Week 12.
- The mean percent change from baseline to Week 12 in the %BSA.
- The proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12.
- The proportion of subjects who achieve a 2 step reduction on the static IGA at Week 12.

The exploratory efficacy endpoints of the study will be:

- The proportion of subjects who achieve a ≥ 50% reduction from baseline in PASI at Week 12.
- The proportion of subjects who achieve a ≥ 25% reduction from baseline in PASI at Week 12.
- Proportion of subjects achieving both a ≥ 75% reduction from baseline in PASI and a static IGA score of 0 (cleared) or 1 (minimal) at Week 12.

3.7 Safety Endpoint

The secondary endpoint of the study under safety will include adverse events (AEs), PE, vital sign measurements, 12-lead ECG, and laboratory assessments.

3.8 Exploratory Endpoint

Concentration of LYC-30937 will be measured in plasma and in skin as an exploratory endpoint.

4 ANALYSIS SETS

4.1 Full Analysis Set (FAS)

The FAS is defined as all randomized subjects. Subjects will be included in the treatment group to which they were randomized, regardless of the treatment they actually received. All efficacy analyses will be performed on the FAS.

4.2 Safety Set

The safety set is defined as all randomized subjects who received at least one dose of study drug. For summaries and listings where treatment group is included, subjects will be included in the treatment group to which they were actually treated. All safety analyses will be performed on the Safety Set.

4.3 Plasma PK Set

The plasma PK set is defined as all randomized subjects who received at least one dose of study drug and who have a blood sample collected to assess LYC-30937 and/or it's metabolite (LYC-53552) concentrations. For listings where treatment group is included, subjects will be included in the treatment group to which they were actually treated.

4.4 Skin PK Set

The skin PK set is defined as the subset of all randomized subjects who received at least one dose of study drug and who have a skin biopsy sample collected to assess LYC-30937 concentrations. For listings where treatment group is included, subjects will be included in the treatment group to which they were actually treated.

4.5 Protocol Deviations and Treatment Misallocations

The list of major and minor protocol deviations will be determined while the data are still blinded, prior to database lock. The list will be prepared and maintained by clinical CRO, reviewed by Lycera team for major/minor classification and submitted for inclusion in the clinical database (SDTM.PD) as an Excel file. Protocol deviations will be used to assess the

quality of study conduct but there are no plans to use them to define an additional population for analyses. Treatment misallocation will be handled as described below.

Efficacy data will be summarized "as randomized," meaning the subject will be summarized under the treatment they were randomized to, regardless of what treatment was actually received.

Safety, PK and skin biopsy data will be summarized "as treated," meaning the subject will be summarized based on the treatment that was actually received.

5 ANALYSIS PLAN OVERVIEW

5.1 General Methodology

Continuous safety and efficacy endpoints will be summarized using mean, standard deviation, median, minimum, and maximum. Discrete safety and efficacy endpoints will be summarized by the number and percentage of subjects in each category. Continuous efficacy endpoints will be analyzed using an analysis of covariance model with treatment as a factor and baseline value as a covariate. Discrete variables will be analyzed using a chi-square test.

The primary efficacy endpoint will be analysed using a 2-sided significance level $\alpha = 0.05$. All secondary and exploratory efficacy endpoints will also be analysed using 2-sided $\alpha = 0.05$ level of significance. The p-values for the secondary and exploratory endpoints will be considered descriptive and no adjustments will be made for multiplicity.

The analysis of Safety endpoints will be limited to descriptive statistics and by subject listings.

Concentrations of LYC-30937 in plasma and skin tissue will be limited to listings.

5.2 Statistical Power and Sample Size Considerations

A total of approximately 30 subjects will be randomized into the study and using a 2:1 randomization ratio of LYC-30937-EC 25 mg or placebo daily.

A sample size of 30 subjects (20 LYC-30937-EC and 10 placebo) will achieve approximately an 80% power to detect difference in the mean percent change from baseline in PASI at Week 12 in the LYC-30937-EC treatment group compared to the placebo treatment group. The mean percent change from baseline in PASI at Week 12 in the placebo treatment group is assumed to be 16.7% with SD=32.0. The power was

computed assuming the mean percent change from baseline in PASI at Week 12 in the LYC-30937-EC treatment group is at least 52.7% (SD=32.0) for a mean difference of at least 36.0%. The test statistic used is the two-sided t-test. The alpha level of the test was targeted at 0.05.

5.3 Baseline Definition

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained before the randomization. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment. All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

Re-randomization will not be used for baseline definition and only one baseline value will be defined referring to the first randomization.

5.4 Change from Baseline

Change from baseline (CFBL) will always be calculated as (post-baseline – baseline). It will be calculated for Subjects with both a baseline and post-baseline value as applicable.

If a baseline value has not been recorded for a parameter, then CFBL will not be calculated for that parameter, and the subject will be excluded from CFBL analysis.

Percent CFBL is the CFBL divided by the baseline value multiplied by 100. Subjects with a value of 0 at baseline or with no baseline value recorded cannot have percent CFBL calculated and they will be excluded from percent CFBL analysis.

5.5 End of Treatment Value

For Safety parameters, the end of treatment value is defined as the last value collected for each subject excluding the follow-up visit.

5.6 Visit Windows

Data at scheduled visits will be assigned to analysis visits as defined in the Visit Window table below. To ensure that all visits have the possibility to be included in the summaries, the visit window will also classify all unscheduled and early termination visits. The analysis visits will be derived in terms of study days since the first dose of study

treatment for safety assessments, or since the date of randomization for efficacy assessments. These analysis visits will be utilized in the summary and analyses of efficacy and safety endpoints.

If a subject has more than 1 assessment in a visit window, only the assessment that is closest to the Scheduled Visit Day will be used for analysis. In case 2 assessments have the same distance from the Scheduled Day, the later assessment will be used for analysis. The early termination visit will be assigned to an analysis visit based on the window below.

Separate visit window tables are provided based on how frequently the assessments were done. For assessment which has only 1 scheduled post-baseline assessment, say at Week 12, Scheduled Visit Day will be similar as either of the tables below with visit window upper limit of Day 92, and all previous rules will apply.

No visit windows will be applied for summaries of the follow-up period data.

Table 1 Visit Windows for Assessments Done at Baseline and Weeks 2, 4, 8, and 12

Analysis Visit	Scheduled Visit Day	Visit Window for Summarization
Baseline	Day 1	≤ Day1
Week 2	Day 15	Day 2 – Day 22
Week 4	Day 29	Day 23 – Day 43
Week 8	Day 57	Day 44 – Day 71
Week 12	Day 85	Day 72 – Day 92

Table 2 Visit Windows for Assessments Done at Baseline and Weeks 4, 8, and 12

Analysis Visit	Scheduled Visit Day	Visit Window for Summarization
Baseline	Day 1	≤ Day1
Week 4	Day 29	Day 2 – Day 43
Week 8	Day 57	Day 44 – Day 71
Week 12	Day 85	Day 72 – Day 92

5.7 Handling of Missing Data

Missing data will be handled differently depending on the parameter and analysis:

- No imputation for missing values will be applied for PASI and static IGA response variables. The summaries will be based on observed cases only.

- Missing baseline values will not be imputed in any situation.
- Post-baseline values for by-visit data will be summarized and/or analyzed using the Visit Windows from Section 5.6. If a value is not available within a given window, no imputation will be done.
- Missing data for AE relationship will be imputed as "Related."
- Refer to Appendix 3 for details of imputing partial dates for AE, when applicable.
- Refer to Appendix 4 for details of imputing partial dates for prior and concomitant medication, when applicable.

6 STATISTICAL ANALYSES

6.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the mean percent change from baseline in PASI score at Week 12. The endpoint will be calculated by taking the Week 12 PASI score and subtracting the baseline PASI score then dividing by the baseline PASI score and multiplying by 100 to get the percentage.

The mean percent change from baseline in PASI scores will be compared between the LYC-30937-EC treatment group and placebo using analysis of covariance with treatment as a factor and baseline as a covariate to assess the null hypothesis that mean percent change from baseline in PASI score at Week 12 in LYC-30937-EC treatment arm equals the mean percent change from baseline in PASI score at Week 12 in the placebo arm.

The mean difference (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval of the difference. If the confidence interval does not contain 0 the null hypothesis will be rejected and the mean percent change from baseline in PASI score at Week 12 will be considered different due to treatment arm.

The observed PASI score at baseline, at Weeks 4, 8, and 12, and the percent change from baseline in PASI score to Week 4, 8, and 12 will be summarized by treatment group using descriptive statistics. The percent change from baseline in PASI score at Week 4 and at Week 8 will be calculated using the same rules as for percent change from baseline at Week 12. In addition, a plot of the mean percent change from baseline in PASI score over visit with one line per treatment (LYC-30937-EC and placebo) will be prepared.

6.2 Secondary Efficacy Endpoints Analyses

The following secondary efficacy endpoints will be summarized and compared between the LYC-30937-EC treatment arm and placebo:

- The proportion of subjects who achieve ≥ 75% reduction from baseline in PASI score at Week 12 will be calculated by taking the number of subjects who achieve a percent change from baseline to Week 12 in PASI score of ≥ 75% divided by the total number of subjects in each treatment group. The proportion of subjects in each treatment group will be compared using chi-square test. The difference in proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI score at Week 12 (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval. If the confidence interval does not contain 0 the null hypothesis will be rejected and the proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI score at Week 12 will be considered different due to treatment arm.

- The mean percent change from baseline to Week 12 in the %BSA will be calculated by taking the Week 12 %BSA and subtracting the baseline %BSA then dividing by the baseline %BSA and multiplying by 100 to get the percentage of baseline. The mean percent change from baseline to Week 12 in the %BSA in each treatment group will be compared using the same methodology for the primary efficacy endpoint. The mean difference (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval of the difference. If the confidence interval does not contain 0 the null hypothesis will be rejected and the mean percent change from baseline in %BSA at Week 12 will be considered different due to treatment arm. The observed %BSA at baseline, at Weeks 4, 8, and 12, and the percent change from baseline in %BSA to Week 4, 8, and 12 will be summarized by treatment group using descriptive statistics. The percent change from baseline in %BSA score at Week 4 and at Week 8 will be calculated using the same rules as for percent change from baseline at Week 12. In addition, a plot of the mean percent change from baseline in %BSA over visit with one line per treatment (LYC-30937-EC and placebo) will be prepared.

- The proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 will be calculated by taking the number of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 divided by the total number of subjects in each treatment group.

The proportion of subjects in each treatment group will be compared using chi-square test. The difference in proportion of subjects of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval. If the confidence interval does not contain 0 the null hypothesis will be rejected and the proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 will be considered different due to treatment arm.

- The proportion of subjects who achieve at least a 2 step reduction on the static IGA at Week 12 will be calculated by taking the number of subjects who achieve at least a 2 step reduction on the static IGA at Week 12 (i.e., a score of 5 at baseline to a score of 3 or less at Week 12) divided by the total number of subjects in each treatment group. The results will be summarized and analyzed using the same methodology as for the proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12.

6.3 Exploratory Efficacy Endpoints Analyses

The following exploratory efficacy endpoints will be summarized and compared between the LYC-30937-EC treatment arm and placebo:

- The proportion of subjects who achieve a $\geq$ 50% reduction from baseline in PASI at Week 12 will be calculated by taking the number of subjects who achieve a percent change from baseline at Week 12 in PASI score $\geq$ 50% divided by the total number of subjects in each treatment group. The proportion of subjects in each treatment group will be compared using chi-square test. The difference in proportion of subjects who achieve a $\geq$ 50% reduction from baseline in PASI score at Week 12 (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval. If the confidence interval does not contain 0 the null hypothesis will be rejected and the proportion of subjects who achieve a $\geq$ 50% reduction from baseline in PASI score at Week 12 will be considered different due to treatment arm.

- The proportion of subjects who achieve a $\geq$ 25% reduction from baseline in PASI at Week 12 will be calculated by taking the number of subjects who achieve a percent change from baseline at Week 12 in PASI score $\geq$ 25% divided by the total number of subjects in each treatment group. The proportion of subjects in each treatment group will be compared using chi-square test. The difference in

proportion of subjects who achieve a ≥ 25% reduction from baseline in PASI score at Week 12 (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval. If the confidence interval does not contain 0 the null hypothesis will be rejected and the proportion of subjects who achieve a ≥ 25% reduction from baseline in PASI score at Week 12 will be considered different due to treatment arm.

- Proportion of subjects achieving both a ≥ 75% reduction from baseline in PASI and static IGA score of 0 (cleared) or 1 (minimal) at Week 12 in each treatment group will be compared using chi-square test. The difference in proportion of subjects who achieve both a ≥ 75% reduction from baseline in PASI score and a static IGA score of 0 or 1 at Week 12 (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval. If the confidence interval does not contain 0 the null hypothesis will be rejected and the proportion of subjects who achieve both a ≥ 75% reduction from baseline in PASI score at Week 12 and a static IGA score of 0 or 1 will be considered different due to treatment arm.

6.4 Safety Analyses

Safety is assessed through the analysis of AEs, clinical laboratory assessments, vital signs, ECGs, and physical examinations. All Safety analyses will be completed on the Safety Population and will include descriptive statistics only.

Unless otherwise specified, safety analyses that include summaries of number and percent (e.g., AEs) will be displayed by treatment groups and overall.

All safety parameters will be listed by subject, treatment group and time point. Adverse events reported by screen failures will be included in a separate listing.

6.5 Adverse Events

Adverse event tables will only include summaries of treatment-emergent adverse events (TEAE). TEAEs are defined as AEs which first occur, or worsen, after the first dose of study drug and within 14 days after the permanent discontinuation of the study drug (i.e., first dose date ≤ AE start date ≤ last dose date + 14 days).

Severity of AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

All TEAEs will be summarized by system organ class (SOC) and preferred term and by descending frequency of preferred terms, by maximum severity (maximum NCI CTCAE grade), and by strongest relationship to study treatment. This will be done by treatment group and overall.

For subjects not randomized, only SAEs and AEs leading to screen failure will be collected on the CRFs from the time the subject has signed informed consent. If reported, these AEs/SAEs will be listed by subject.

Below are the rules to follow for AE summaries:

- For the summary of AEs by severity, if a subject has multiple events occurring in the same body system or same preferred term, then the event with the highest NCI CTCAE grade will be counted. AEs for which the severity is missing are counted only in the overall column.
- A related AE is defined as an AE with an assigned causality of "related," "suspected," or if causality is missing.
- Refer to Appendix 3 for details of imputing partial dates for AE.

AEs will be coded using MedDRA version 19.0.

6.6 Clinical Laboratory

Clinical labs are reported for hematology, chemistry, and urinalysis and they include the following parameters:

- Chemistry: glucose, calcium, sodium, albumin, total protein, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, lactate, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), reflexive bilirubin (total, direct, indirect), alkaline phosphatase (ALP), cholesterol, triglycerides, creatine phosphokinase (CPK), high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL), and low density lipoprotein (LDL).
- Hematology: platelets, white blood cells (WBCs) with differential if abnormal (% and absolute counts), hematocrit, red blood cells (RBCs), hemoglobin, , mean corpuscular volume (MCV), mean corpuscular hematocrit concentration (MCHC), and mean corpuscular hematocrit (MCH).

- Urinalysis: color, appearance, specific gravity, leukocyte esterase, pH, protein, glucose, ketones, blood, and nitrates. Microscopic urinalysis will be performed on samples with abnormal blood, leukocyte esterase, protein, and nitrate.

Hematology and chemistry are collected at Screening, Week 2, Week 4, Week 8, Week 12, and at Week 14 (follow-up). Values and change from baseline will be summarized by visit, for the end of treatment visit, and for the overall worst value post-baseline (which includes unscheduled visits), within each treatment group. Appendix 5 provides the directionality of the worst values for each laboratory parameter.

Urinalysis is collected at Screening and Week 12. Results will be listed by subject. .

Out-of-range values will be assessed through shift tables. Each lab value will be assessed as low, normal or high based on the normal ranges provided by the central lab. Frequencies of each combination of shifts from baseline to post-baseline visits will be provided by treatment group for hematology and chemistry lab parameters only. Separate by subject listings will also be produced and out-of-range values will be flagged.

Over the course of the study, there may be some labs tests performed that were not mentioned in the protocol. These tests will not be summarized but will be included in the listings and flagged as non-protocol tests.

6.7 Vital Signs

Vital signs are assessed at Screening, Randomization, Week 2, Week 4, Week 8, Week 12 and at Week 14 (follow-up) and will consist of systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and temperature. Vital sign measurements at each visit and the change from baseline to each post-baseline visit will be summarized by treatment group. Post-baseline vital signs will be defined as clinically notable if they meet the criterion value or both the criterion value and the change from baseline criterion listed in the table below.

Table 3 Vital Signs Clinically Notable Values/Changes from Baseline

Vital Sign	Criterion Value	Change Relative to Baseline
Pulse	≥ 100 bpm	Increase of ≥ 15 bpm
	≤ 50 bpm	Decrease of ≥ 5 bpm
Systolic blood pressure	≥ 140 mmHg	Increase of ≥ 20 mmHg
	≤ 90 mmHg	Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 100 mmHg	Increase of ≥ 15 mmHg
	≤ 50 mm Hg	Decrease of ≥ 15 mmHg
Body temperature	≥ 37.5°C	Change of ≥ 1.1°C

The incidence of clinically notable vital signs will be summarized by time point and treatment group, and will be listed and flagged in by-subject listings. The overall post-baseline incidence of clinically notable values for each vital sign parameter, which includes values from unscheduled post-baseline visits, will also be summarized.

6.8 Electrocardiogram

ECG will be assessed only at Screening and at Week 12 (End of Treatment). The following ECG parameters will be reported: heart rate, PR interval, QRS duration, QT interval, and QTc interval, and principal investigator's (PI) overall assessment of the ECG profile (normal, abnormal clinically significant, abnormal not clinically significant). The QTc interval will be presented by the Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections. The ECG findings will be listed by subject, treatment group and by time point.

6.9 Physical Examinations

Physical examinations are assessed at Screening, and at Weeks 2, 4, 8 and 12. The findings for each assessment (HEENT, etc.) will be presented in a by subject data listing. Abnormal findings on the physical examination will also be provided in data listing. Clinically significant changes from screening will be recorded as adverse events.

6.10 Additional Statistical Analysis Methods

6.10.1 Disposition

Subject disposition will be summarized for FAS, using counts and percentages. The summary will include the number of subjects who were, randomized, received the study drug, completed the study, discontinued prematurely, and the primary reason for early discontinuation. These will be summarized by treatment group and overall and listed by subject. A separate listing will be prepared to include subjects who are screen failures and reason for screen failure.

6.10.2 Demographics and Baseline Characteristics

Demographic information and subject characteristics such as sex, race, age, smoking status, drug and alcohol consumption, menopausal status, duration of chronic plaque-type psoriasis, will be summarized for FAS by treatment group and overall and listed by subject.

6.10.3 Medical and Surgical History

Medical and surgical history will be included in a by subject listing for all subjects in FAS.

6.10.4 Drug Accountability and Treatment Compliance

Duration of exposure will be summarized quantitatively using the number of days of exposure to study drug for each subject, displayed by treatment group. Duration of exposure will be calculated as (last dose date – first dose date + 1).

Days on treatment will be computed as sum of days study drug was taken (i.e., exclude any days when study drug was interrupted). Number of days on treatment and number of days study drug was interrupted will be summarized quantitatively. Reason for study drug interruption (adverse event, other) will be summarized as counts and percentages.

Treatment compliance will be calculated as a percentage using the total number of capsules that were dispensed and returned at each post-baseline visit and will be recorded on eCRF.

Overall compliance will be computed only for subjects who were dispensed study drug and who returned all bottles dispensed during the study using the following algorithm:

1. Capsules taken during study: total capsules dispensed – total capsules returned.
2. Total number of capsules dispensed = number of bottles dispensed x 17 capsules per bottle.
3. Total number of capsules returned will be the value recorded on drug accountability eCRF.
4. Capsules expected to be taken during study: same as duration of exposure (see above definition) (i.e., it will be assumed one capsule per day).
5. Overall Percentage Compliance: (Capsules taken during study / Capsules expected to be taken during study) * 100.

Summary results for duration of exposure, duration of treatment and overall compliance will be prepared by treatment group for subjects in safety set.

6.10.5 Prior and Concomitant Medications

Concomitant medications are medications taken prior to the date of first dose of study drug which are either ongoing or with a stop date after the first day of dosing, or with a start date on or after the date of first dose of study drug and prior to or on the date of last

dose of study drug. Any medication with a start and stop date prior to first day of dosing is considered a prior medication.

Any medication with a missing start date will also be classified as a concomitant medication or procedure, unless the end date is prior to the first day of study dosing. Partial dates will be imputed as detailed in Appendix 4.

Prior and concomitant medications will be coded using WHO Drug 2016 March 1.

Prior Chronic Plaque-Type Psoriasis Treatment will be listed for all subjects in FAS with anatomical therapeutic chemical (ATC) codes and preferred terms.
Prior Chronic Plaque-Type Psoriasis procedures (e.g., photo treatment) will be listed by subject with reported term only.

Concomitant and other prior medications will be presented in listings with anatomical therapeutic chemical (ATC) codes and preferred terms for all subjects in the safety set.

6.11 Pharmacokinetics and Skin Biopsy

The plasma drug concentration data and skin biopsy results will be listed for each subject by the treatment to which they were actually treated.

6.12 Childbearing Potential Evaluation and Pregnancy Tests

Serum FSH in postmenopausal female subjects and a serum hCG (pregnancy test) in premenopausal females will be evaluated at the central lab at screening.

Urine pregnancy tests for female subjects of childbearing potential will be performed at the time points indicated in the schedule of assessments (Appendix 1).

Serum FSH and hCG results will be listed by subject.

7 CHANGES FROM PROTOCOL SPECIFIED ENDPOINTS AND ANALYSES

Primary endpoint definition was updated to be: mean percent change from baseline at Week 12 in PASI.

The following exploratory efficacy endpoints were included:

- The proportion of subjects who achieve a ≥ 50% reduction from baseline in PASI at Week 12.
- The proportion of subjects who achieve a ≥ 25% reduction from baseline in PASI at Week 12.
- Proportion of subjects achieving both a ≥ 75% reduction from baseline in PASI and a static IGA score of 0 (cleared) or 1 (minimal) at Week 12.

Two additional analyses sets were defined: Plasma PK Set and Skin PK Set.
Specific analyses for the exploratory efficacy endpoints were included in Section 6.3.

Adverse events reporting: the SAP does not include any planned summary results for SAEs by system organ class, by severity, and by relationship; and serious adverse events resulting in death will not be listed and summarized separately as noted in the protocol.

APPENDICES

Appendix 1 Schedule of Events

Protocol Activity	Screening	Randomization and Dosing	Treatment				Follow-up
			Week 2	Week 4	Week 8	Week 12/ ET	Week 14
Study Day	-14 to -1	1	15 ± 2 days	29 ± 2 days	57 ± 3 days	85 ± 3 days	99 ± 3 days
Visit Number	1	2	3	4	5	6	7
Informed consent	X						
Demography a	X						
Medical/surgical history	X						
Serology b	X						
Prior psoriasis treatments	X						
Serum pregnancy test (pre-menopausal female subjects)	X						
FSH (post-menopausal female subjects) c	X						
Vital signs d	X	X	X	X	X	X	X
Assess protocol eligibility [l]	X	X					
Randomization		X					
Dispense study drug		X	X	X	X		
Administer study drug at the clinic		X					
Telephone reminder to subject regarding taking study drug after fasting overnight		X [n]					
Review study drug compliance			X	X	X	X	
PASI and %BSA	X	X		X	X	X	
Static IGA	X	X		X	X	X	
Photographs [j]		X				X	
Skin biopsy [k]					X		
Urine pregnancy test (female subjects of childbearing potential)		X	X	X	X	X	X

Protocol Activity	Screening	Randomization and Dosing	Treatment				Follow-up
			Week 2	Week 4	Week 8	Week 12/ ET	Week 14
Study Day	-14 to -1	1	15 ± 2 days	29 ± 2 days	57 ± 3 days	85 ± 3 days	99 ± 3 days
Visit Number	1	2	3	4	5	6	7
Height	X						
Weight	X		X	X	X	X	
Physical examination	X		X	X	X	X	
12-Lead ECG	X					X	
Chemistry panel e	X		X	X	X	X	X
Hematology panel f	X		X	X	X	X	X
Urinalysis [g]	X					X	
Plasma PK sample collection [h]					X		
Concomitant medications	X	X	X	X	X	X	X
Assess AEs [i]	X	X	X	X	X	X	X

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram;; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high density lipoprotein; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IGA = Investigator's Global Assessment; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PASI = Psoriasis Area and Severity Index;; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cell

[a] Demography includes smoking status, drug and alcohol consumption, and date of chronic plaque-type psoriasis diagnosis.

[b] HBsAg, HCV antibodies, and HIV-1/2 antibodies.

[c] Post-menopausal is defined as having no menses for ≥ 6 months prior to screening and a serum FSH level > 25 mIU/mL at screening.

[d] Vital signs will be collected after the subject has been sitting quietly for ≥ 5 minutes and include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.

[e] Chemistry panel includes: glucose, calcium, sodium, albumin, total protein, potassium, bicarbonate, chloride, BUN, creatinine, lactate, LDH, ALT, AST, reflexive bilirubin (total, direct, indirect), ALP, cholesterol, triglycerides, CPK, hsCRP, HDL, and LDL.

[f] Hematology Panel includes: platelets, WBCs with differential if abnormal (% and absolute counts), hematocrit, RBCs, hemoglobin, MCV, MCHC, and MCH.

[g] Urinalysis (dipstick) includes: color, appearance, specific gravity, leukocyte esterase, pH, protein, glucose, ketones, blood, and nitrites. Microscopic urinalysis will be performed on samples with abnormal blood, leukocyte esterase, protein, and nitrate.

[h] All subjects will have one blood sample collected at Week 8 (any time post study drug dose) to measure plasma LYC-30937 concentration.

[i] AEs will be assessed after the informed consent is signed.

[j] Photographs will be taken at randomization (pre-dosing) and at Week 8 in a subset of subjects.

[k] Optional skin biopsy will be collected at Week 8 in a subset of approximately 6 consenting subjects. Biopsy collection instructions will be included in a separate document. This tissue will be assayed for concentration of LYC-30937.

[l] Note that confirmation of moderate plaque-type psoriasis is determined at both Screening and Visit 2 (baseline, prior to first dose).

[m] Site will telephone subjects the day after randomization visit to remind them to take study drug in the morning after fasting overnight and to wait approximately 1 hour before eating a meal.

Appendix 2 PASI Scoring System

Body Region	Erythema (E)	Thickness (I) (plaque elevation, induration)	Scaling (S) (desquamation)	Area score % (A) [4]
Head (H) [1]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%
Trunk (T) [2]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%
Upper extremities (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%
Lower extremities (L) [3]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%

[1] Neck is evaluated as part of the head (H).

[2] Axillae and groin are evaluated as part of the Trunk (T).

[3] Buttocks are evaluated as part of the Lower extremities (L).

[4] Degree of involvement as a percentage for each body region affected.

In the PASI the body is divided into 4 regions: head (H), trunk (T), upper extremities (U) and lower extremities (L). Each region is considered to account for the following % of total BSA, head = 10% (0.1), trunk = 30% (0.3), upper extremities = 20% (0.2) and lower extremities = 40% (0.4).

Estimation of the % body area affected by psoriatic plaque in each region is done by the trained clinician using the palm (fingers included) and then converted the corresponding numeric score (0 to 6) as indicated in column 5 in the above table.

Each region is also evaluated separately for signs of disease (erythema (E), thickening (I), and scaling (D), which are rated and given a score (0 to 4), as indicated in the above table.

The PASI generates a numeric score that can range from 0 (no signs of psoriasis) to 72. Scores from the 4 regions are combined to get the PASI score using the PASI formula:

$$PASI = 0.1(E_H + IH + S_H)A_H + 0.3(E_T + I_T + S_T)A_T + 0.2(E_U + I_U + S_U)A_U + 0.4(E_L + I_L + S_L)A_L$$

Appendix 3 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: AE = Adverse Event
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 4 Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 5 Directionality of Worst Laboratory Parameters

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Red blood cell count	Lowest value
	Mean cell hemoglobin	Lowest value
	Mean cell hemoglobin concentration	Lowest value
	Hemoglobin	Lowest value
	Mean cell volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Neutrophils	Lowest value
	Lymphocytes	Lowest value
	Monocytes	Lowest value
	Eosinophils	Highest value
	Basophils	Lowest value
Chemistry	Albumin	Lowest value
	Alkaline phosphatase (ALP)	Highest value
	Alanine aminotransferase (ALT/SGPT)	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Blood Urea Nitrogen	Highest value
	Calcium	Both highest value and lowest value
	Cholesterol	Highest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine kinase (CK)	Highest value
	Glucose	Both highest value and lowest value
	Lactate dehydrogenase (LDH)	Highest value
	Lactate and hsCRP (high sensitivity C-reactive protein)	Highest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
	Total carbon dioxide	Lowest value
	Total protein	Lowest value
	Triglycerides	Highest value
	High density lipoprotein (HDL)	Highest value
	Low density lipoprotein (LDL)	Highest value