DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-10004-PPSO-001

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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STATISTICAL ANALYSIS PLAN

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF APREMILAST (CC-10004) IN PEDIATRIC SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

STUDY DRUG: **Apremilast (CC-10004)**

PROTOCOL NUMBER: **CC-10004-PPSO-001**

DATE FINAL: **15-MAR-2017**

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SAP AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	Statistical analysis plan for a Phase 2, Multicenter, Open-label Study to Assess the Safety, Tolerability and Pharmacokinetics of Apremilast (CC-10004) in Pediatric Subjects with Moderate to Severe Plaque Psoriasis
SAP VERSION, DATE	Final V1.0, 15-MAR-2017
SAP AUTHOR	Printed Name and Title / Signature and Date
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PROTOCOL VERSION, DATE	Amendment 1 Final, 17-AUG-2015, Amendment 2 Final, 29-APR-2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this Statistical Analysis Plan (SAP) and find its contents to be acceptable.
Statistical Therap	
Signature	
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Study Statistician	
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Lead Product Safety Physician	
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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamic pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomical Therapeutical Chemical (coding)
BID	Twice daily
BLQ	Below the limit of quantification
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case report form
CV	Coefficient of variation
DBS	Dried blood spot
DMC	Data monitoring committee
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
HR	Heart rate
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	Non-linear mixed effect modeling
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
PR	Interval from the beginning of the P wave to the beginning of the QRS complex
PT	Preferred term
QT	Interval between the start of the Q wave and the end of the T wave
QTcB	QT Interval corrected (Bazett's correction)
QTcF	QT Interval corrected (Fridericia's correction)
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SI	Standard international (unit)
SOC	System organ class
TBD	To be determined
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-10004-PPSO-001, "A Phase 2, Multicenter, Open-label Study to Assess the Safety, Tolerability, and Pharmacokinetics of Apremilast (CC-10004) in Pediatric Subjects with Moderate to Severe Plaque Psoriasis".

The initial analysis will include data cut off when all subjects complete the PK treatment period at Week 2. The final analysis will summarize data from the entire study, which includes the screening to the final long-term follow-up visit.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the Week 2 analysis. The SAP will be finalized and signed prior to database lock for Week 2 analyses. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is:

- To select a pediatric dose of apremilast based on the safety, tolerability, and PK of apremilast in adolescents and children with moderate to severe plaque psoriasis.

3.2. Secondary Objective

The secondary objective is:

- To evaluate the taste and acceptability of apremilast tablet using a faces Likert Scale.

3.3. Exploratory Objective

The exploratory objective is:

- To evaluate the effect of apremilast on psoriasis in adolescents and children as measured by the Psoriasis Area and Severity Index (PASI).

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 2, multicenter, open-label study of apremilast (CC-10004) in subjects aged 6 to 17 years, inclusive, with moderate to severe plaque psoriasis. The study will assess the safety, tolerability, and PK of apremilast during the first 2 weeks of treatment followed by a 48-week extension of apremilast treatment. The total study duration for each subject will last for up to a total of 107 weeks which includes screening, treatment (including the PK portion of the study and the extension treatment period), two short-term follow-up periods and a long-term follow-up period (Figure 1).

Figure 1: Overall Study Design

PK= Pharmacokinetics; OL= Open Label (Apremilast); F/U= Follow Up

Each subject will undergo a screening period of up to 5 weeks, a treatment period of 2 weeks with PK sample collection, and an extension treatment period of 48 weeks, to allow subjects access to apremilast treatment if medically appropriate (following the completion of the 2-week PK portion). Regardless of when they stop treatment, subjects should complete 2 post treatment follow-up visits at approximately 4 and 8 weeks after the last dose.

All subjects should complete the final follow-up visit at Week 102 or at a time point 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

At least 32 subjects will be enrolled into this study to provide an adequate PK profile and safety assessment in subjects of different ages and body weight ranges. Subjects will be divided into 2 age groups (adolescents [ages 12 to 17 years, inclusive] and children [ages 6 to 11 years, inclusive]), with at least 16 subjects in each group. Apremilast treatment will start in older and heavier subjects.

A staggered, stepwise approach by age range and weight (starting with older and heavier subjects) is considered appropriate for this first-time-in-children study. Doses for younger and lower body weight subjects will be adjusted based on safety and PK data from older and heavier subjects. Dosing within and between groups will be staggered as described below, and in Figure 2, based on PK data collected and a minimum of 2 weeks of safety data.

Group 1 (ages 12 to 17 years, inclusive; weight ≥ 35 kg)

- At least 8 subjects will initially be enrolled into Group 1 and will weigh ≥ 35 kg.
  - Dosing for subjects with a weight ≥ 35 kg to < 70 kg will be administered as a 20 mg twice daily (BID) dose regimen (10 mg BID less than the adult dose).
  - Dosing for subjects with a weight ≥ 70 kg will be administered as a 30 mg BID dose regimen (same as for adults).

- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 1 will be determined based on PK and safety assessments from the first 8 subjects in Group 1 to complete this period. These data will be reviewed by an independent data monitoring committee (DMC) to determine if it is appropriate to proceed with dosing the balance of Group 1 subjects and to proceed with dosing in the Group 2 subjects.

- For the remaining subjects in Group 1, the dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure. In the event of a dose regimen adjustment, some or all of the first 8 subjects in Group 1, depending on weight, will return to the site for the appropriate dosing adjustment. Group 2 will open to enrollment once at least 8 subjects from Group 1 have completed the 2 weeks of apremilast dosing, PK data analysis, and safety assessments and an evaluation of these data by the DMC has been completed.

Group 2 (ages 6 to 11 years, inclusive; weight ≥ 15 kg)

- At least 8 subjects will initially be enrolled into Group 2 and will weigh ≥ 15 kg. The dose regimens (dose strength and/or dose frequency) for these first 8 subjects will be based upon the PK and safety assessments from the first 8 subjects in Group 1. If PK and safety are not affected by age and body weight, 20 mg BID will be administered to Group 2 children.

- Dose regimens (dose strength and/or dose frequency) for the remaining subjects in Group 2 will be determined based on PK and safety assessments from the data collected from the first 8 subjects in each group. These data will be reviewed by an independent DMC to determine if it is appropriate to proceed with dosing the balance of Group 2 subjects.

- For the remaining subjects in Group 2, the dose (dose strength and/or dose frequency) will be based upon the subject weight as determined by the PK and safety assessments. The dose strength and/or dose frequency will be adjusted for any safety concerns or for unexpected changes in exposure. In the event of a dose regimen adjustment after the second PK and safety assessment, the first 8 subjects in Group 2 will return to the site for the appropriate dosing adjustment.

An independent DMC will review available safety and PK data at the following time points:

1. After the first 8 subjects in Group 1 have completed the first 2 weeks of apremilast dosing, PK, and safety assessments.

2. After the first 8 subjects in Group 2 have completed the first 2 weeks of apremilast dosing, PK, and safety assessments.

At this time, there are no consistent adverse events (AEs) or laboratory findings that would generally constitute a reliable stopping rule for this study. Subjects will be monitored for AEs, vital signs, and laboratory assessments at each study visit. All AEs, clinically significant changes in laboratory measures and clinically meaningful changes in vital signs will be recorded. Clinically meaningful changes that increase the risk to the subject, as assessed by the Investigator or Sponsor, may result in discontinuation of the subject from the study. Subjects who have psoriasis disease flare at any time during treatment (PK, or extension treatment period) in the study and require additional psoriasis medication including conventional systemic therapies such as methotrexate, systemic corticosteroids, or biologics, will be discontinued from the study and treated according to local treatment guidelines.

Figure 2: Subject Treatment Groups

Group 1:

N=16

Ages: 12 to 17 years, inclusive

Weight: ≥ 35 kg

Group 1:

Initial Dose:

20 mg BID for subjects weighing ≥ 35 kg to < 70 kg

30 mg BID for subjects weighing ≥ 70 kg

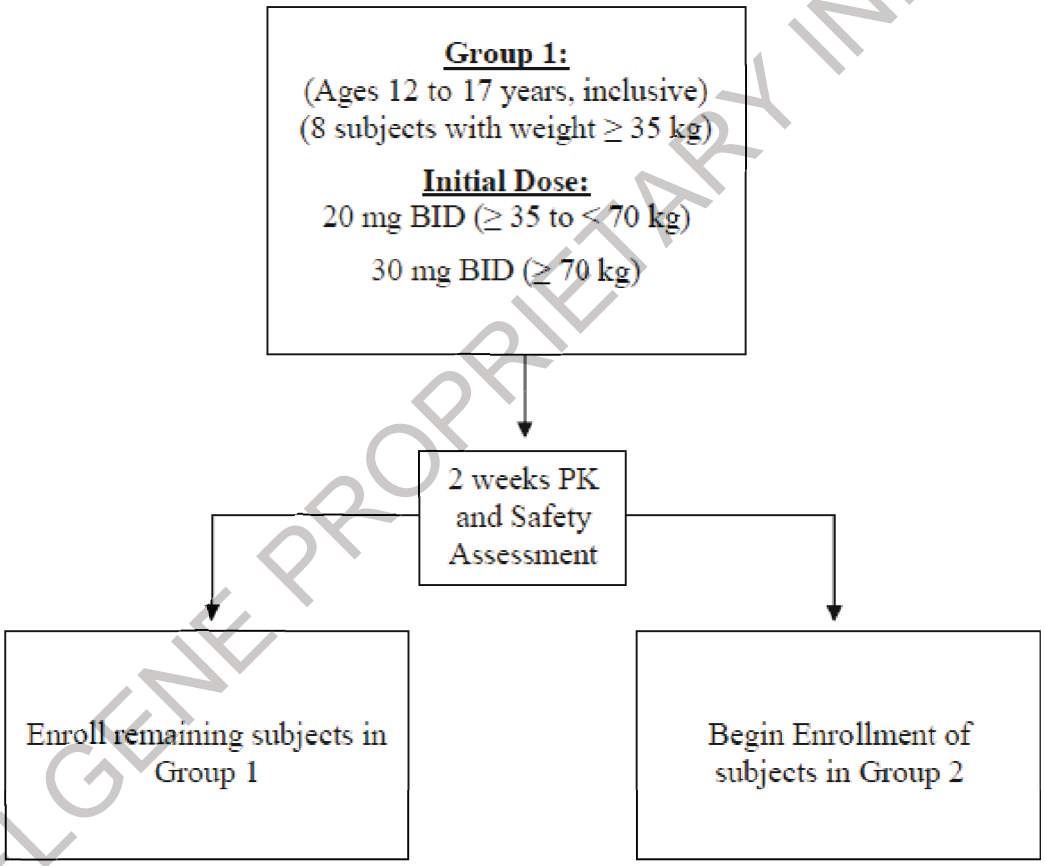


Figure 2: Subject Treatment Groups (Continued)

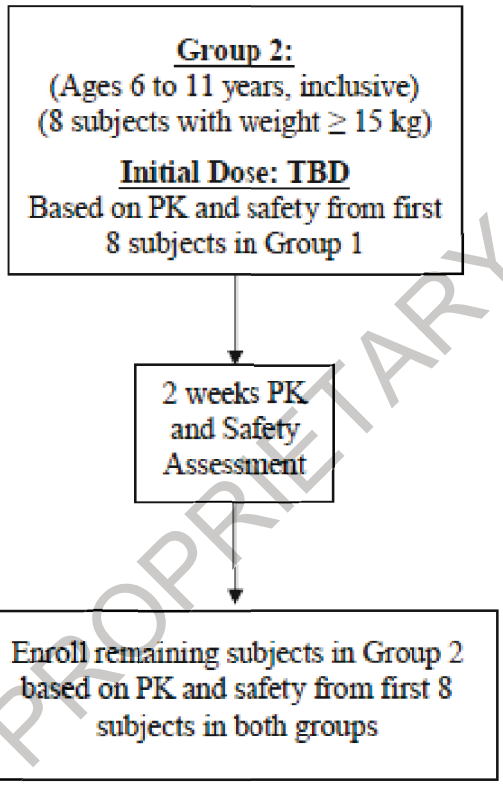
Group 2:

N=16

Ages: 6 to 11 years, inclusive

Weight: ≥ 15 kg

Dose: Based upon completion of PK and safety data analysis from at least 8 subjects from Group 1.



BID = twice daily; N = number of subjects; PK = pharmacokinetic; TBD = to be determined.

4.2. Study Endpoints

4.2.1. Primary Endpoint(s)

Safety

The safety (reported AEs) and laboratory findings of subjects in each age group will be described and evaluated in relation to the extent of exposure to apremilast.

The following will be monitored, evaluated, recorded and reported:

- Adverse events
- Physical examinations
- Vital sign measurements
- Clinical laboratory safety tests
- 12-lead electrocardiograms (ECGs)
- Concomitant medications / procedures

Pharmacokinetics

The following PK parameters will be estimated for apremilast using a non-compartmental approach if data permit:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$)
- Area under the plasma concentration-time curve from time zero to 12 hours postdose (AUC_{0-12})
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t})
- Apparent total plasma clearance when dosed orally (CL/F)
- Apparent total volume of distribution when dosed orally, based on steady-state (Vss/F) or the terminal phase (Vz/F)
- Terminal-phase elimination half-life ($t_{1/2}$)

The following population PK parameters will be determined as appropriate:

- CL/F
- Apparent total volume of distribution when dosed orally (V/F)
- Absorption rate constant (first-order; Ka)
- t_{lag} (if applicable)

4.2.2. Derivation of Safety Endpoints

4.2.2.1. 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 study drug and no later than 28 days after the last dose of study drug for subjects who have completed the study or have discontinued early by the time of database cut.

If the treatment-emergent status of an AE is unclear due to a missing/incomplete start date, it will be considered treatment-emergent. Date imputation rules for missing AE start dates are described in Appendix Section 15.1.1.

4.2.2.2. 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 study drug is withdrawn permanently. A TEAE leading to drug interruption is a TEAE for which the investigator indicates that the action taken with respect to study drug is interrupted. A TEAE leading to death is a TEAE for which the outcome is fatal. Relationship to study drug 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 study drug.

4.2.3. Secondary Endpoint(s)

The secondary endpoint is the taste and acceptability of apremilast tablets, as measured using a faces Likert Scale on Day 1, initial dosing.

4.2.4. Exploratory Endpoint(s)

The exploratory efficacy endpoint is the percent change in PASI scores from Baseline at Weeks 2, 4, 8, 16, 24, 32, 40, and 50.

4.2.5. Derivation of Exploratory Endpoint

The baseline definition for the exploratory efficacy endpoint is given in Section 5.2. Change from baseline is calculated as on-treatment value minus the baseline value. Percent change from baseline is defined as: (Change from baseline / baseline value) * 100%, as long as the baseline value is strictly greater than 0. Handling of time points is described in Section 5.3.

4.2.5.1. Psoriasis Area and Severity Index

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis.

PASI scores range from 0 to 72, with higher scores reflecting greater disease severity (Fredriksson, 1978). Erythema, thickness, and scaling are scored on a scale of 0 (none), 1 (slight), 2 (moderate), 3 (severe), to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each region is scored on a scale

of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. The PASI score will be set to missing if any severity score or degree of involvement is missing. PASI scores will be presented with one digit after the decimal point.

PASI score percent change from baseline (Visit 2/Week 0) is determined at each post Week 0 visit of the study, and is calculated as 100 * (visit score – baseline score)/ baseline score (%). Percent change will be rounded to one decimal place.

4.3. Randomization, Stratification, and Blinding

This is an open-label study in which subjects will be assigned a dose based on their age group and body weight. Therefore, no blinding or randomization is needed for this study.

4.4. Sample Size and Power

No formal sample size calculation will be performed. A sample size of at least 16 subjects per group has been selected to provide an adequate PK profile and safety assessment in subjects of different ages and body weight ranges. If needed, dropouts will be replaced to ensure that evaluable PK data from at least 32 subjects are collected.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Descriptive statistics for continuous variables include sample size (n), mean, standard deviation (SD), median, minimum, and maximum. 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. Frequency summary for categorical variables includes number and percentage. All percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x%). All analysis and summary tables will have the population sample size for each age group and overall in the column heading. P-values will be presented with 4 decimal places. All laboratory data will be reported using standard international (SI) units.

In data derivations requiring the date of the first dose of study drug dispensed at a specific visit, in the absence of a definitive record of this date, the study drug dispense date (from the study drug accountability records) associated with that visit, or if this date is also missing, then the visit date, will be used to estimate the date of the first dose of study drug. In the absence of a definitive record of the date of the last dose of study drug for subjects who have completed the study or have discontinued early, the date of the Week 50/Visit 10 visit or the date of the early termination visit will be used to estimate the last dose date for subjects who have completed the study or have discontinued early and have the discontinuation visit; for subjects who have discontinued but do not have the discontinuation visit, the last “follow-up” date, ie, the maximum date among the subject’s records of study visits, study drug records, AEs (start and end dates), concomitant medications/procedures, laboratory, vital signs, and ECG, will be used to estimate the last dose date.

5.2. Baseline Definition

For the baseline disease characteristics data summary and exploratory efficacy endpoint summaries, baseline is defined as the last value measured prior to or at the baseline visit (Week 0/Day 1).

For the summaries of safety, including laboratory parameters, vital signs, weight, and ECG parameters, baseline is defined as the last value measured prior to or on the day of the first dose of study drug.

5.3. Time Points

Time points in the analyses or summaries of safety or exploratory efficacy endpoint data over time include the scheduled study weeks per protocol, the end of a study period (eg, end of treatment, end of follow-up, end of study), and the observational follow-up visits. Appropriate dates (eg, date of assessment) will first be used to ensure only data (including data from scheduled, unscheduled, discontinuation, and observational follow-up visits) measured or

collected within the specific study period being analyzed or summarized are included, and then the visits/study weeks as recorded in the database will be used to assign one value (possibly missing) to each time point at the subject level. If a subject has more than one assessment for the same panel in the same day for a post-baseline visit, the assessments will be mapped to the same visit and visit number and the first non-missing score will be used for exploratory efficacy endpoint and safety analyses.

The time points for summaries of safety data (laboratory parameters, vital signs, weight, and ECG parameters) are based on study week/visit. Early termination visits will be mapped to the next scheduled visit after the actual last scheduled and completed visit. All subjects should complete the two initial follow-up visits 4 and 8 weeks after taking their last dose of apremilast regardless of when they stop taking apremilast. All subjects should complete the final follow-up visit at Week 102 or at a timepoint 52 weeks after the last dose of apremilast was taken in subjects who have withdrawn at any time prior to Week 50.

Subjects will be expected to visit the clinic for Screening, at Baseline (which includes Day 1 dosing and PK), at Day 14 (for AM dosing and PK), and 7 additional visits at Weeks 4, 8, 16, 24, 32, 40, and 50, during the extension period and for the Follow-up Visits 4 and 8 weeks after the last dose of apremilast is taken (eg, at Weeks 54 and 58). The visit window for the Day 14 Visit is ± 1 day. The visit window for the Week 4, 8, 16, 24, 32, 40, and 50 visits is ± 4 days and for the follow-up visits is ± 7 days.

5.4. Analysis Populations

5.4.1. Enrolled Population

The enrolled population will consist of all subjects who have study medication dispensed by the IVRS system.

5.4.2. Safety Population

The safety population will consist of all enrolled subjects who take at least one dose of apremilast. Safety and exploratory efficacy analyses will be based on this population.

5.4.3. Pharmacokinetic Population

The PK population will consist of all enrolled subjects who take at least one dose of apremilast and have evaluable PK data. PK data are considered evaluable if there are measurable drug levels of apremilast in plasma from at least 3 time points which extend over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

6. SUBJECT DISPOSITION

This section describes subject disposition for both subject study status and the subject analysis populations. Subject disposition will be summarized by age group and overall using frequency and percent for both treatment and follow-up study periods.

The number of subjects screened, the number and percentage of subjects enrolled and not enrolled among all subjects screened, and the reasons for not being enrolled will be summarized. The above percentages will be calculated using the number of subjects screened as the denominator.

The number of subjects enrolled and the number and percentage of subjects included in the safety population and PK population will be summarized by age group and dose regimen. Subjects withdrawing early and primary reason for withdrawal will be summarized. The above percentages will be calculated using the number of subjects enrolled as the denominator. The completion status and the reason for discontinuation will be listed.

Listings of subjects excluded from the analysis populations, with the reasons for exclusions, will be provided.

The number and percentage of subjects enrolled by region, country, and study site will be tabulated by age group and dose regimen. The percentages will be calculated based on the number of subjects enrolled.

Protocol deviations will be summarized using frequency tabulations.

The primary reasons for treatment discontinuation are collected on the treatment disposition case report form (CRF), and the primary reasons for study discontinuation are collected on the study disposition CRF. Those reasons will be summarized with the following categories:

- Adverse event
- Lack of efficacy
- Withdrawal by subject
- Lost to follow-up
- Protocol violation
- Termination by sponsor
- Non-compliance
- Pregnancy
- Death
- Other

Disposition will be provided for the treatment and follow-up study periods:

- Treatment Period – Weeks 0-50: The number and percent of subjects who entered the treatment period, completed the treatment period, did not complete the treatment period, and the reasons for discontinuation will be provided.

- Follow-up (52 weeks): The number and percent of subjects who entered Follow-up, completed Follow-up, did not complete Follow-up, and the reasons for not completing Follow-up will be provided.

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized descriptively by age group and dose regimen using the enrolled population. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively in table format; no statistical hypothesis tests will be performed on these characteristics.

For summaries (number and percentage) of categorical variables in demographics and baseline disease characteristics, a "missing" or "not applicable" level may be added (in addition to the levels specified below) to account for missing or not applicable data as appropriate.

7.1. Demographics

Summary statistics will be provided by age group and dose regimen for the following continuous variables:

- Age (years)
- Weight (kg) at Baseline
- Height (cm) at Baseline
- Body mass index at Baseline (BMI; kg/m^2)

Number and percentage will be provided by age group and dose regimen for the following categorical variables:

- Age category (6-11 years, 12-17 years)
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Caucasian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographic region (USA, Canada, Europe)
- Baseline weight category (< 15, 15 to < 35, 35 to <70, ≥ 70 kg)
- BMI at Baseline category (< 25, 25 to < 30, 30 to < 35, 35 to < 40, ≥ 40 kg/m^2)
- Baseline dose level (20 mg BID, 30 mg BID)

BMI values will be obtained from the CRF.

7.2. Baseline Clinical Characteristics

Baseline clinical characteristics will be summarized descriptively by age group and dose regimen and will include the following:

- Duration of plaque psoriasis (from date of diagnosis to the date of informed consent; year, presented with one decimal of accuracy)
- Duration of plaque psoriasis categories (< 1, 1 to < 2, 2 to <5, ≥ 5 years)
- Baseline PASI score
- Baseline PASI score category (≤ 20, > 20)
- Prior use of phototherapy (Never used, Used)

- Prior use of conventional systemic medications (Never used, Used)

7.3. Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA dictionary Version 18.0). A frequency summary (number and percentage) of medical history will be presented by age group and dose regimen and by system organ class (SOC) and preferred term (PT).

7.4. Prior Therapy and Medication

Prior therapies and medications are defined as those started before the first dose of study drug (whether or not ended before the first dose of study drug). Prior medications that continue after the first dose of study drug will also be reported as concomitant medications.

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) Drug Dictionary (WHODD; Version March 2015) will be used to group medications into relevant categories. A frequency summary of prior medications and prior psoriasis medications will be provided by age group and dose regimen, ATC1 level, and standardized medication name.

Prior procedures will be collected with medical history, coded using MedDRA Version 18.0 and summarized as part of medical history.

8. EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

8.1. Treatment Duration

Treatment duration of tablets will be summarized by age group and dose regimen using the safety population. Total exposure to apremilast will be determined from the treatment period using subjects exposed to apremilast as the treated population.

Subject data listings of study tablet drug records will be provided.

Treatment duration of tablets (in weeks) is calculated as (the date of the last dose of study drug – the date of the first dose of study drug + 1) / 7 and rounded to one decimal place.

The specific definitions of the first dose and last dose dates of study drug are given below:

- First dose date: The date of the first dose of study treatment obtained from the first dose of study treatment CRF, or if missing, the date of the first dose of study drug that is dispensed at Week 0/Visit 2 obtained from the study drug exposure CRF.
- Last dose date: the date of the last dose of apremilast in the study for subjects who have completed the study or discontinued early.

Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (eg, < 1, 1 - < 4 weeks, etc.), will be provided.

8.2. Treatment Compliance

As part of the routine recording of the amount of study drug taken by each subject, the numbers of tablets dispensed and returned will be recorded at each visit, starting at Visit 2. These records will be used to calculate treatment compliance.

Subject data listings of tablet accountability records will be provided.

The tablet compliance (%) 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 treatment period divided by the expected total number of tablets that should have been taken over the same period of time.

Tablet compliance will not be calculated for subjects (if existent) who have only the tablet dispensed record at Week 0/Visit 2 and no other drug accountability records.

Summary statistics for tablet compliance (%) will be provided by age group and dose regimen for the treatment period. A frequency summary of compliance will also be presented with the following categories: < 75%, 75% - ≤ 120%, and > 120%.

Overdose, on a per dose basis, is defined as ingestion of greater than 100 mg of apremilast tablets in any specific dosing period (ie, 24 hours) whether by accident or intentionally. Other required or optional nonstudy drugs intended for prophylaxis of certain side effects, etc, are excluded from this definition. A subject data listing of drug overdoses will be provided.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Concomitant Medications

The ATC coding scheme of the WHODD (Version March 2015) will be used to group medications into relevant categories.

Concomitant medications documented during the study will be summarized. The frequency tabulation will display the number (%) of subjects receiving at least one concomitant medication, the number (%) of subjects receiving at least one medication within a relevant category, and each concomitant medication by age group and dose regimen.

9.2. Concomitant Procedures

Concomitant procedures will be coded according to the MedDRA Version 18.0. Concomitant procedures documented during the study will be summarized.

10. SAFETY ANALYSIS

10.1. General Approaches to Safety Analyses

Safety will be assessed via descriptive statistics and point estimates. Unless otherwise specified, all safety analyses described in Section 10 will be based on the safety population. For the analyses of AEs and marked abnormalities, the following point estimates are distinguished:

- Subject incidence: Subject incidence (ie, 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. 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 study drug.

AEs and marked abnormalities will be summarized by subject incidence and EAIR.

Descriptive statistics will be provided for vital signs, weight, laboratory values (continuous measurements) and ECG measurements by age group and dose regimen and by visit. 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 versus the category at the end of treatment 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 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.

10.2. Adverse Events

AEs will be coded according to the MedDRA Version 18.0. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within SOCs presented in descending order of subject incidence.

10.2.1. Overall Summary of AEs

An overall summary of the following AE categories will be provided:

- 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

Specific TEAEs under each of the above categories will be summarized.

10.2.2. All TEAEs

All TEAEs will be summarized by SOC and PT (in descending order of subject incidence). Each subject will be counted once for each applicable specific TEAE, and a subject with multiple TEAEs within an SOC will be counted once for that SOC.

All TEAEs will be summarized by age group and dose regimen.

All TEAEs occurring after the date of the last dose of study drug and up to 28 days after the last dose of study drug will be summarized by SOC and PT for subjects who enter first short-term follow-up. The EAIR will not be provided in this summary.

All new TEAEs will be summarized by exposure interval of <=1 week, >1 to <=8 weeks, >8 to <=16 weeks, >16 to <=24 weeks, >24 to <=32 weeks, >32 to <=40 weeks, >40 to <=48 weeks, and >48 weeks.

10.2.3. Common TEAEs

TEAEs with subject incidence ≥ 5% (or another cut-off if justified) will be summarized by SOC and PT in descending order of subject incidence.

10.2.4. Drug-related TEAEs

Drug-related TEAEs will be summarized by SOC and PT.

10.2.5. TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing). If a subject reports multiple occurrences of a specific event within a specific analysis 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.

10.2.6. Serious TEAEs

Serious TEAEs and serious drug-related TEAEs will be summarized.

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

10.2.7. TEAEs Leading to Drug Interruption and TEAEs Leading to Drug Withdrawal

TEAEs leading to drug interruption and TEAEs leading to drug withdrawal will be summarized by study period and by age group and dose regimen.

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

10.2.8. Deaths

TEAEs leading to death will be summarized. A subject data listing of all deaths will be provided.

10.2.9. TEAEs for Selected PTs

A frequency summary of the onset day and duration of TEAEs for selected PTs (diarrhoea, headache/tension headache, nausea, and upper respiratory tract infection) will be presented in 30 day intervals until Day 150, after which they will be summarized in one single category. In the duration summary, ongoing events will be summarized as a separate category. Frequencies within the first 30 days will be summarized in these categories: 1-3 days, 4 -7 days, 8 – 15 days, 16 – 23 days, and 24 – 30 days.

10.3. Clinical Laboratory Evaluations

Summary statistics of observed values and changes from baseline in laboratory parameters will be provided over time. For each hematology and chemistry analyte, frequency summaries of shifts from baseline to post-baseline time points and to the worst post-baseline value during the treatment period will be provided.

If a subject has reported a value for a laboratory test during the treatment period that is abnormally low and another value that is abnormally high, then that subject will be summarized in a High/Low column for the worst category. If the subject has only abnormalities that are abnormally high, then that subject will be summarized in a High column for the worst category. Similarly, if a subject has only abnormalities that are low, then that subject will be summarized in a Low Column for the worst category. Otherwise, if all values for the subject are within normal range, the worst category will be Normal.

Laboratory marked abnormalities 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. Data collected later than 28 days after the last dose of apremilast will be excluded from those summaries. A subject data listing of laboratory marked abnormalities will be provided. For these listings, all recordings of a laboratory analyte will be displayed for the subject if that subject has one or more marked abnormalities for the test.

Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and subjects with abnormal values at baseline separately.

Subject data listings of all laboratory data, including urinalysis, will be provided. A subject data listing of serum and urine pregnancy testing will also be provided.

10.4. Vital Signs, Waist Circumference and Weight

Summary statistics for observed values and changes from baseline in vital signs will be provided over time. A summary of change and percent change in body weight will also be provided. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be provided for pulse and blood pressure.

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

10.5. Electrocardiogram

Summary statistics of observed values and changes from baseline in numeric intervals will be provided over time. Frequency summaries from the investigator's assessment of normality will be provided.

A subject data listing of all ECG data and a subject data listing of clinically significant abnormal ECG interpretation by independent assessor will be provided.

10.6. Physical Examination

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.

Assessments of sexual maturity (Tanner Staging) will be performed at baseline and the 8 week post last dose follow-up visit (Visit 12). A summary and subject data listing of Tanner Staging assessment findings will be provided.

10.7. Stool Diary

Subjects and their parent/guardian will be supplied with paper diaries that will be filled out daily to record and describe any diarrhea, including duration, frequency, treatment, and associated symptoms. Subjects and their parent/guardian will complete the Stool Diary every day beginning after the first dose of apremilast, up to the 4-week post last dose follow-up visit (Visit 11).

A summary and subject data listing of stool diary entries will be provided.

10.8. Psychiatric Evaluation

All 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 (Posner, 2011). The assessment will be completed at screening, baseline, and at post-baseline visits.

A summary and subject data listing of psychiatric evaluation results will be provided.

11. PHARMACOKINETIC ANALYSIS

PK analyses will be based on the PK population, defined as all enrolled subjects who take at least one dose of study drug and have evaluable PK data. Blood samples, with volumes appropriate for the weight of the child, will be collected at prespecified times to determine levels of apremilast in plasma/blood. PK data are considered evaluable if there are measurable drug levels of apremilast in plasma from at least 3 time points which extend over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

11.1. Values Below the Limit of Quantification or Missing

Predose concentrations that are below the limit of quantification (BLQ) or missing will be assigned a numerical value of zero. A BLQ value that occurs between predose and the first quantifiable concentration point will be assigned a numerical value of zero. A BLQ value that occurs between quantifiable concentration points will be treated as missing. If BLQ values occur at the end of the collection interval, they will be assigned a numerical value of zero, unless otherwise warranted by the concentration-time profile. Postdose concentrations that are BLQ but occur after the first quantifiable concentration will be treated as missing for PK analysis.

Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. A concentration value of zero will be included for the computation of arithmetic mean, and a post-dosing zero concentration will be substituted with a value equal to 50% of the low limit of quantification (LLOQ) for the computation of geometric mean. If 50% or more of the values are BLQ at one time point, the arithmetic mean and geometric mean will be reported as BLQ.

11.2. Plasma Concentrations

Blood samples will be collected through an indwelling venous cannula, by direct venipuncture or by finger sticks at pre-specified time points for measurement of apremilast in plasma and/or blood. Concentrations of apremilast in plasma or blood will be measured using a validated liquid chromatography tandem mass spectrometry assay and dried blood spot (DBS) assay, respectively.

Blood samples for PK analysis of apremilast will be collected for Group 1 (ages 12 to 17 years, inclusive, at the time of Screening) at 2 hours post morning dose on Day 1 and at these time points on Day 14: Predose (prior to morning dose) and at 1, 2, 3, 5, 8, 12, and 24 hours post morning dose. For Group 2 (ages 6 to 11 years, inclusive, at the time of Screening), blood samples for PK analysis will be taken at 2 hours post morning dose on Day 1 and at these time points on Day 14: Predose (prior to morning dose) and at 2, 5, and 12 hours post morning dose. If a subject terminates prior to Day 14, and has been compliant (75% to 120%) with study drug, then PK collection may be done if the subject consents, but not after Day 14.

Actual PK blood sample collection times will be recorded in the source documents and eCRF. Explanations should be provided in the source documents and eCRF for missed or mishandled

samples and for samples collected outside the acceptable time window as described in Table 2.

Table 2: Acceptable Time Windows for PK Blood Sampling

Scheduled PK Blood Draw Time	Acceptable Time Window
Predose	Within 60 minutes prior to dosing
0 to 3 hours postdose (inclusive)	± 5 minutes
4 to 24 hours postdose (inclusive)	± 10 minutes

Plasma and whole blood concentrations will be summarized by nominal time points and age group, including mean (95% CI), SD, % coefficient of variation (CV%), geometric mean, geometric CV%, minimum, median, and maximum. The number of subjects with quantifiable concentrations at each nominal time point will be summarized by age group. Mean (95% CI) and individual plots of plasma and whole blood concentrations will be presented in both linear scale and semi-logarithmic scale by age group.

Linear regression will be utilized to obtain measurement agreement between the plasma and whole blood pharmacokinetic methods. Results from a regression model, with whole blood concentrations as the independent variable, and plasma concentrations as the dependent variable, will be summarized. A scatter plot with those regression results will also be created.

11.3. Non-compartmental PK Analysis

PK parameters will be calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times will be used in the calculations of PK parameters. PK parameters and plasma concentrations for apremilast will be presented as descriptive statistics. The descriptive statistics will include but will not be limited to the following: sample size (n), mean, SD, CV%, geometric mean, and geometric CV%. Results will be presented in tabular and graphic formats as appropriate.

The following PK parameters will be estimated for apremilast using a non-compartmental approach provided sufficient data are available:

- Maximum observed plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$)
- Area under the plasma concentration-time curve from time zero to 12 hours postdose (AUC_{0-12})
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-t})
- Apparent total plasma clearance when dosed orally (CL/F)
- Apparent total volume of distribution when dosed orally, based on steady-state (Vss/F) or the terminal phase (Vz/F)

- Terminal-phase elimination half-life ($t_{1/2}$)

11.3.1. Software for Non-compartmental PK Analysis

The software to be used in the data analysis and data presentation includes:

- Phoenix WinNonlin 6.3 (Phoenix™ WinNonlin®) or higher
- RStudio Version 0.98.1087 or higher

11.4. Population PK Analysis

Population PK analyses will be performed using non-linear mixed effect modeling (NONMEM). The PK data from this study will be pooled with adult PK data as appropriate for the population PK analyses. The effect of relevant demographic factors such as body weight on the PK of apremilast may be evaluated.

The following population PK parameters may be determined as appropriate:

- Apparent clearance of drug from plasma after extravascular administration (CL/F)
- Apparent volume of distribution after extravascular administration (V/F)
- Absorption rate constant (first-order) (Ka)
- t_{lag} (if applicable)

The results of population PK analyses will be included in the final report and appendices as appropriate.

11.4.1. Software for Population PK Analysis

The software to be used in the population PK analysis includes:

- NONMEM Version VII or higher
- R Version 3.3.1 or higher

12. EFFICACY ANALYSIS

12.1. General Approaches to Efficacy Analysis

Efficacy evaluations will be conducted using the safety population.

Descriptive statistics will be presented for all endpoints. Specifically, for continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum values), for baseline, specified time points, and change or percent change from baseline will be provided. Categorical variables will be summarized with frequency tabulations.

12.2. Analysis of the Secondary Endpoint

The secondary endpoint is the taste and acceptability of apremilast tablets, as measured using a faces Likert Scale on Day 1, initial dosing. Frequency tabulations will be utilized to summarize Likert Scale Ratings on Day 1. A subject data listing of Likert Scale Ratings on Day 1 will be provided.

12.3. Analysis of the Exploratory Efficacy Endpoint

The exploratory efficacy endpoint is the percent change in PASI scores from Baseline. Descriptive statistics will be used to summarize total score, change and percentage changes in the PASI score from Baseline at scheduled assessments.

13. INTERIM ANALYSIS

No formal interim analysis is planned for this study. However, an analysis of the PK and 2 weeks of safety data from the initial 8 adolescent subjects enrolled into Group 1 will be used to model the most appropriate dose for subsequently enrolled subjects. Similarly, 2 week PK and safety data from the first 8 subjects from Group 2 will be used to model the most appropriate dose for subsequently enrolled subjects.

14. REFERENCES

Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. *Dermatologica.* 1978;157:238-244.

Gordon KB, Feldman SR, Koo JYM, Menter A, Rolstad T, Krueger G. Definitions of measures of effect duration for psoriasis treatments [editorial]. *Arch Dermatol* 2005 Jan;141(1):82-4.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011 December;168(12):1266-1277.

15. APPENDICES

15.1. Imputation Rules for Partially Missing Dates

15.1.1. Adverse Events

Partially missing AE start dates will be imputed in the ADaM dataset for AEs, but 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.

The principle of the imputation rules is to treat the AE as treatment-emergent, ie, occurring on or after the date of the first dose of study drug, if possible.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", and the date of the first dose of study drug as "$D_{SD}/M_{SD}/Y_{SD}$". The following table gives the imputation rules for partially missing AE start dates.

Table 3: Imputation Rules for Partially Missing AE Start Dates

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

15.1.2. 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.

15.1.3. 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 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.

15.2. Marked Abnormalities Criteria for Laboratory Assessments

Category / Analyte	SI Units	Criteria
Chemistry/ Alanine Aminotransferase (SGPT)	U/L	> 2*ULN
Albumin	Kg/m3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 2*ULN
Total Bilirubin	µmol/L	> 2*ULN
Total Bilirubin and Alanine Aminotransferase /Aspartate Aminotransferase	µmol/L and U/L	Bilirubin Value > 2xULN with (ALT or AST value > 2xULN)
Blood Urea Nitrogen	mmol/L	> 24
Calcium	mmol/L	< 1.8 > 3.0
Cholesterol	mmol/L	> 7.8
Creatinine	µmol/L	> 1.5*ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 6.5
Lactate Dehydrogenase (LDH)	U/L	> 2*ULN
Magnesium	mmol/L	> 1.2
Phosphate	mmol/L	<1.03 >1.94
Potassium	mmol/L	<3.0 >5.4
Sodium	mmol/L	<132 >147
Triglycerides	mmol/L	> 3.4
Urate	umol/L	Male: > 480 Female: > 480
Hematology/ Hemoglobin	g/L	Female <110, Male <110 Female >150, Male >150
Leukocytes	10^9/L	< 2.0
Lymphocytes	10^9/L	< 1.0

Category / Analyte	SI Units	Criteria
Neutrophils	10^9/L	< 1.5
Platelets	10^9/L	<100 >500