Study Identifier: CC-10004-PSOR-023
NCT number: NCT03930186

Official Title on page 1 of the Protocol: OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Official Title on page 5 of the Protocol: A PHASE 3B, OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Official Title in the Statistical Analysis Plan (SAP): A PHASE 3B MULTI-CENTER, OPENLABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

Note: The official title in the Protocol (page 1 and 5) and Statistical Analysis Plan (SAP) are slightly different but these documents pertain to the same study CC-10004-PSOR-023.

This cover page has been appended to the document for purpose of posting on Clinicaltrials.gov.

STATISTICAL ANALYSIS PLAN

A PHASE 3B MULTI-CENTER, OPEN-LABEL, SINGLE-ARM STUDY OF THE EFFICACY AND SAFETY OF APREMILAST, IN SUBJECTS WITH PLAQUE PSORIASIS THAT IS NOT ADEQUATELY CONTROLLED BY TOPICAL THERAPY

STUDY DRUG: Apremilast (CC-10004)

PROTOCOL NUMBER: CC-10004-PSOR-023

DATE FINAL: 30APR2020

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SAP TITLE	Statistical Analysis Plan for A Phase 3B multi-center, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy
SAP VERSION, DATE	Version 1.0, 30APR2020
SAP AUTHOR	[redacted] Associate Manager, Biostatistics — Printed Name and Title [redacted] Digitally signed by [redacted] Date: 2020.05.01 01:39:27 +09'00' — Signature and Date
PROTOCOL TITLE	A Phase 3B multi-center, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy
INVESTIGATIONAL PRODUCT	Apremilast (CC-10004)
PROTOCOL NUMBER	CC-10004-PSOR 023
PROTOCOL VERSION, DATE	1.0, 30JAN2019; 2.0, 28APR2020
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head Signature Printed Name	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document [redacted] PM PDT 48F5746066164620985A4781ACD363E3
Lead Clinical Research Physician / Clinical Research Physician Signature Printed Name	[redacted] Digitally signed by [redacted] DN: cn=[redacted] Date: 2020.05.01 12:40:14 -04'00'
Lead Product Safety Physician	

Signature	[redacted] Digitally signed by [redacted] DN: cn=[redacted] Date: 2020.04.30 13:52:37 -04'00'
Printed Name	[redacted]

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BID	Twice Daily
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
EAIR	Exposure-Adjusted Incidence Rate
FCBP	Females of Childbearing Potential
GCP	Good Clinical Practice
ICH	International Council for Harmonization
IP	Investigational Product
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
[redacted]	
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
MI	Multiple Imputation
MMRM	Mixed-effect Model for Repeated Measures
[redacted]	
NA	Not Applicable
NAPSI	Nail Psoriasis Severity Index
NRI	Non-responder Imputation
PASI	Psoriasis Area and Severity Index

PBI	Patient Benefit Index
PBQ	Patient Benefit Questionnaire
[redacted]	
PNQ	Patient Needs Questionnaire
PP	Per-Protocol
PsA	Psoriatic Arthritis
PT	Preferred Term
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
ScPGA	Scalp Physician Global Assessment
SI	Standard International (unit)
SOC	System Organ Class
sPGA	Static Physician Global Assessment
STDEV	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TSQM	Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analog Scale
WHO DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Amgen's protocol CC-10004-PSOR-023 "A Phase 3B multi-center, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy".

The objective of this study is to assess the efficacy and safety of the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.

This SAP provides a more technical and detailed elaboration of the statistical analyses as outlined and/or specified in the study protocol. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to assess the efficacy and safety of the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.

3.2. Secondary Objectives

The secondary objectives are:

- To assess the efficacy of the combination of apremilast plus topical therapies for the treatment of subjects with scalp psoriasis who have not achieved an adequate response with topicals alone.
- To assess the impact on quality of life for the combination of apremilast plus topical therapies for the treatment of subjects with plaque psoriasis who have not achieved an adequate response with topicals alone.

3.3. Exploratory Objectives

The exploratory objectives are:

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 3B multi-center, open-label, single-arm study of the efficacy and safety of apremilast, in subjects with plaque psoriasis that is not adequately controlled by topical therapy. Approximately 150 subjects will be enrolled at approximately 30 sites in Japan. After a 5-day titration, subjects will receive apremilast 30 mg tablets orally twice daily (BID) for 32 weeks in addition to their existing topical therapy. Beginning at Week 16, subjects will be permitted to decrease the use of topical therapy at their discretion.

The study consists 4 phases:

- Screening Phase – Week -4 ± 1 week
- Open-label Combination Therapy Phase – Weeks 0 to 16

  Subjects will receive treatment with:

  – apremilast 30 mg tablets orally BID, AND

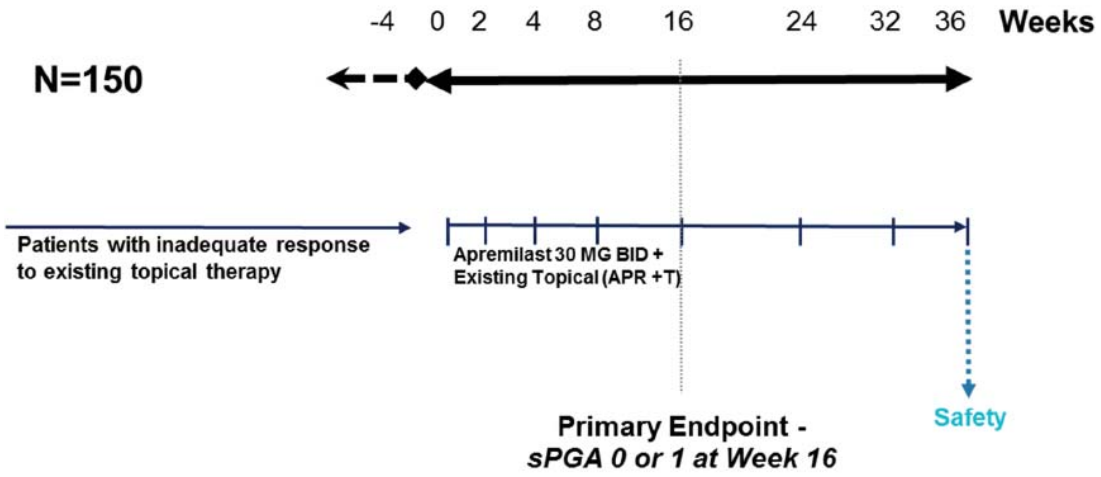
  – existing topical therapy
- Open-Label Combination Therapy Phase with Optional Topical Reduction – Weeks 16 to 32

  – All subjects will continue to receive apremilast 30 mg tablets orally BID AND existing topical therapy

  – Subjects will be permitted to decrease the use of topical therapy at their own discretion
- Post-treatment Observational Follow-up Phase

  – Four-week Post-treatment Observational Follow-up Phase for all subjects who complete the study or discontinue from the study early. Subjects who transition to commercial supply of apremilast after the Week 32 visit are not required to attend the post-treatment observational follow-up visit

Figure 1: Study Design



The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint(s)

The primary endpoint is the proportion of subjects who achieve static Physicians Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) at week 16.

4.2.2. Secondary Efficacy Endpoint(s)

The secondary endpoints include below.

Name	Description	Timeframe
Static Physicians Global Assessment (sPGA)	Proportion of subjects who achieve sPGA 0 or 1	Week 32
Scalp Physicians Global Assessment (ScPGA)	Proportion of subjects who achieve ScPGA score of 0 or 1	Weeks 16, 32
Body Surface Area (BSA)	Mean percent change from baseline in psoriasis-affected BSA	Weeks 16, 32
Pruritus Visual Analog Scale (VAS)	Mean percent change from baseline	Weeks 2, 16, 32

Name	Description	Timeframe
Shiratori's Pruritus Severity Score	Mean change in severity score from baseline	Weeks 2, 16, 32
Nail Psoriasis Severity Index (NAPSI)	Proportion of subjects that achieve a ≥ 50% reduction from baseline in NAPSI score (NAPSI-50) at Week 32 among subjects with NAPSI ≥ 1 at baseline	Weeks 16, 32
Dermatology Life Quality Index (DLQI)	Mean change from baseline	Weeks 16, 32
Psoriasis Area and Severity Index (PASI)	• Mean percentage change from baseline • Proportion of subjects who achieve ≥ 75% reduction from baseline (PASI-75) • Proportion of subjects who achieve ≥ 50% reduction from baseline (PASI-50)	Weeks 16, 32
Treatment Satisfaction Questionnaire for Medication (TSQM)	Mean score in domains	Weeks 0, 16, 32
Patient Benefit Index (PBI)	Proportion of subjects who achieve PBI ≥ 1	Weeks 16, 32

4.2.3. Exploratory Endpoint(s)

The exploratory efficacy endpoints include:

[redacted]

4.2.4. Safety Endpoints

Safety endpoints will include:

- Adverse Events (AEs)
  - Type, frequency, severity, and relationship of AEs to apremilast
  - Number of subjects who discontinue apremilast due to any AE
- Pregnancy tests for females of childbearing potential (FCBP)
- Vital signs and body weight

- Clinical laboratory tests

4.2.5. Assessments and Derivations of Efficacy Endpoints

The assessment and derivation of each efficacy endpoint is described below. Baseline definition for all efficacy endpoints is given in Section 5.4. Change from baseline is calculated as on-treatment 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 5.5.

4.2.5.1. Static Physician Global Assessment (sPGA)

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

4.2.5.2. Scalp Physicians Global Assessment (ScPGA)

The ScPGA is a measurement of overall scalp involvement. The ScPGA is a 5-point scale that assesses three dimensions (Plaque Elevation, Scaling, and Erythema) on a scale of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe).

4.2.5.3. Body Surface Area (BSA)

BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palm surface or "handprint"), which equates to approximately 1% of total body surface area.

4.2.5.4. Pruritus Visual Analog Scale (VAS)

The Pruritus VAS is a continuous scale comprised of a vertical line range from 0 to 100 mm on which the left-hand boundary (0 mm) represents no itch and the right-hand boundary (100 mm) represents itch as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded.

4.2.5.5. Shiratori's Pruritus Severity Score

Shiratori's Pruritus Severity Score is assessment tool for daytime and nighttime symptoms, separately, on a 5-point scale (0, Nothing; 1, Minimal; 2, Mild; 3, Moderate; 4, Severe).

4.2.5.6. Nail Assessments/Nail Psoriasis Severity Index (NAPSI)

The NAPSI will assess one target thumb nail or fingernail representing the worst nail psoriasis involvement at baseline. The target nail is graded for nail matrix psoriasis and nail bed psoriasis, both ranges from 0 to 4 for numbers of involved nail quadrants. The sum of these scores is the total NAPSI score for the target nail, which range from 0 to 8 (worst).

Subject whose NAPSI score is reduced by at least 50% (percent change ranges from −100% to −50%) are classified as having achieved NAPSI-50 response.

4.2.5.7. DLQI

The DLQI is questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains 10 items pertaining to the subject's skin. With the exception of Item Number 7, the subject responds on a four-point scale, ranging from "Very Much" (score 3) to "Not at All" or "Not relevant" (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the subject's skin prevented them from working or studying (Yes or No, scores 3 or 0 respectively), and if "No," then the subject is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score is derived by summing all item scores, which has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best.

The DLQI can be grouped into six subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores correspond to poorer quality of life.

4.2.5.8. Psoriasis Area Severity Index (PASI)

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

A subject is classified as having achieved PASI-75 (PASI-75 response) if the PASI score is reduced by at least 75% from baseline, which is equivalent to a percent change from baseline ranging from −100% to −75%. PASI-50 is similarly defined except the percent changes that must be achieved are at least −50%.

4.2.5.9. Treatment Satisfaction Questionnaire for Medication (TSQM) Version II

The TSQM version II is an 11-question self-administrated instrument to understand a subject's satisfaction on the current therapy. The TSQM comprises 11 items across 4 domains focusing on effectiveness (Item 1 and 2), side effects (Item 4 to 6), convenience (Item 7 to 9), and global satisfaction (Item 10 and 11). With the exception of Item 3 (experience any side effects; yes or no), all items have five or seven responses. Item 4 to 6 have five responses (1, A Great Deal; 2, Quite a Bit; 3, Somewhat; 4, Minimally; 5, Not at All) and the other items (1 and 2, and 7 to 11) have seven responses (1, Extremely Dissatisfied; 2, Very Dissatisfied; 3, Dissatisfied; 4, Somewhat Satisfied; 5, Satisfied; 6, Very Satisfied; 7, Extremely Satisfied). Item scores are summed to give four domain scores, which are in turn transformed to a scale of 0-100 as below.

- EFFECTIVENESS: ([(Item 1 + Item 2) − 2] divided by 12) × 100
- SIDE EFFECTS: ([(Sum of Item 4 to Item 6) − 3] divided by 12) × 100
  - If one item is missing: ([(Sum of the two completed items) − 2] divided by 8) × 100
- CONVENIENCE: ([(Sum of Item 7 to Item 9) − 3] divided by 18) × 100
  - If one item is missing: ([(Sum of the two completed items) − 2] divided by 12) × 100
- GLOBAL SATISFACTION: ([(Sum of Item 10 to Item 11) − 2] divided by 12) × 100

4.2.5.10. Patient Benefit Index (PBI)

The PBI is a validated patient-reported instrument to assess patient-relevant benefits of psoriasis treatment and represents the subject benefits realized as a function of most important subject needs. PBI consist of 2 questionnaires:

- Patient Needs Questionnaire (PNQ): Prior to starting therapy, subjects are asked to assess their treatment expectations by completing the PNQ. Individual importance of treatment objectives is collected by marking the importance of a total of 25 treatment goal statements. The score ranges from 0 (not at all) to 4 (very) for each treatment objective will be recorded in the database.
- Patient Benefit Questionnaire (PBQ): After a period of treatment, subjects are then asked to assess the benefits of treatment by completing the PBQ with the same 25 treatment goal statements. The score ranges from 0 (not at all) to 4 (very) will be recorded in the database.

The PBI is calculated for each subject at a given visit by weighing the achievement values of the treatment objectives by their importance to the individual patient using the following Algorithm. The preferences before treatment (PNQ) and achieved benefit after treatment (PBQ) are converted into a weighted index value, the PBI. The PBI is calculated by taking the individually determined importance for each item (PNQ) divided by the sum of all individual importance and multiplied by the respective benefit achieved (PBQ). The sum of the resulting products is the PBI which can have a value between 0 (no benefit) up to 4 (maximal benefit).

$$PBI = \sum_{i=1}^{k} \frac{PNQ_i}{\sum_{i=1}^{k} PNQ_i} PBQ_i$$

$$i = the\ ith\ treatment\ goal\ statement$$

$$k = total\ number\ of\ the\ \ applicable\ preference\ items\ (PNQ)\ and\ benefit\ items\ (PBQ)$$

For score calculation, both “does/did not apply” and “question unanswered” will be treatment as missing values. The global score will be calculated using only the items pairs (i.e., importance item and benefit items) for which the patient has given a response other than “does/did not apply” in both PNQ and PBQ. For example, importance items for which the corresponding benefit item has been rated as “did not apply” (or vice versa) will not be included in the denominator within the algorithm.

4.3. Stratification, Randomization, and Blinding.

Not Applicable

4.4. Sample Size Determination

The primary endpoint of this study is the proportion of subjects who achieve a static Physicians Global Assessment (sPGA) score of 0 or 1 at Week 16, in subjects on combined therapy of apremilast and topicals. Because there is no control arm for the study, if the lower bound of the 95% confidence interval (CI) of the observed response rate is above 8% (ie, the upper bound of 95% CI of the response rate from the placebo group in pooled Phase III studies, namely, PSOR-008 and PSOR-009), one can safely conclude that the treatment effect from the combined therapy is real. A sample size of 150 subjects will support a 95% confidence interval (CI) with at least 80% probability that the length of the interval is within 13%, assuming the expected response rate of 15% [8.5% to 21.5%] (conservatively estimated based on data of Phase III clinical trials). This sample size allows for a 10% discontinuation rate prior to week 16. The sample size calculation is based on nQuery software version 7.0, and the 80% probability supporting the margin of error is based on simulation results.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- No statistical comparisons will be made for this single-arm study;
- Confidence intervals (CIs) are presented as 2-sided 95% CIs;
- Summary statistics consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, Q1, Q3, Standard Deviation, minimum, and maximum for continuous variables;
- All mean and median values are formatted to one more decimal place than the measured value, standard deviation values are formatted to two more decimal places than the measured value, minimum and maximum values are presented to the same number of decimal places as the measured value, the 95% CI are formatted to two more decimal places than the measured value;
- All percentages are rounded to one decimal place. The number and percentage of responses are presented in the form XX (XX.X), where the percentage is in the parentheses, the 95% CI are presented to two decimal places. Exact 100% that is not rounded from a percent >99.50% is presented in the format xx (100);
- All analysis and summary tables have the analysis population sample size (i.e., number of subjects);
- All laboratory data will be reported using standard international (SI) units;
- All collected data will be listed and the listings are sorted for presentation in order of subject, and date of procedure or event;
- Summary table may not be provided if few data are obtained.

5.2. Analysis Phases or Periods

Data summary and analysis will be provided for the following analysis phases/periods.

5.2.1. Open-label Combination Therapy Phase – Weeks 0 to 16

This phase starts on the day of baseline visit (Week 0/Visit 2), and stops on either: (1) the day of the first IP dispensed for the next phase at Week 16/Visit 6; or (2) the day of the discontinuation visit if the subject discontinues prior to or at Week 16/Visit 6; or (3) the last known study day if the subject is lost to follow-up prior to Week 16/Visit 6 during the phase.

5.2.2. Open-label Combination Therapy Phase with Optional Topical Reduction – Weeks 16 to 32

This phase starts on the next day of the first IP dispensed for the phase at Week 16/Visit 6, and stops on either: (1) the day of the discontinuation visit if the subject discontinued prior to or at Week 32/Visit 8; or (2) the last known study day if the subject lost to follow-up prior to Week 32/Visit 8 during the phase.

5.2.3. Post-Treatment Observational Follow-Up

For all subjects who complete the study or discontinue the study early, the Four-week Post-Treatment Observational Follow-Up starts at the completion or discontinuation visit and stops at the follow-up visit or the last assessment date.

5.3. Analysis Populations

5.3.1. Enrolled Population

The Enrolled population will consist of all subjects who receive an IWRS identification number and are enrolled into the study. This will be the population for all efficacy analyses unless otherwise specified.

5.3.2. Per-Protocol Population

The per protocol (PP) population will consist of all subjects included in the enrolled population who have both baseline sPGA and at least one post-baseline sPGA evaluation and no important protocol deviations.

5.3.3. Safety Population

The safety population will consist of all subjects who received at least one dose of study medication (IP). All safety endpoints, study treatment duration, and concomitant medication summaries are based on the safety population.

5.4. Definition of baseline and day 1

Baseline is defined as the last value measured on or before the day of the first IP.

5.5. Time Points

Time points in all analyses are based on the remapped visits/study weeks using the following visit mapping algorithm, which may or may not be the same as the visits/study weeks as recorded in the database.
All visit-based data, except for those with the recorded visit being a follow-up visit, will be assigned to analysis visits based on study day (the date of assessment/collection relative to the reference date) and the defined analysis visit windows (Table 2), rather than the recorded visit. The only exception is that data with the recorded visit being a follow-up visit will be assigned to the analysis visit corresponding to the follow-up visit.

Table 2: Table for Visit Mapping for by Time Point Analysis

Analysis Visit	Target Day	Visit Window
Week 0 (Baseline)	1	≤ 1
Open-label Combination Therapy Phase		
Week 2	15	2 – 21
Week 4	29	22 – 42

Analysis Visit	Target Day	Visit Window
Week 8	57	43 – 84
Week 16	113	85 – End of Phase
Open-Label Combination Therapy Phase with Optional Topical Reduction		
Week 24	169	Start of Phase – 196
Week 32	225	197 – End of Phase

Time points in the analyses or summaries of efficacy data over time include the scheduled study weeks per protocol, the end of a study phase, and the post-treatment observational follow-up phase when applicable. It is possible that multiple assessment values will fall into the same visit window. The following rule may be used to select the unique value for that analysis visit:

1. Among all assessments in the same visit window for the analysis visit, select the value with the assessment date closest to the target day of the analysis visit;
2. If the relative days from 2 assessments are equally close to, but on different sides of the target day, then the latter assessment will be used for that analysis visit;
3. If multiple assessments are available on the same relative day, then the worst value of these assessments will be used for that relative day.

6. SUBJECT DISPOSITION

The number and percentage of screened subjects will be summarized. The failed inclusion/exclusion criteria of subjects who are screened will be included in the summary. The percentages will be based on the number of subjects screened.

The number of subjects in the Enrolled population, PP population, and Safety population will be summarized.

The numbers and percentages of subjects who enrolled, completed, and discontinued the study treatment and each protocol phase will also be summarized. The percentages will be based on the number of subjects entered in each phase.

The number and percentage of subjects enrolled by study site will be tabulated. The percentages will be calculated based on the number of the Enrolled population.

Listings will be provided for enrolled subjects, for the reason of treatment discontinuation, and for subjects excluded from the PP population along with the reason.

7. PROTOCOL DEVIATIONS

The protocol deviations and important protocol deviations are identified and assessed by clinical research physician or designee following company standard operational procedure. The protocol deviations and important protocol deviations will be summarized for the Enrolled population.

A by-subject listing of subjects with protocol deviations and important protocol deviations in the Enrolled population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics, baseline characteristics, and prior medication/procedure will be presented for the Enrolled population. Summaries for the concomitant medication/procedure will be presented for the Safety population. Subject data listings will also be provided.

8.1. Demographics

Summary statistics will be provided for the continuous variables include below:

- Age (years)
- Weight (kg)
- Height (cm)
- Baseline Body Mass Index (BMI; kg/m^2), BMI will be calculated as: BMI (kg/m^2) = Weight (kg)/ Height (m^2)
- Waist circumference (cm)

Number and percentage will be provided for categorical variables include below:

- Age category (< 65, 65 to < 75, ≥ 75 years)
- Sex (Male, Female)
- Race
- Baseline BMI category (<18.5, 18.5 to < 25, 25 to < 30, 30 to <35, 35 to <40, ≥ 40 kg/m^2)
- Weight category (< 40, 40 to < 55, 55 to < 70, 70 to < 85, 85 to < 100, ≥100 kg)

8.2. Baseline Disease Characteristics and Baseline Summary of Efficacy Variables

Descriptive statistics will be provided for the following continuous variables:

- Duration of psoriasis (from date of diagnosis to the date of informed consent; year, presented one digit after the decimal point)
- Baseline BSA (%)
- Baseline pruritus VAS score
- Baseline Shiratori's Pruritus Severity Score (Day and Night Time)
- Baseline NAPSI score for the target nail
- Baseline DLQI total score
- Baseline PASI score
- Baseline Treatment Satisfaction Questionnaire for Medication (TSQM) Version II and 4 domains (effectiveness, side effects, convenience, and global satisfaction).

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

- Duration of psoriasis category: < 5, ≥ 5 to < 10, ≥ 10 to < 20, ≥ 20 years
- Baseline sPGA score: 0 (Clear), 1 (Almost Clear), 2 (Mild), 3 (Moderate), 4 (Severe)
- Baseline ScPGA score: 0 (Clear), 1 (Almost Clear), 2 (Mild), 3 (Moderate), 4 (Severe)
- Baseline Shiratori's Pruritus Severity Score (Day/Night Time): 0 (Nothing), 1 (Minimal), 2 (Mild), 3 (Moderate), 4 (Severe)
- Baseline NAPSI score for the target nail (0-8)
- Baseline BSA (%): <=5, >5 to <=10, >10 to <=15, >15
- Baseline PNQ: the importance of each of the 25 treatment goals will be summarized with number and percentage
- Baseline active psoriatic arthritis (PsA) (Yes, No).

8.3. Medical History

A summary of relevant medical history and concomitant diseases will be presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0 or higher, using frequency distributions (counts and percentages).

8.4. Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. Frequency summaries of prior and concomitant procedures will be provided by SOC, and PT. Prior procedures are defined as those started before the first dose of IP (whether or not ended before the first dose of IP). A concomitant procedure is defined as non-study procedure started during the phase, or non-study procedure started before the phase and ended or remained ongoing during the phase.

8.5. Prior and Concomitant Medications

The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version Global B3 March 2019 or higher) will be used to group prior and concomitant medications into relevant categories. Frequency summaries will be provided by ATC 2 level, and standardized medication name.

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

Concomitant medications are defined as non-study medications started during the phase, or non-study medications started before the phase and ended or remained ongoing during the phase. Medications in the Follow-up Phase will include those medications started after the date of last dose of IP.

Prior medications and prior medications for psoriasis will be summarized. Summaries will be provided for concomitant medications as well as concomitant medications for psoriasis in each phase.

9. STUDY TREATMENTS

Summaries of study treatment duration and treatment compliance will be based on the safety population.

9.1. Study Treatment Duration

Study treatment duration in weeks is calculated as (the date of the last dose of study treatment – the date of the first dose of study treatment + 1) / 7 and rounded to one decimal place for each subject for a given analysis phase/period.

Descriptive statistics will also be provided for treatment duration.

Study treatment duration will be summarized using duration of IP exposure categories of < 2, 2 - < 4, 4 -< 8, 8 - < 16, 16 - < 24, 24 - < 32, ≥ 32 weeks.

A subject data listing of study drug records including the reasons for missed dose will be provided.

9.2. Treatment Compliance

Summaries on the compliance rate are provided for the Open-label Combination Therapy Phase, for the Open-label Combination Therapy Phase with Optional Topical Reduction, and overall.

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and/or returned will be recorded at visits. 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 analysis phase or period divided by the intended total number of tablets that should have been taken over the same phase or period.

Summary statistics for compliance (%) will be provided. 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.

10. EFFICACY ANALYSIS

10.1. General Approaches to Efficacy Analysis

All efficacy evaluations will be conducted using the Enrolled population. Supplemental analysis of the primary efficacy endpoint using the PP population will be conducted, if applicable.

Listings will be provided for efficacy endpoints.

10.2. Multiplicity

There will be no multiplicity adjustment.

10.3. Analysis of Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects that achieve sPGA score of 0 (clear) or 1 (almost clear) at Week 16. It will be analyzed using descriptive statistics which involve the sample size, the number of responders, point estimate of proportion of responders along with the associated 95% confidence intervals (CI) using a normal approximation based on the Enrolled population. In addition, a supplemental analysis will be performed using the PP population, if applicable.

All reasonable attempts will be made to prevent missing data from occurring in this study, especially through Week 16. However, in the case of missing data at Week 16, multiple imputation method will be incorporated into the primary analysis. The aim of the multiple imputation approach is to incorporate a representative random sample in place of the missing data such that an unbiased estimation can be made.

The multiple imputation (MI) method will be used to impute missing sPGA score at Week 16 using an imputation model involving previous sPGA scores in the open-label combination therapy phase (Weeks 0-16). The SAS procedure MI will be used to create M=100 complete datasets. The missing data patterns will be checked at the scheduled analysis visits, i.e., Baseline (Week 0), and Weeks 2, 4, 8 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing scores to create M=100 imputed data sets with monotone missing patterns. The seed will be set to 804529, the imputed values will be rounded to the nearest integers and a single chain will be used to produce imputations. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest sPGA scores.

In the second step, the predictive mean matching method will be used to impute the remaining missing scores for the 100 datasets with monotone missing patterns. The imputation procedure will use the monotone statement to create one complete dataset for each of the monotone datasets from the first step, and the variables will include sPGA scores at scheduled analysis visits from baseline to Week 16. The seed will be set to 55218163.

After the completion of imputation, sPGA response at Week 16 will be derived based on both observed and imputed scores. The SAS procedure MIANALYZE will be used to combine the

results for the statistical inferences.

Sensitivity analysis will be conducted to account for missing data using the NRI method and the LOCF method. A sensitivity analysis using the PP population will also be performed, if applicable.

10.4. Analyses of Secondary and Exploratory Efficacy Endpoints

The analyses for the secondary endpoints are described below. All efficacy endpoints listed below will be summarized at each applicable study visits including baseline and Week 16 based on the observed data.

10.4.1. Binary/Categorical Variables

- sPGA
  - sPGA score shift table
  - Proportion of subjects who achieve sPGA score improvement of ≥ 2 from baseline
- ScPGA
  - Proportion of subjects who achieve ScPGA score of 0 or 1 among subjects with baseline ScPGA score of 2 or greater
  - ScPGA score shift table
- Shiratori's Pruritus Severity Score
  - Shiratori's Pruritus Severity Score shift table in Day and Night time
- NAPSI
  - Proportion of subjects that achieve ≥ 50% reduction from baseline in NAPSI score (NAPSI-50) among subjects with NAPSI ≥ 1 at baseline
  - NAPSI score shift table
- DLQI
  - Proportion of subjects who achieve DLQI improvement of ≥ 5 from baseline
  - Proportion of subjects who achieved DLQI score of 0 or 1 among subjects with DLQI Score ≥ 2 at baseline
- PASI
  - Proportion of subjects who achieve ≥ 50% reduction from baseline (PASI-50)
  - Proportion of subjects who achieve ≥ 75% reduction from baseline (PASI-75)
  - Proportion of subjects who achieve ≥ 90% reduction from baseline (PASI-90)
- PBI
  - PNQ and PBQ: the importance of each of the 25 treatment goals will be summarized with number and percentage
  - Proportion of subjects who achieve PBI ≥ 1

A similar MI method as the primary endpoint will be applied for binary variables. Sensitivity analysis will be conducted for binary variables using the NRI method and LOCF method. In the non-responder imputation (NRI) analyses, missing data will be imputed by the worst value of each efficacy assessment category. In the last observation carried forward (LOCF) analyses, missing data will be imputed by the last post-baseline non-missing observation. For an efficacy endpoint which consists of multiple individual sub-scores, the LOCF method will be applied to the individual sub-scores rather than directly to the endpoint, and then the endpoint will be calculated based on the observed or imputed sub-scores. The only NRI method will be applied for a subject with no post-baseline data.

10.4.2. Continuous Variables

- BSA (psoriasis-affected)
  - Mean change and percent change from baseline in psoriasis-affected BSA
- Pruritus VAS
  - Mean change and mean percent change from baseline in Pruritus VAS
- Shiratori's Pruritus Severity Score
  - Mean change in severity score from baseline in Shiratori's Pruritus Severity Score in Day time and Night time
- NAPSI
  - Mean total score change and percent change from baseline for the target nail
- DLQI
  - Mean total score change from baseline
- PASI
  - Mean change and percentage change from baseline
- TSQM
  - Mean score in domains

[redacted]

Continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change from baseline as the response variable and include visit time as a fixed effect, subject as a random effect and the baseline value as a covariate. Within-group least-squares means and the associated standard errors and two-sided 95% CIs will be derived from the MMRM model. A sensitivity analysis will be conducted for continuous variables using LOCF method to impute the missing data.

10.5. Subgroup Analysis

Subgroup analysis will be carried out for sPGA response at Week 16. Summary and analysis will be based on Enrolled population and missing values will be imputed using MI method. The categorical groups of each subgroup may be pooled based on the number of observations available.

The following subgroup variables will be used:

- Baseline sPGA score: 2 (mild), 3 (moderate)
- Sex (Male, Female)
- Age (< 65, 65 to < 75, ≥ 75 years)
- Baseline weight (< 40, 40 to < 55, 55 to < 70, 70 to < 85, 85 to < 100, ≥100 kg)
- Baseline BMI (<18.5, 18.5 to < 25, 25 to < 30, 30 to <35, 35 to <40, ≥ 40 kg/m^2)
- Duration of psoriasis (< 5, 5 to < 10, 10 to < 20, ≥ 20 years)
- Baseline PASI score (≤7, >7)
- Baseline BSA (%) (<=5, >5 to <=10, >10 to <=15, >15)

11. SAFETY ANALYSIS

Safety analyses will be performed based on the safety population.

For the analyses of AEs, the following endpoints will also be summarized:

- 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. 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.

Descriptive statistics will be provided for vital signs, weight, waist circumference, laboratory values (continuous measurements) by visit. The baseline value, value at the time point, and change from baseline (also percent change from baseline if applicable) 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, 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.

As necessity requires, additional safety information may be provided.

11.1. Adverse Events

AEs will be coded according to the MedDRA version 21.0 or higher. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence.

An adverse event is a 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.

Unless otherwise specified, TEAEs summaries include new events of TEAE by exposure interval (≤ 1, 1 to ≤ 2, 2 to ≤ 4, 4 to ≤ 16, 16 to ≤ 32, > 32 weeks).

11.1.1. Overall Summary of TEAEs

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

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

11.1.2. All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence). All TEAEs occurring after the date of the last dose of IP and up to 28 days after the last dose of IP will also be summarized by SOC and PT for subjects who enter the observational follow-up phase. A listing of AEs including all TEAE will be provided.

11.1.3. Common TEAEs

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

11.1.4. Drug-related TEAEs

Drug-related TEAEs will be summarized. Serious drug-related TEAEs and severe drug-related TEAEs will be also summarized.

11.1.5. TEAEs by Maximum Severity

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

11.1.6. Serious TEAEs

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

11.1.7. 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. Drug-related TEAEs leading to drug interruption and drug-related TEAEs leading to drug withdrawal will be summarized. A subject data listing of TEAEs leading to drug withdrawal will be provided.

11.1.8. Deaths

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

11.2. Clinical Laboratory Evaluations

Summary statistics (N, Mean, Standard Deviations, Median, Q1, Q3, Minimum, and Maximum) and the corresponding changes from baseline and frequency summaries of shifts from baseline to post-baseline time points in terms of normal/abnormal will be provided for the selected serum chemistry parameters.

A subject data listing of all laboratory data, including urinalysis, will be provided.

11.3. Vital Sign, Weight, and Waist Circumference Measurements

The endpoints for vital sign parameters, weight, and waist circumference include:

- Observed value and change from baseline over time in vital sign parameters including temperature, pulse, and blood pressure
- Shifts from baseline to post-baseline time points 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)
- Observed value, change and percent change from baseline over time in weight and waist circumference

Summary statistics (N, Mean, Standard Deviations, Median, Q1, Q3, Minimum, and Maximum) of observed values, changes from baseline, and percent change from baseline (applicable for weight and waist circumference) will be provided over time. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points in terms of normal/abnormal will be provided for pulse and blood pressure.

Frequency summaries of percent change in weight from baseline to the end of the study phase/period will be provided by baseline BMI category (<18.5, 18.5 to < 25, 25 to < 30, 30 to <35, 35 to <40, ≥40 kg/m2) and by baseline weight category (< 40, 40 to < 55, 55 to < 70, 70 to < 85, 85 to < 100, and ≥100 kg). The categories of weight change (kg) and percent change (%) are < -20, ≥-20 to < -10, ≥-10 to < -5, ≥-5 to < 0, 0, > 0 to ≤ 5, > 5 to ≤ 10, > 10 to ≤ 20, and > 20.

A subject data listing of all vital sign parameters, weight and waist circumference data will be provided.

12. INTERIM ANALYSIS

No interim analysis will be conducted.

13. APPENDICES

13.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS).

13.1.1. Calculation Using Dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
    - Else use STUDY DAY = TARGET DATE – DSTART.

  Depending on the study day definition, DSTART can be Day 1 for core baseline or the Day 1 for Apremilast treatment baseline. Negative study days are reflective of observations obtained before the corresponding baseline. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.
- Age (in years) at the time of informed consent is collected.
    - When age in years is not available, age in days is calculated as (informed consent date – July 15 on the year of birth) + 1. Then age in years will be transformed to years by dividing age in days by 365.25 days, then truncating
    - If year of birth is also missing, set age missing
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4167

13.2. Date Imputation Guideline

13.2.1. 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. 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 apremilast as "$D_{APR}/M_{APR}/Y_{APR}$". The following table gives the imputation rules for partially missing AE start at Week 0/Visit 2.

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

13.2.2. 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.

13.2.3. 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.

13.2.4. 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, ECG assessment date, AE start or end dates, concomitant medications start or end dates, concomitant procedure date, last dose date from 'Disposition- Treatment' page, treatment exposure start or end dates where doses were completely or partially taken, death date).