

STATISTICAL ANALYSIS PLAN

**Open Label Study to Evaluate the Efficacy of Etanercept Treatment in Subjects
With Moderate to Severe Plaque Psoriasis who Have Failed Therapy With
Apremilast**

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Table of Abbreviations

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DRE	Disease-Related Event
EOS	End Of Study
ET	Early Termination
ICH	International Conference on Harmonization
IP	Investigational Product
IPD	Important Protocol Deviation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PRO	Patient Reported Outcome
PSI	Psoriasis Symptom Inventory
PsO	Psoriasis
SAP	Statistical Analysis Plan
sPGA	Static Physician's Global Assessment of Psoriasis
WHODRUG	World Health Organization Drug dictionary

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for Etanercept Study 20150252 dated 05Feb2016. The scope of this plan includes the final analysis that is planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the efficacy of etanercept at week 12 as measured by a 75% improvement in Psoriasis Area and Severity Index (PASI 75) in adult subjects with moderate to severe plaque psoriasis (PsO) who have failed therapy with apremilast (Otezla®).

2.2 Secondary

To evaluate the effect of treatment with etanercept on other efficacy endpoints (PASI, Static Physician's Global Assessment [sPGA], Body Surface Area [BSA]), and patient reported outcomes (PRO), including Psoriasis Symptom Inventory (PSI), Patient Assessment of Treatment Satisfaction, and Dermatology Life Quality Index (DLQI).

2.3 Safety

To evaluate the safety and tolerability of etanercept in apremilast failures.

3. Study Overview

3.1 Study Design

This is a multicenter, open-label, single-arm, phase 4 estimation study in subjects with PsO who have failed apremilast. Approximately 80 subjects will be enrolled in the study, among which at least 10 subjects (and not to exceed 20) will be enrolled for reasons of intolerability to apremilast in the investigator's opinion. The remaining 60 to 70 subjects will be enrolled for reasons of primary or secondary failure to apremilast in the investigator's opinion. The study consists of up to a 45 day screening period, a 24-week treatment period with study visits every 4 weeks, and a 30-day follow-up period for safety. Etanercept dosing will follow the recommended label dosing for patients with plaque PsO.

3.2 Sample Size

This study will estimate the proportion of subjects with PsO who achieve a PASI 75 after 12 weeks of treatment with etanercept following failure of treatment with apremilast. In recent etanercept studies, the 12-week PASI 75 response rate for etanercept was ~50 to 60%. The assumed response for a population with failure of treatment with apremilast is

40%. In placebo-controlled phase 3 studies, the PASI 75 placebo response rate was ~5% in subjects with moderate to severe plaque PsO. Therefore, in this single-arm study, if the lower bound of the 95% confidence interval for the proportion of PASI 75 response is above 10%, we can safely conclude that in spite of limitations of a single-arm study (ie, regression to the mean and/or placebo effect), the etanercept effect is real.

The sample size of 80 is more than adequate to achieve a half-width of less than 15% for the 95% confidence interval for the proportion of subjects who achieve a PASI 75 response, assuming a sample proportion of 40% and a lower bound of the confidence interval above 10%.

In a phase 3, randomized, double-blind, placebo-controlled apremilast trial, 17% of subjects reported diarrhea and/or nausea. Of the 80 subjects enrolled, 60 subjects will be enrolled for reasons of failure to achieve adequate response (primary failure) or loss of adequate response (secondary failure) to apremilast in the investigator's opinion. In addition, between 10 and 20 (up to 25%) will be enrolled for reasons of intolerability to apremilast in the investigator's opinion.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Efficacy Endpoint

- PASI 75 at week 12

4.1.2 Secondary Efficacy Endpoints

- PASI 75 at all other visits
- PASI 50 and 90 at all visits
- Percent PASI improvement from baseline at all visits
- sPGA of 0 or 1 at all visits
- sPGA of 0, 1, or 2 at all visits
- sPGA at all visits
- One and two grade improvement from baseline in sPGA at all visits
- Percent BSA improvement from baseline at all visits
- PSI total and component scores at all visits
- Patient Assessment of Treatment Satisfaction at week 12 and 24
- DLQI improvement from baseline at week 12 and 24

4.1.3 Safety Endpoints

- Adverse events
- Laboratory assessments

4.2 Covariates and Subgroups

The following predictors and subgroup analyses may be performed to assess their influence on the primary endpoint:

- Body mass index ($\leq 35 \text{ kg/m}^2$ or $> 35 \text{ kg/m}^2$)
- Age (<65 , ≥ 65)
- Gender (male vs. female)
- Race (white, non-white)
- Baseline PASI score (\leq median, $>$ median)
- Baseline BSA with psoriasis involvement (%) (\leq median, $>$ median)
- History of psoriatic arthritis (yes, no)
- Baseline sPGA score (3, 4 or 5)
- Reasons for apremilast failure at screening, 1) failure to achieve adequate response, 2) loss of adequate response or 3) intolerability

5. Hypotheses and/or Estimations

A formal hypothesis will not be tested in this study. This study will estimate the proportion of subjects with PsO who achieve a PASI 75 after 12 weeks of treatment with etanercept following failure of treatment with apremilast.

6. Definitions

Adverse Event

In addition to the International Conference on Harmonization (ICH) Guidance definition, an adverse event also includes any occurrence or worsening of a pre-existing medical condition.

Age

Age will be collected at baseline.

Baseline

The last measurement for the endpoint of interest taken before the first dose of investigational product.

Body Mass Index (BMI)

A growth measure utilizing both height and weight, as given by the following formula:

$$\frac{\text{weight (kg)}}{\text{squared height (m}^2\text{)}}$$

Body Surface Area (BSA)

A measurement of psoriasis involvement, given as the physician's assessment of the proportion of the subject's total body surface area involved with psoriasis.

Dermatology Life Quality Index (DLQI)

A skin disease-specific instrument to evaluate health related quality of life ranging from 0 (best possible score) to 30 (worst possible score).

Disease-Related Event (DRE)

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Disease related events for the purposes of this study include worsening of the skin symptoms associated with PsO. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition. Events categorized as Disease-Related Events starting on or after first dose of IP as determined by the flag indicating if the AE started prior to the first dose on the Events CRF and up to and including 30 days after the end of IP.

DLQI Responder

A subject who achieves at least a 5 point improvement from baseline or a 0 (best possible) score at a particular visit.

Duration of Psoriasis

The number of years between the date of diagnosis and the enrollment date rounded to 1 decimal place, as given by the following formula:

$$\frac{[(\text{year}(\text{ENRLDT}) - \text{year}(\text{DXDT})) * 12 + ((\text{month}(\text{ENRLDT}) - \text{month}(\text{DXDT})))]}{12}$$

where ENRLDT=enrollment date; DXDT=date of diagnosis

Note: month(DXDT) is considered to be 0 if month of diagnosis date is missing.

End of Study Date

For each subject, this is the date of the End of Study (EOS) visit at week 24 (for subjects who complete the study) or Early Termination (ET) visit (for subjects who withdraw from the study prematurely).

Enrollment Date

The date of the first dose of investigational product.

First Dose Date

The date of the first dose of investigational product.

Full Analysis Set

Patient population including all enrolled subjects who received at least one dose of investigational product during the study.

Improvement from Baseline

The arithmetic difference between the baseline value and a post-baseline value, as given by the following formulas:

For endpoints with higher scores as better clinical results,
Improvement from baseline = (Post-baseline Value – Baseline Value)

For endpoints with lower scores as better clinical results,
Improvement from baseline = (Baseline Value – Post-baseline Value)

Imputed Value

A value substituted for a missing value.

Infectious Event

An event recorded on the Adverse Events electronic case report form that is coded to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class “Infections and Infestations.”

Injection Site Reaction

An event recorded on the Adverse Events electronic case report form that is coded to the MedDRA high level term of “Injection and Infusion Site Reactions,” excluding events with the preferred terms “Injection Site Bruising” and “Injection Site Haemorrhage.”

Last Dose Date

The date of the last dose of investigational product.

Last Observation Carried Forward (LOCF) Imputation

A method of imputation where missing post-baseline efficacy data will be carried forward from the last non-missing post-baseline value for that endpoint.

Non-infectious Adverse Event

An event recorded on the Adverse Events electronic case report form that is neither infectious nor an injection site reaction.

Non-responder Imputation (NRI)

A method of imputation where missing post-baseline efficacy data will be imputed with a value of zero (for binary endpoints) or with the baseline value (for ordinal and continuous endpoints) to indicate no response.

Patient Satisfaction with Treatment

A measure of a subject’s level of satisfaction with the medication’s control of psoriasis, ranging from “very satisfied” to “very dissatisfied.”

Patient Years on Drug

The number of days between the first dose date and the last dose date, inclusive, in a given time period divided by 365.25 and summed over all subjects within a treatment group.

Percent Improvement from Baseline

The improvement from baseline divided by baseline and multiplied by 100, as given by the following formula:

$$(\text{Improvement from Baseline} / \text{Baseline}) * 100$$

Note: If improvement from baseline is 0, the percent improvement from baseline will be set to 0 regardless of the baseline value. If the baseline value is 0, substitute 1 in the denominator for the percent improvement from baseline calculation.

Psoriasis Area and Severity Index (PASI)

Assessment of psoriasis based on severity of erythema, infiltration, and desquamation as well as area of involvement.

PASI 50 Response

A 50% or greater improvement from baseline in PASI score.

PASI 75 Response

A 75% or greater improvement from baseline in PASI score.

PASI 90 Response

A 90% or greater improvement from baseline in PASI score.

Psoriasis Symptom Inventory (PSI)

A measurement of a subject's severity of psoriasis signs and symptoms on an 8-item questionnaire (itch, redness, scaling, burning, stinging, cracking, flaking, pain). Each item is scored from 0 (not at all severe) to 4 (very severe). A 7-day recall period will be utilized and the PSI will be completed by the subject on paper version at baseline and weeks 1, 2, 3 and then at each visit.

Serious Event

An adverse event or infection that is fatal, life-threatening, requires in-patient hospitalization, results in persistent/significant disability, or is a congenital anomaly/birth defect or other significant medical hazard.

Static Physician Global Assessment (sPGA)

Assessment of psoriasis based on severity of induration, scaling, and erythema.

sPGA Clear or Almost Clear Status

A score of 0 (clear) or 1 (almost clear) on the sPGA assessment.

sPGA 0, 1, or 2 Status

A score of 0, 1, or 2 on the sPGA assessment.

sPGA 1 Grade Improvement From Baseline

An improvement on the sPGA assessment of at least 1 point.

sPGA 2 Grade Improvement From Baseline

An improvement on the sPGA assessment of at least 2 points.

Study Completion Date

The date of the last subject's last visit is the date of study completion.

Study Day

The number of days from Study Day 1, inclusive, given by the following formula:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1}) + 1$$

Study Day 1

The first day of investigational product administration.

Study Treatment Period

The time between the first dose of investigational product and the date of the subject's last visit (approximately 6 months).

Subject Incidence Rate

The subject incidence rate for a given event in a given time period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered the time period. For subjects with multiple occurrences of the same event in a given time period, the event will only be counted once per subject.

Treatment Emergent Adverse Event

A treatment emergent adverse event is defined as an event that occurs after the initiation of investigational product or an event that is present prior to the initiation of investigational product but worsens either in intensity or frequency after the initiation of investigational product.

Treatment Related Adverse Event

A treatment related adverse event is defined as an event that is deemed by the investigator to be related to investigational product.

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set will include all subjects who received at least one dose of investigational product during the study. All safety and efficacy endpoints will be analyzed using the full analysis set.

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. Data collection will be electronic and will be stored in the RAVE database. Laboratory data will be non-CTDB data located on the file server. Reasons for apremilast failure will be captured via IXRS and transferred to Data Management in SAS data format.

9.3 Handling of Missing and Incomplete Data

Subjects may be missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from the study, a missed visit, or non-evaluability of an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing.

9.3.1 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

9.3.2 Missing Post-baseline Evaluation

Subjects with missing post-baseline efficacy data will be imputed using the last observation carried forward (LOCF) method for the primary analysis for all efficacy endpoints. For LOCF imputation, missing post-baseline efficacy data will be carried forward from the last non-missing post-baseline value for that endpoint. Baseline efficacy data will not be carried forward to any missing post-baseline value.

For the primary endpoint, PASI 75 at week 12, missing post-baseline efficacy data will also be imputed using non-responder imputation as a sensitivity analysis. For non-responder imputation, the missing binary endpoint will be imputed with a value of zero to indicate no response. Patients without at least one post-baseline observation will also be defined as non-responders for the NRI analysis.

Missing post-baseline safety data will not be imputed.

9.3.3 Missing Components of Composite Endpoints

Missing components will not be imputed. Missing composite endpoint at post-baseline will be imputed by carrying forward from the last non-missing post-baseline value for that endpoint.

9.4 Detection of Bias

Factors that may bias the results of the study include:

- major protocol deviations likely to impact the analysis
- investigational product dosing compliance
- reasons for early withdrawal from treatment and from study

The incidence of these factors will be assessed. Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be summarized in the clinical study report (CSR). If a significant number of major protocol deviations are observed, an additional sensitivity analysis may be performed on efficacy data excluding subjects with major protocol deviations.

In addition, a summary of IP dosing compliance will be provided. A sensitivity analysis including subjects who completed all scheduled doses of IP may be performed on PASI 50, 75, and 90 responses and sPGA 0 or 1 response to assess the potential bias of IP compliance if a significant IP non-compliance issue is detected.

Reasons for early withdrawal from treatment and early withdrawal from study will be summarized. If a significant pattern is observed, additional sensitivity analyses may be performed on efficacy data adjusting for reasons for early withdrawal.

9.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Frequency tables of the categorical data used in the analyses will be examined to identify unexpected values.

Outliers due to data entry errors will be corrected by the study team before data lock. Outliers that are not due to data entry error will be included in the analysis. If it is deemed necessary after the team reviews the output from the planned analyses after data lock, a post-hoc sensitivity analysis excluding subjects with outliers may be performed.

9.6 Distributional Characteristics

Since efficacy endpoints will not be analyzed using parametric tests, assessment of the normality of the data will not be performed.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System version 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The final analysis will be performed after all subjects have completed the week 24 assessments and all data through week 24 and the 30-day safety follow-up have been finalized.

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively for all subjects.

For efficacy analyses, 95% confidence intervals for estimated responses will be generated as descriptive statistics. All categorical endpoints will be summarized using number and percentage of subjects. In addition to being summarized using number and percentage of subjects, ordinal categorical endpoints will also be summarized using number of observations, mean, standard error, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum. All continuous endpoints will be summarized using number of observations, mean, standard error, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum.

The primary analysis for all efficacy endpoints will be performed using the full analysis set. Missing values will be imputed using post-baseline last observation carried forward method. A sensitivity analysis for the primary endpoint will be performed using non-responder imputation as described in [Section 9.3.2](#). Sensitivity analyses on all the primary and secondary endpoints will be performed using observed cases as well. In addition, the primary endpoints may be examined using the covariates listed in [Section 4.2](#). Summary statistics will be generated as well as confidence intervals and p-values as appropriate. No multiplicity adjustments will be made for the p-values.

Safety endpoints will be summarized descriptively for all subjects.

10.2 Subject Accountability

Subject disposition will be summarized descriptively for all enrolled subjects. The summary will include the number of subjects who are enrolled and dosed with IP, who complete the study, who complete IP, and who withdraw prematurely including reasons

for withdrawal. In addition, the summary will include the date of study initiation (ie, first patient enrolled, last subject enrolled) and the date of study completion (ie, last subject last visit).

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs Demographic and Baseline Characteristics.

Subject demographic and baseline disease characteristics will be summarized descriptively for all enrolled subjects. Demographic data collection including sex, age, race, height, weight, body mass index and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. The baseline disease summary will include duration of disease, presence of psoriatic arthritis, reasons for apremilast failure, history of tobacco use, history of alcohol use, and the baseline value of each efficacy measure. A summary of prior psoriasis medication use, tabulated by preferred term, will be tabulated also.

10.4 Efficacy Analyses

The primary analysis for all efficacy endpoints will be conducted using the full analysis set.

For the primary analysis, all efficacy endpoints will be analyzed using LOCF method for missing data imputation. For all the efficacy endpoints, analyses on observed cases will be performed as sensitivity analyses. In addition, a sensitivity analysis for the primary endpoint will be performed using non-responder imputation as described in [Section 9.3.2](#).

Summary statistics will be generated as well as 95% confidence intervals for the estimated responses. For absolute improvement and percent improvement endpoints, both 95% confidence intervals and p-values will be provided. No multiplicity adjustments will be made for the p-values.

Table 1. Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
<p>Primary Endpoint</p> <ul style="list-style-type: none"> • PASI 75 at week 12 	<ul style="list-style-type: none"> • Full analysis set with LOCF imputation for missing data 	<ul style="list-style-type: none"> • Full analysis set using observed cases • Full analysis set with NRI imputation for missing data • Full analysis set with possible covariates
<p>Secondary Endpoint</p> <ul style="list-style-type: none"> • PASI 75 at all other visits • PASI 50 and 90 at all visits • Percent PASI improvement from baseline at all visits • sPGA of 0 or 1 at all visits • sPGA of 0, 1, or 2 at all visits • sPGA at all visits • One and two grade improvement from baseline in sPGA at all visits • Percent BSA improvement at all visits • PSI total and component scores at all visits • Patient Assessment of Treatment Satisfaction at week 12 and 24 • Improvement in DLQI at week 12 and 24 	<ul style="list-style-type: none"> • Full analysis set with LOCF imputation for missing data 	<ul style="list-style-type: none"> • Full analysis set using observed cases
<p>Exploratory Endpoints</p> <ul style="list-style-type: none"> • PASI 50, 75 and 90 at all visits • Percent PASI improvement at all visits • sPGA of 0 or 1 at all visits • sPGA of 0, 1, or 2 at all visits • sPGA at all visits • One and two grade improvement in sPGA at all visits • Percent BSA improvement at all visits • PSI total and component scores at all visits • Patient Assessment of Treatment Satisfaction at week 12 and 24 • Improvement in DLQI at week 12 and 24 	<ul style="list-style-type: none"> • By reasons of apremilast failure (failure to achieve adequate response, loss of adequate response or intolerability) • Full analysis set with LOCF imputation for missing data 	<ul style="list-style-type: none"> • Full analysis set using observed cases

10.4.1 Analyses of Primary Efficacy Endpoint

The primary analysis for the primary efficacy endpoint will estimate the proportion of subjects achieving PASI 75 at week 12. The primary analysis for the primary efficacy endpoint will be conducted using the full analysis set and LOCF imputation for missing post-baseline data. Sensitivity analyses will be performed using observed cases, non-responder imputation.

10.4.2 Analyses of Secondary Efficacy Endpoints

The primary analysis for the secondary efficacy endpoints will estimate the efficacy responses throughout the study. The primary analysis for the secondary efficacy endpoints will be conducted using the full analysis set and LOCF imputation for missing post-baseline data. Secondary efficacy endpoints will also be analyzed using observed cases.

10.4.3 Analyses of Patient Reported Outcomes Endpoints

The health related quality of life endpoints in this study include the DLQI, Patient Assessment of Treatment Satisfaction and PSI (See [Appendix C](#)). These endpoints are considered secondary and will be analyzed as described in [Appendix C](#) as well.

DLQI will be summarized as absolute score, absolute improvement, and percent improvement from baseline for total score and the following subscales: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. The proportion of DLQI responders, defined as subjects who achieve a 5 point or greater improvement from baseline or 0-score, will be summarized. In addition, the proportion of subjects who achieve a DLQI 0-score and the proportion of subjects who achieve a DLQI 0 or 1 score will be summarized.

Patient Assessment of Treatment Satisfaction will be summarized as categorical data.

PSI and component scores will be summarized as absolute score at all visits.

10.4.4 Covariate and Subgroup Analyses

The following predictors and subgroup analyses may be performed to assess their influence on the primary endpoint:

- Body mass index ($\leq 35 \text{ kg/m}^2$ or $> 35 \text{ kg/m}^2$)
- Body Weight (\leq median, $>$ median)
- Age (<65 , ≥ 65)
- Gender (male vs. female)
- Race (white, non-white)

- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Baseline PASI score (\leq median, $>$ median)
- Baseline BSA with psoriasis involvement (%) (\leq median, $>$ median)
- History of psoriatic arthritis (yes, no)
- Baseline sPGA score (3, 4 or 5)

10.4.5 Other Efficacy Analyses

All the efficacy endpoints will be analyzed by the reasons of apremilast failure at screening: 1) failure to achieve adequate response, 2) loss of adequate response or 3) intolerability.

10.5 Safety Analyses

10.5.1 Adverse Events

Safety analyses will be conducted using the full analysis set. The Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or later will be used to code all adverse events (AEs) to a system organ class and a preferred term. Subject incidence of adverse events will be summarized for all treatment-emergent, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, those leading to study withdrawal, and fatal.

The subject incidence of all treatment-emergent, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, those leading to study withdrawal, fatal, and fatal treatment-related adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

A summary of all treatment-emergent adverse events occurring in at least 5% of the subjects will be provided by preferred term in descending order of frequency.

Subgroup analyses by age group (< 65 , ≥ 65), sex (male, female), race (White, non-white) may be presented for AEs summarized by system organ class and preferred term in descending order of frequency.

Subject listings of all treatment-emergent, serious, treatment-related, those leading to withdrawal of investigational product, those leading to study withdrawal, and fatal adverse events will be provided.

10.5.2 Laboratory Test Results

Laboratory parameters will be summarized descriptively by study visit for all subjects in the full analysis set. Laboratory analytes are provided in the protocol Table 2. In addition, laboratory toxicities based on the Common Toxicity Criteria (CTC) grading

system will be summarized descriptively by study visit. Modifications to CTC version 4.0 used for this analysis are described in [Appendix D](#). Subject incidence of analytes with CTC Grades 3 and 4 will be provided.

10.5.3 Vital Signs

Vital signs will be summarized descriptively at baseline for all subjects in the full analysis set.

10.5.4 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product including patient-month exposure to IP, number of doses, duration of dosing, number of missed doses, and maximum number of days between doses.

10.5.5 Exposure to Concomitant Medication

A summary of all concomitant medications reported in at least 5% of the subjects will be provided by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.5.6 Other Safety

The analyses of subject incidence of all treatment-emergent, serious, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, those leading to study withdrawal, fatal, and fatal treatment-related adverse events tabulating by system organ class and preferred term in descending order of frequency will be repeated by the reasons of apremilast failure at screening: 1) failure to achieve adequate response, 2) loss of adequate response or 3) intolerability.

11. Changes From Protocol-specified Analyses

The analyses on all the efficacy and safety endpoints will be repeated by the reasons of apremilast failure at screening: 1) failure to achieve adequate response, 2) loss of adequate response or 3) intolerability. This was not pre-specified in the protocol but will be conducted to assess the potential bias of how the different reasons of apremilast failure would impact the efficacy and safety endpoints in this study.

12. Literature Citations / References

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

13. Appendices

Appendix A. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Visit Windows for All Efficacy and Selected Safety Evaluations

Per protocol, visits are to be performed within 5 days of the protocol-specified study day. To allow for variations in scheduling, the following visit windows will be applied to all efficacy and select safety evaluations (ie, vital signs, laboratory evaluations, and physical measurements) to assign a most appropriate nominal visit for analysis. **If more than one actual visit falls within the same defined window, the closest visit to the target day (ie, scheduled visit week x 7 + 1) will be considered for analysis. If two assessment dates are the same distance from the target day, then the latest visit will be considered for analysis.** Any visit that falls in an unscheduled visit for that assessment (eg, a DLQI assessment done at week 16) will be excluded from the analysis and reported in listings only.

Visit Week	Target Day	Window Definition	Interval (days)
Baseline	1	Last Evaluation prior to or on Study Day 1	n/a
Week 4	29	Study Day 15 to 42	28
Week 8	57	Study Day 43 to 70	28
Week 12	85	Study Day 71 to 98	28
Week 16	113	Study Day 99 to 126	28
Week 20	141	Study Day 127 to 154	28
Week 24	169	Study Day 155 to 182	28

Appendix B. Code Fragments

CCI



Appendix C. Patient-reported Outcome Forms/Instruments

CCI



CCI



Appendix D. Reference Values/Toxicity Grades

Adverse event severity is graded based on the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 (see Protocol Appendix B).

Laboratory toxicity is graded based on the National Cancer Institute Common Toxicity Criteria (CTC) version 4.0 with the following additions:

	Grade				
	0	1	2	3	4
BUN	WNL	>1.5 – 2.0 x ULN	>2.0 – 3.0 x ULN	>3.0 – 4.0 x ULN	>4.0 x ULN
HGB	WNL	>ULN	>(ULN+1) – (ULN+2)	>(ULN+2)	-
Urine Protein	NEG, NEGATIVE, TRACE, NORMAL, NOT DETECTED	+, +1, 1+	++, +2, 2+, +++, +3, 3+	++++, +4, 4+	-
Platelet Count	WNL	> ULN – 1.0x10 ¹² /L	> 1.0x10 ¹² /L	-	-
Leukocyte Count	WNL	> ULN – 2.0x10 ¹⁰ /L	> 2.0x10 ¹⁰ /L – 4.0x10 ¹⁰ /L	> 4.0x10 ¹⁰ /L	-