Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
BID	Twice Daily
BMI	Body Mass Index
CI	Confidence Interval
CRF or eCRF	(electronic) Case Report Form
CRMD	Clinical Research Medical Director
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	Data as Observed
EAIR	Exposure-Adjusted Incidence Rate
IP	Investigational Product
MedDRA	Medical Dictionary for Regulatory Activities
NRI	Non-responder Imputation
PT	Preferred Term
SAP	Statistical Analysis Plan
SD or STDEV	Standard Deviation
sPGA	Static Physician Global Assessment
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
USA	United States of America

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 apremilast (CC-10004, AMG 407) Study CC-10004-PPSO-004 (20200057), dated 08 May. 2020. The scope of this plan includes the analyses that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of apremilast in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis	• Adverse events (AEs): type, frequency, severity, duration and relationship to apremilast from Week 0 (Visit 1) through end of observational Follow-up • Columbia-Suicide Severity Rating Scale (C-SSRS) for study duration • Tanner Staging of sexual development at selected visits • Body weight, height and body mass index (BMI) by all visits
Secondary	
• To evaluate the maintenance of effect as measured by static Physician Global Assessment (sPGA) in children and adolescents (ages 6 through 17 years) with moderate to severe plaque psoriasis.	• sPGA 0/1: Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline through all visits

2.2 Hypotheses and/or Estimations

No formal hypothesis will be tested in this study. The aim of this study is to monitor long term safety and efficacy of subjects that have completed Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003.

3. Study Overview

3.1 Study Design

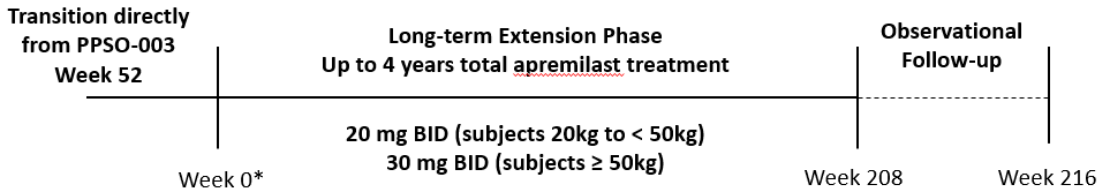
This study was created to provide subjects who complete Week 52 (end of Apremilast Extension Phase) of study CC-10004-PPSO-003 (Core Study) the option to continue to

receive open-label uninterrupted apremilast therapy. In study CC-10004-PPSO-004, treatment will be assigned by weight category at Visit 1 with subjects 20 kg to < 50 kg receiving apremilast 20 mg twice daily (BID) and subjects ≥ 50 kg receiving apremilast 30 mg BID. Treatment assignment will change for those subjects receiving apremilast 20 mg BID during the study once the subject's weight reaches 50 kg.

The study will consist of up to 208 weeks of long-term treatment followed by an 8-week observational follow-up phase (Figure 1).

- Long-term Extension Phase – up to 208 weeks
- Observational Follow-up Phase – 8 weeks
  - Subjects who complete all 208 weeks of treatment or discontinue the study early, should return for observational follow-up visits 4 and 8 weeks after the last dose of apremilast.

Figure 1: Overall Study Design



* Data and study assessments scheduled to be collected for Visit 1 (Week 0) will be populated with information collected at Visit 16 (Week 52) of study Core Study (PPSO-003) with the exception of consent/assent forms and eligibility criteria.

Subjects must withdraw from the study once the age of 18 years is reached or if apremilast becomes commercially available for pediatric psoriasis in a subject's age group.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

3.2 Sample Size

Approximately 140 subjects in North America, the EU, and rest of world may become eligible and choose to be enrolled in this study. This is an estimate of the number of subjects from Core Study (PPSO-003) that may complete Week 52 and choose to

continue receiving apremilast in Long-term Extension Study (PPSO-004). For a common adverse event with subject incidence rate of 5%, 10% or 15% in this extension study, the two-sided 95% confidence intervals will be (1.4%, 8.6%), (5.0%, 15.0%), or (9.1%, 20.9%) respectively.

Assuming two years as the average for subjects receiving apremilast treatment in the extension study, the overall apremilast exposure in the extension study will be estimated as 280 subject-years. For a common adverse event with the exposure adjusted incidence rate (EAIR) of 3.0, 5.0 or 7.0 per 100 subject-years in the extension study, the two-sided 95% confidence interval for EAIR ranges are (0.9, 5.1), (2.2, 7.8) or (3.7, 10.3) respectively, using a normal approximation approach based on the Poisson distribution assumption.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable.

4.2 Subgroups

Not applicable.

5. Definitions

5.1 Baseline Definitions

Three approaches for baseline will be used:

- Assessment by the randomization date in the Core Study (PPSO-003)

This approach will be used for Efficacy (sPGA) data based on the Long-term Extension Treatment Population.

- Assessment by the first apremilast dose date in the Core Study (PPSO-003)

This approach will be used for all Safety analyses using Clinical Laboratory data based on the Long-term Extension Treatment Population in the Long-Term Extension Phase and Apremilast-exposure Period, Vital Signs data based on the Long-term Extension Treatment Population in the Apremilast-exposure Period.

- Assessment by the first apremilast dose date in the Long-term Extension Study (PPSO-004)

This approach will be used for Safety analyses using Vital Signs data based on the Long-term Extension Treatment Population in the Long-Term Extension Phase.

5.2 Time Points

Time points for Apremilast-exposure Period are based on the remapped visits/study weeks using the visit mapping algorithm table listed in Appendix B, which may or may not be the same as the visits/study weeks as recorded in the database.

Post-baseline time points in all analyses will come from original visit information from database, terminated visit will be mapped to next scheduled visit accordingly.

The details are specified in Appendix B.

5.3 Analysis Phases or Periods

5.3.1 Analysis Phases

Per protocol specification, data summary and analysis will be provided for the following phases.

- Long-term Extension Phase – up to 208 weeks

This phase starts on the day of Visit 1/Week 0 of the Long-term Extension Study (PPSO-004) which corresponds to Visit 16/Week 52 of the Core Study (PPSO-003), and stops on either: (1) the day of Visit 11/ Week 208; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Visit 11/Week 208; or (3) the last known study day if the subject is lost to follow-up prior to Visit 11/Week 208 during the phase.

- Observational Follow-up Phase – 8 weeks

This 8 weeks Observational Follow-up Phase starts at the next day after the completion or discontinuation visit and stops at the last follow-up visit or the last assessment date. The follow-up period consists of two visits, one 4 weeks after last dose of apremilast and one 8 weeks after last dose of apremilast.

5.3.2 Apremilast-exposure Period for Safety Analysis

In addition to the above defined phases, the Apremilast-exposure Period will be used for safety analyses. This period which covers both the Core Study (PPSO-003) and the Long-term Extension Study (PPSO-004), starts on the date of either: (1) the first dose of apremilast following randomization (Visit 2/Week 0) in the Core Study for subjects who are treated with apremilast from Week 0 of the Core Study; or (2) the first dose of apremilast from the apremilast dispensed at Visit 7/Week 16 of the Core Study for

subjects who were originally treated with placebo and then treated with apremilast at Week 16 of the Core Study.

For subjects who received treatment in the Long-term Extension Study, this period stops on either: (1) data cut-off date; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Visit 11/Week 208 of the Long-term Extension Study; or (3) the last known study day if the subject lost to follow-up prior to Visit 11/Week 208 of the Long-term Extension Study; or (4) Visit 11/Week 208 of the Long-term Extension Study visit date.

5.4 Definition of Analysis Populations

5.4.1 Long-term Extension Treatment Population

This will consist of all subjects who received at least one dose of apremilast in the Long-term Extension Study (PPSO-004). Both the safety and efficacy analyses will be performed using this analysis population. The treatment groups will be presented as:

For safety analysis:

- APR Total

For efficacy and other analysis:

- Placebo/APR/APR
- APR/APR/APR

Which based on the initial treatment in Core study (PPSO-003).

5.5 Derivation of Efficacy Endpoints

The derivation of efficacy endpoint is described below. Baseline definition for efficacy endpoint is given in Section 5.1. Handling of time points is described in Section 5.2.

5.5.1 Static Physician Global Assessment (sPGA)

The sPGA is the assessment of whole body psoriasis by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from clear (0), almost clear (1), mild (2), moderate (3), to severe (4), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation.

The sPGA response at a post-baseline visit is defined as achieving sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline.

5.6 Derivation of Safety Endpoints

Baseline definition for all safety endpoints is given in Section 5.1. Change from baseline is calculated as post-baseline visit value minus the baseline value. Percent change from baseline is defined as 100* Change from baseline/Baseline value (%). Handling of time points is described in Section 5.2.

5.6.1 Treatment-emergent Adverse Event

An AE is a treatment-emergent AE (TEAE) if the AE start date is:

- On or after the date of the first dose of IP and no later than 28 days after the last dose of IP for subjects who have completed study treatment or have discontinued early by the time of database cut, or
- On or after the date of the first dose of IP for subjects who are ongoing with study treatment at the time of database cut.

If the treatment-emergent status of an AE is unclear due to a missing/incomplete start date, it will always be considered treatment-emergent, unless shown otherwise by data. Date imputation rules for missing AE start dates are described in Appendix C.

For the Long-Term Extension Phase (Week 0 to 208), TEAEs include AEs started on or after the first apremilast dose date of the Long-term Extension Study and within 28 days of the last dose date.

For the Apremilast-exposure Period, TEAEs include adverse events started on or after the first apremilast dose date and within 28 days of the last apremilast dose date.

Adverse event started more than 28 days after the last dose of apremilast will not be considered as a TEAE.

5.6.2 Treatment-emergent Adverse Events Leading to Drug Withdrawal, Leading to Drug Interruption, and Leading to Death, and Drug-related Treatment-emergent Adverse Events

A TEAE leading to drug withdrawal is a TEAE for which the investigator indicates that the action taken with respect to IP is withdrawn permanently. A TEAE leading to drug interruption is a TEAE for which the investigator indicates that the action taken with respect to IP is interrupted. A TEAE leading to death is a TEAE for which the outcome is fatal. Relationship to IP is based on the investigator's causality judgment; that is, a drug-related AE is an AE indicated by the investigator to have a suspected relationship to IP.

5.6.3 Psychiatric Evaluation

Subjects will complete the C-SSRS assessment. This questionnaire is suitable for assessment of suicidal ideation and behavior in clinical and research settings. The assessment will be completed at baseline, and at post-baseline visits.

Any subject that answers 'Yes' to any question on the C-SSRS at any time during the study will be immediately withdrawn from study treatment.

5.6.4 Psoriasis Flare and Psoriasis Rebound

Psoriasis flare will be considered an AE (and will be recorded as an AE) and represents an atypical or unusual worsening of disease during treatment. It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. A more typical, gradual worsening of plaque psoriasis will not be recorded as an AE.

Rebound will be considered as an AE and is defined as a severe and sudden worsening of disease or a new generalized pustular, erythrodermic, or more inflammatory psoriasis that occurred after treatment had been discontinued.

Psoriasis AEs will be selected as those containing the word "psoriasis" in the coded preferred term (PT). A psoriasis flare is defined as a psoriasis AE started during treatment with IP. A psoriasis rebound is defined as a psoriasis AE started after the last dose of IP.

5.6.5 Body Weight, Height and Body Mass Index (BMI)

Body weight (kg) and height (cm) will be measured and recorded at study visits. The BMI (kg/m2) is calculated as BMI = Weight / $(Height/100)^2$. The variables include the observed value, change and percent change from baseline over time.

It is now common practice to express child growth status in the form of the BMI standard deviation scores (Z-score). The LMS method provides a way of obtaining normalized growth centile standards. It assumes that the data can be normalized by using a power transformation, which stretches one tail of the distribution and shrinks the other, removing the skewness. The LMS parameters are the power in the Box-Cox transformation (L), the median (M), and the generalized coefficient of variation (S).

For a given value of BMI of a boy or girl with known age, the corresponding z-score (Z) can be calculated as:

$Z = [(BMI/M)L – 1]/LS,$

where the coefficients L, M, S are from the BMI percentile values in Data Table of BMI-for-age Charts (male and female 2 to 20 years) (CDC 2002). The L, M, and S parameters and selected percentiles for BMI will be used for classification.

BMI are classified as:

- Underweight: Percentile < 5
- Healthy Weight: Percentile ≥ 5 to < 85
- Overweight: Percentile ≥ 85 to < 95
- Obesity: Percentile ≥ 95

5.6.6 Vital Signs

Vital signs include:

- Observed value and change from baseline over time in vital signs (temperature, pulse, and blood pressure)
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal in pulse and blood pressure (normal ranges are defined as: 60 100 beats/minute for pulse, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure)

5.6.7 Clinical Laboratory Evaluations

Laboratory evaluations include:

- Observed value and change from baseline over time in hematology and serum chemistry parameters
- Laboratory marked abnormalities
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low or high) in hematology and serum chemistry parameters

6. Analysis Sets

6.1 Full Analysis Set

6.1.1 Long-term Extension Treatment Population

This will consist of all subjects who received at least one dose of apremilast in the Long-term Extension Study (PPSO-004).

6.2 Safety Analysis Set

Safety Analysis will use Long-term Extension Treatment Population as analysis set.

6.3 Per Protocol Set(s)

Not applicable.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable.

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

Not applicable.

6.6 Interim Analyses Set(s)

Not applicable.

6.7 Study-specific Analysis Sets

Not applicable.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim analysis will be conducted. However, safety and efficacy data of this Long-term extension study may be analyzed before study completion. For those analysis, data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible. The data supporting the interim analysis will be locked to prevent further changes.

7.2 Primary Analysis

Not applicable.

7.3 Final Analysis

The final analysis will be conducted after study completion (end of study for the last subject) is reached and all study data are collected. Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the final lock.

8. Data Screening and Acceptance

8.1 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.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

Missing values for efficacy endpoint will be imputed by non-responder imputation (NRI) and data as observed (DAO) for binary endpoints.

The handling of incomplete and partial dates for adverse events and concomitant medications etc. will be described in Appendix C.

8.4 Detection of Bias

Not applicable.

8.5 Outliers

Data outliers will be identified through the data quality review process and visual examination of the distribution of the variables, and queried as appropriate. Any outliers that have been verified through the query process will be treated as valid data and analyzed accordingly in the analysis.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required, data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 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 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

The efficacy endpoint will be summarized descriptively. To evaluate the responses over time, the proportion of subjects achieving the response along with two-sided 95% confidence intervals at the specified time points will be presented.

Safety will be assessed by clinical review of all relevant parameters including treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, height, weight, BMI, Tanner staging, and C-SSRS.

Descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) will be presented for continuous variables at specified time points. Specifically, for continuous variables, descriptive statistics for assessment values and change (plus percentage change when specified) from baseline will be provided.

Frequency and percentage will be summarized by treatment arm for binary and categorical variables.

9.2 Subject Accountability

The number and percent of subjects who entered, received study treatment, and completed the study will be summarized by treatment group. The number and percent of subjects who discontinued study treatment, and study will be tabulated, along with the reason for discontinuation. Reason for subject exclusion will also be presented.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of IP, and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Protocol deviations and important protocol deviations will be categorized by the Clinical Research Medical Director (CRMD). A list of protocol deviations and important protocol deviations for all subjects for any interim analysis will be defined prior to the database lock. The list of protocol deviations and important protocol deviations for all subjects for final analysis will be finalized prior to the final database lock.

Protocol deviations and important protocol deviations will be summarized for the Long-term Extension Phase (Weeks 0 to 208). Summary tables showing the number and percent of subjects with at least one protocol deviation and important protocol deviations and by each category of protocol deviations and important protocol deviations will be provided. Listings of subjects with important protocol deviations and protocol deviations impacted by COVID-19 will be provided. Further details about the analysis methods that will be used are specified in Appendix D.

9.3.1 Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and/or returned and/or lost will be recorded at visits in the long-term extension phase. These records will be used to calculate treatment compliance.

The treatment compliance (in %) for each subject will be computed as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) over the long-term extension phase divided by the intended total number of tablets that should have been taken over the Long-term Extension Phase.

Summary statistics for compliance (%) will be provided by treatment arm for the long-term extension phase. Frequency summary tables of compliance will also be presented with the following categories: < 75%, >= 75% - <= 120%, and > 120%. A subject data listing of drug accountability records will be provided.

Treatment compliance will be calculated for the treatment duration in the phase specified in 5.3 and will be summarized for the Long-term Extension Treatment Population.

9.4 Subject Disposition

The number of subjects who consent to participate to the Long-term Extension Study (PPSO-004), the number and percentage of subjects who receive at least one dose of apremilast will be summarized. The failed inclusion/exclusion criteria of subjects who consented to participate and did not receive apremilast will be included in the summary. Also, a summary of number of subjects by site will be provided. The above percentages will be based on the number of subjects who consented to participate. Further details about the analysis methods that will be used are specified in Appendix D.

Subject disposition will be provided by phase:

- Long-term Extension Phase – up to 208 weeks

Summary will be based on subjects who entered the Long-term Extension Phase. Subjects who entered the phase, took at least one dose of IP, completed, discontinued early, and primary reason for discontinuation will be provided.

- Observational Follow-up Phase (8 weeks)

Summary will include subjects who entered Follow-up Phase. Subjects who entered the phase, completed, discontinued early, and primary reason for discontinuation will be provided.

The primary reasons for discontinuation are collected in the treatment disposition and follow-up disposition electronic case report form (eCRF) using the following categories:

- Adverse event

- Lack of efficacy
- Withdrawal by subject
- Withdrawal by parent/guardian
- Death
- Lost to follow-up
- Non-compliance with study drug
- Protocol deviation
- Pregnancy
- Study terminated by Sponsor
- Other

Subjects disposition due to COVID-19 will also be summarized.

9.5 Demographic and Baseline Characteristics

Summaries for the demographics, baseline characteristics, prior medication/procedure, and concomitant medications/procedure will be presented for the Long-term Extension Treatment Population by treatment group and overall in both Core Study (PPSO-003) and Long-term Extension study (PPSO-004). The summaries will be based on data collected by date of randomization in the Core Study and data collected by the first visit of the Long-term Extension Study. Further details about the analysis methods that will be used are specified in Appendix D.

9.5.1 Demographics

Summary statistics will be provided for the following continuous variables:

- Age (years)
- Weight (kg)
- Height (cm)
- Baseline Body Mass Index (BMI; kg/m^2)

These continuous variables will be summarized both at randomization in the Core Study and at first visit in the Long-term Extension Study.

Number and percentage will be provided for the following categorical variables:

- Sex (Male, Female)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age category (6-11, 12-17 years) both at randomization in the Core Study and at first visit of the Long-term Extension Study

· Weight category (≥ 20 kg to < 50 kg, ≥ 50 kg) both at randomization in the Core Study and at first visit of the Long-term Extension Study

· BMI category (underweight, healthy weight, overweight, obesity) both at randomization in the Core Study and at first visit of the Long-term Extension Study

· Geographical region (USA, Canada, Europe, Rest of the World)

Treatment sequence will be presented in the listings to specify treatment dose information in treatment phases repectively.

9.5.2 Baseline Disease Characteristics

Baseline disease characteristics will include sPGA score category at randomization in the Core Study (PPSO-003) and at first visit in the Long-term Extension Study (PPSO-004).

9.5.3 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. A frequency summary (counts and percentage) of medical history will be presented by system organ class (SOC) and PT.

Subject data listing will be presented for medical history.

9.5.4 Concomitant Procedures

Concomitant procedures will be coded using the MedDRA version 24.0 or higher.

A concomitant procedure is defined similarly as a TEAE. Concomitant procedures will be summarized similarly as TEAEs for the Long-term Extension Phase (Weeks 0 to 208) and Apremilast-exposure Period.

9.5.5 Prior and Concomitant Medications

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version March 2020 or higher) will be used to group prior and concomitant medications and prior psoriasis medications into relevant categories.

Prior medications will be those that started before the first dose of IP in the Core Study (PPSO-003) study and concomitant medications are all non-study medications that started either during the Core Study or the Long-term Extension (PPSO-004) study.

Medications in the Observational Follow-up Phase will include those medications started on or after the date of last dose of Apremilast in the Long-term Extension Phase (PPSO-004).

9.6 Treatment Duration

Treatment duration will be summarized for apremilast for the Long-term Extension Phase and for the Apremilast-exposure Period based on the Long-term Extension Treatment Population.

Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories and exposure categories will be provided.

9.6.1 Long-term Extension Phase (Weeks 0 to 208)

Treatment duration is calculated from the first dose date in the Long-term Extension Phase for the IP dispensed at Visit 1/Week 0 to the date of the last dose of IP in the study for subjects who discontinue in the phase or who complete the study at Visit 11/Week 208. The imputation rule for partially or completely missing last dose date is specified in Appendix C.

9.6.2 Apremilast-exposure Period

Treatment duration for Apremilast-exposure Period is calculated from the date of the first dose of apremilast, which is the date of the first dose of apremilast after randomization in the Core Study (PPSO-003) at Visit 2/Week 0 or switched to apremilast at Visit 7/Week 16, to the last apremilast dose date in the Long-term Extension Study (PPSO-004). The imputation rule for partially or completely missing last dose date is specified in Appendix C.

9.7 Efficacy Analyses

The only efficacy endpoint is the proportion of subjects achieving sPGA response at all visits (defined as sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline).

The analysis will be conducted using the Long-term Extension Treatment Population. Assessment timepoints during the Long-term Extension study will be included.

This endpoint will be summarized descriptively with frequency (counts and percentages) tabulations at all time points (Section 5.2) and will be presented both by DAO (data as observed) and NRI (non-responder imputation). The summary table will present data for Placebo/APR/APR and APR/APR/APR based on initial randomization in the Core Study (PPSO-003). To evaluate the responses over time, the proportion of subjects achieving the response at the specified time points will be presented. Figure will also be presented using DAO method. There will be no formal comparisons between treatments (dose levels). Also, a listing of sPGA scores will be provided. Further details about the analysis methods that will be used are specified in Appendix D.

Baseline will be based on the last value measured prior to or on the randomization date in the Core Study (PPSO-003).

Missing data will be handled by non-responder imputation (NRI) and data-as-observed (DAO).

No formal interim analysis will be conducted. However, efficacy data of this Long-term Extension Study (PPSO-004) may be analyzed before study completion.

9.8 Safety Analyses

Safety will be assessed via descriptive statistics and point estimates. Unless otherwise specified, all safety analyses described in this section will be performed for both the Long-term Extension Phase and the Apremilast-exposure Period based on the Long-term Extension Treatment Population and presented by APR Total group. Further details about the analysis methods that will be used are specified in Appendix D.

The analyses of TEAEs for Long-term Extension as well as for Apremilast-exposure period will include those from first dose date and within the 28 days of the last dose date. Other analyses of safety data, such as, Vital Signs, Clinical Laboratory, will also include data from assessments within 28 days of last dose, but excluding follow-up visit data for Long-term Extension study.

For the analyses of AEs and marked abnormalities, the following point estimates are distinguished:

- Subject incidence: Subject incidence (i.e., percentage [%] used in a frequency summary) is defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.

• Exposure-adjusted incidence rate (EAIR) per 100 subject-years: The EAIR per 100 subject-years is defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator. The exposure time for a subject without the specific event is the treatment duration, whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event. For subjects only having the specific event started after and within the 28 days of the last dose date, the exposure time will be calculated to the last dose date. The total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25. The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 subject-years of exposure to the IP.

Adverse events and marked abnormalities will be summarized by subject incidence and EAIR for the Long-term Extension Phase (Week 0 to 208) and for the Apremilast-exposure Period. In addition, selected summaries for the Observational Follow-up Phase (Week 208 to 216) from the last dose date will be presented.

Descriptive statistics will be provided for vital signs, weight, height and BMI, C-SSRS, laboratory values (continuous measurements) by treatment and visit, including the end of treatment visits. The baseline value, value at the time point, and change from baseline will be summarized for subjects who have values at baseline and at the time point.

Shift tables, that is, tables that summarize the baseline categories (normal, abnormal) versus the category at the end of the respective periods or versus the worst post-baseline category, include subjects who have values at baseline and at least one post-baseline value. Similarly, in frequency summaries (counts and percentages) of shifts from baseline at scheduled study weeks per protocol, only subjects who have values at baseline and at the time point will be included. Tanner staging of sexual development shift table will also be provided, respectively.

No formal interim analysis will be conducted. However, safety data of this Long-term Extension Study may be analyzed before study completion.

9.8.1 Adverse Events

Adverse events will be coded according to the MedDRA version 24.0 or higher. Unless otherwise specified, AEs will be summarized by SOC and PT frequency (counts and

percentages), with SOCs presented in the standard international order and PTs within SOCs presented in descending order of subject incidence.

9.8.1.1 Overall Summary of TEAEs

An overall summary of frequency (counts and percentages) of subjects in the following TEAE categories will be provided for the Long-term Extension Phase (Weeks 0 to 208) for subjects with:

- Any TEAE
- Any drug related TEAE
- Any severe TEAE
- Any serious TEAE
- Any serious drug related TEAE
- Any TEAE leading to drug interruption
- Any TEAE leading to drug withdrawal
- Any TEAE leading to death

In addition, overall summary of TEAEs will also be provided for the Apremilast-exposure Period.

9.8.1.2 All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence). Summaries will be provided for the Long-term Extension Phase (Weeks 0 to 208) and the Apremilast-exposure Period.

New events of all TEAEs by exposure interval will be summarized for the Apremilast exposure period. Also, new events of all TEAEs by exposure interval will be summarized for the Long-term extension phase will be presented. Each subject is counted once for either subject incidence or EAIR for each applicable specific TEAE in each exposure interval where an event started. The denominator of a subject incidence is the number of subjects with treatment duration exceeding the lower bound of the particular exposure interval, while the denominator of an EAIR is the sum of the exposure time during the exposure interval (up to the first event start date for subjects with at least one event starting in the interval) among the same number of subjects as in the denominator of the corresponding subject incidence.

All TEAEs will be summarized by age category (6-11, 12-17 years), sex, and race. Specifically, age category is based on the age collected at the first visit in the Long-Term Extension Study (PPSO-004) for the Long-term Extension Phase and at randomization in the Core Study (PPSO-003) for the Apremilast-exposure Period.

All AEs more than 28 days after the last dose date will be summarized by SOC and PT for the observational follow-up phase. All AEs occurring after 28 days of the last dose date will be listed.

TEAEs in the Gastrointestinal systerm organ class will also be summarized.

9.8.1.3 Common TEAEs

The TEAEs with subject incidence ≥ 5% in any treatment group will be summarized by SOC and PT in descending order of subject incidence for the Long-term Extension Phase and the Apremilast-exposure Period.

9.8.1.4 Drug-related TEAEs

Drug-related TEAEs will be summarized and new events of drug-related TEAEs by exposure interval will be summarized for both the Long-term Extension Phase and the Apremilast-exposure Period.

9.8.1.5 TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing). If a subject reports multiple occurrence of a specific event within a specific analysis phase or period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the “missing” category of severity. TEAEs by maximum severity will be summarized for both the Long-term Extension Phase and the Apremilast-exposure Period. Severe TEAEs will also be summarized for both the Long-term Extension Phase and the Apremilast-exposure Period.

9.8.1.6 Serious TEAEs

Serious TEAEs and serious drug-related TEAEs will be summarized for both the Long-term Extension Phase and the Apremilast-exposure Period.

A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

9.8.1.7 TEAEs Leading to Drug Interruption and TEAEs Leading to Drug Withdrawal

All TEAEs leading to drug interruption and TEAEs leading to drug withdrawal will be summarized for the Long-term Extension Phase and the Apremilast-exposure Period.

A subject data listing of TEAEs leading to drug withdrawal will also be provided.

9.8.1.8 Deaths

TEAEs leading to death by SOC and PT will be summarized for both the Long-term Extension Phase and the Apremilast-exposure Period. A subject data listing of all deaths will also be provided.

9.8.1.9 Onset and duration

For selected TEAE events, categories for onset (start) day from the first dose date and event duration (from start date to end date) will be summarized for the Long-term Extension Phase and the Apremilast-exposure Period.

9.8.2 Laboratory Test Results

Summary statistics of observed values and changes from baseline in laboratory parameters will be provided at each time point. Frequency summaries (counts and percentages) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be also provided .

Laboratory marked abnormalities (Appendix A) will be summarized; subject incidence and EAIR for each abnormality will be calculated based on subjects with a baseline value and at least one post-baseline value for criteria requiring baseline or subjects with at least one post-baseline value for criteria not requiring baseline. A subject data listing of laboratory marked abnormalities will be provided. Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and for subjects with abnormal values at baseline separately. For the purposes of these summaries, subjects with abnormal (normal) values at baseline are defined as those whose baseline value is low (not low) for criteria concerning low values and those whose baseline value is high (not high) for criteria concerning high values; both low and high are relative to the laboratory normal range.

Subject data listings for clinical laboratory data, grouped by hematology, serum chemistry and urinalysis, will be provided.

9.8.3 Vital Signs

Summary statistics of observed values and changes from baseline in vital signs will be provided at each time point. Frequency summaries (counts and percentages) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal categories will also be provided for pulse and blood pressure.

A subject data listing of all vital signs will be provided.

9.8.4 Physical Measurements

The protocol specified that physical examination findings of clinical significance (as defined by the investigator) are to be reported as AEs. No summary of physical examination findings will be provided.

9.8.5 Psychiatric Evaluation

Subjects will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) assessment. This questionnaire is suitable for assessment of suicidal ideation and behavior in clinical and research settings. The assessment will be completed at all study visits.

Summary (counts and percentages) and subject data listing of C-SSRS results will be provided.

9.8.6 Weight, Height and BMI

Body weight and height will be measured at each study visit. Body mass index will be calculated using weight and height.

Body weight, height and BMI will be summarized using change and percent change from baseline in the Long-term Extension Phase.

Weight change (kg) and percent change (%) from baseline will also be summarized using categories (same for both) as < -20, <= -20 to < -10, <= -10 to < -5, <= -5 to < 0, 0, > 0 to <= 5, > 5 to <= 10, > 10 to <= 20, and > 20 (same for both parameters with unit kg for weight change and % for percent change) at the end of treatment phase or period.

The BMI will also be summarized for shifts from baseline to post-baseline time points using the following four categories: Underweight: percentile < 5; Healthy Weight: percentile >= 5 to < 85; Overweight: percentile >= 85 to < 95; Obesity: percentile >= 95. The BMI percentile values in Data Table of BMI-for-age Charts (male and female 2 to 20 years) were used (2000 CDC Growth Charts for the United States: Methods and Development, https://www.cdc.gov/growthcharts/clinical_charts.htm).

Data listing will be provided for weight, height and BMI. Subjects with a weight decrease from baseline of >= 10% will be flagged in the overall listing (e.g. using a *).

9.8.7 Tanner Staging of Sexual Development

Assessments of sexual maturity (Tanner Staging) will be performed at Week 0 (Visit 1) and then every 52 weeks or at the Early Termination visit for subjects that do not complete the study. Summary and subject data listing of Tanner Staging assessment findings will be provided.

9.8.8 Psoriasis Flare and Rebound

Subjects with psoriasis flare will be summarized for the Long-term Extension Phase and for the Apremilast-Exposure Period. Subjects with psoriasis rebound will be summarized for Subjects who entered Follow-up after Long-term Extension Treatment.

9.8.9 Exposure to Concomitant Medication

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version March 2020 or higher) will be used to group prior and concomitant medications and prior psoriasis medications into relevant categories. Frequency summaries (counts and percentages) will be provided by treatment group, ATC level, and standardized medication name for the Long-term Extension Treatment Population.

Frequency summaries (counts and percentages) will be provided for prior medications. Frequency summaries (counts and percentages) will also be provided for concomitant medications in the: (1) Long-term Extension Phase (Weeks 0 to 208), (2) Apremilast-exposure Period, and (3) Observational Follow-up Phase.

9.8.10 Exposure to Concomitant Procedures

Concomitant procedures will be coded using the MedDRA version 24.0 or higher. Frequency summaries (counts and percentages) of concomitant procedures will be provided for the Long-term Extension Treatment Population and in the Observational Follow-up Phase by SOC and PT.

A concomitant procedure is defined similarly as a TEAE. Concomitant procedures will be summarized similarly as TEAEs for the Long-term Extension Phase (Weeks 0 to 208) and Apremilast-exposure Period.

9.9 Other Analyses

9.9.1 Analyses of COVID-19 impacted data

Analyses will be performed to assess the impact of COVID-19 on the amount of data collected for the study.

9.9.2 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Not applicable.

9.9.3 Analyses of Clinical Outcome Assessments

Not applicable.

9.9.4 Analyses of Health Economic Endpoints

Not applicable.

9.9.5 Analyses of Biomarker Endpoints

Not applicable.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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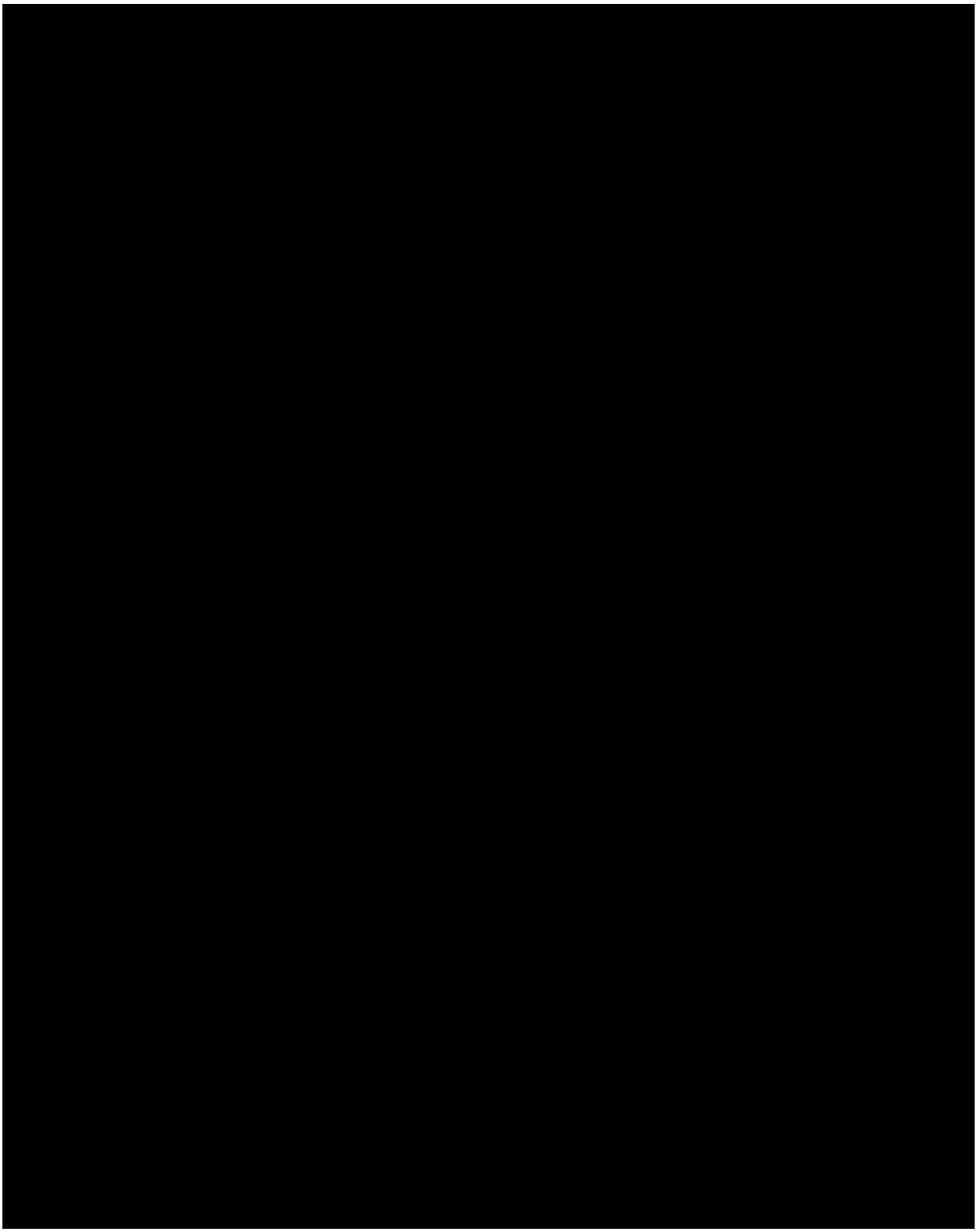
12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

14. Appendices



Appendix B. Analytical Windows

For analysis in the Apremilast-exposure Period (PPSO-003 and PPSO-004), the re-mapped visits as specified in Table 1 be used.

Table 1: Re-Mapped Visits for Analysis in the Apremilast-exposure Period

Subjects Initially Treated with Apremilast at Week 0 of Core Study		**Subjects Initially Treated with Placebo at Week 0 of Core Study**	
Original Visit (Week)	Re-mapped Visit (Week)	Original Visit (Week)	Re-mapped Visit (Week)
PPSO-003 Visits		PPSO-003 Visits	
0	0		
2	2		
4	4		
8	8		
12	12		
16	16	16	0
20	20	20	4
24	24	24	8
28	28	28	12
32	32	32	16
36	36	36	20
40	40	40	24
44	44	44	28
48	48	48	32
52/ Week 0 in PPSO-004	52	52/ Week 0 in PPSO-004	36
PPSO-004 Visits		PPSO-004 Visits	
13	65	13	48
26	78	26	65
39	91	39	78
52	104	52	91
78	130	78	104
104	156	104	130
130	182	130	156
156	208	156	182
182	234	182	208
208	260	208	234

Data collected in the observational Follow-up Phase will be summarized separately using up to two follow-up visits, i.e., 4-Week Follow-up, 8-Week Follow-up.

Appendix C. Partially Missing Date Imputation

Adverse Events

Partially missing AE start dates will be imputed in the ADaM dataset for AEs that started on or after the first dose of IP in the Long-term Extension Study otherwise, AE dates will be imputed in the ADaM dataset using the imputed dates from the Core Study. Partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", and the date of the first dose of IP as "$D_{IP}/M_{IP}/Y_{IP}$". Table 4 gives the imputation rules for partially missing AE start dates for subjects who were treated with apremilast in the Long-term Extension Study.

Table 2: Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Apremilast in the Long-Term Extension Study

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{IP}$	$12/31/Y_{Event}$
2	Otherwise, i.e., $Y_{IP} \leq Y_{Event}$	Max (date of first dose of IP, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{IP}$, or ($Y_{Event} = Y_{IP}$ and $M_{Event} < M_{IP}$)	Last date of M_{Event}/Y_{Event}
2	Otherwise, i.e., $Y_{IP} < Y_{Event}$, or ($Y_{IP} = Y_{Event}$ and $M_{IP} \leq M_{Event}$)	Max (date of first dose of IP, $1/M_{Event}/Y_{Event}$)

Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

Medical History

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history (for the purposes of calculating durations of PsA and psoriasis). The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

Treatment Duration

Partially or completely missing last dose dates will be imputed in the ADaM dataset for treatment duration.

When partially missing last dose date is available, set last dose date to the maximum of [the earliest possible date given the non-missing field(s) of last dose date, the minimum of (the latest possible date given the non-missing field(s) of last dose date, last known date in database, first non-missing Early Termination (ET) visit date)].

When last dose date is completely missing, set last dose date to the minimum of (last known date in database, first non-missing Early Termination (ET) visit date).

Last known date in database is defined as maximum of (last visit date, lab, vital signs, AE start or end dates, concomitant medications start or end dates, concomitant procedure date, last dose date from 'Disposition- Treatment' page, death date).

Appendix D. Reporting conventions

· Summary tabulation will be provided by dose level (20 mg BID, 30 mg BID);

· Statistical test of the treatment difference will use two-sided significance level 0.05 for significance or nominal significance.

· P-values will be rounded to 4 decimal places. p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';

· Standard errors (SEs) and confidence intervals (CIs) will be presented as two-sided 95% CIs unless specified differently in specific analysis;

· Summary statistics will consist of

. the number and percentage of subjects in each category for discrete variables, OR

. the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables.

· the 25th (Q1) and 75th (Q3) percentiles will also be included for efficacy continuous variables;

· Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value;

· Percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses;

· Analysis and summary tables will have the analysis population sample size (i.e., number of subjects) in the column header;

· Subject data listings will be provided to support the tables and graphs. Listings will be sorted for presentation in order of subject number and date of procedure or event.