DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-10004-BCT-002

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLEBLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY, FOLLOWED BY AN ACTIVE-TREATMENT PHASE TO EVALUATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN THE TREATMENT OF SUBJECTS WITH ACTIVE BEHÇET'S DISEASE

STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Study, followed by an Active-Treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects with Active Behçet's Disease.

STUDY DRUG:	**Apremilast (CC-10004)**
PROTOCOL NUMBER:	**CC-10004-BCT-002**
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TABLE OF CONTENTS

LIST OF TABLES

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL	
SAP TITLE	Statistical analysis plan for Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Study, followed by an Active-Treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects with Active Behçet's Disease.
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PROTOCOL NUMBER	CC-10004-BCT-002
PROTOCOL VERSION, DATE	Amendment No.1, 02 FEB 2016 and Amendment No. 1.1 DE, 05 JUL 2017
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

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Printed Name   _____   Date   _____

1. LIST OF ABBREVIATIONS

Table 1:   Abbreviations and Specialist Terms

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANCOVA	Analysis of covariance
APR	Apremilast
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to 12 hours postdose
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{85}	Area under the curve for the number of ulcers from baseline to Week 12/Day 85
BD	Behçet's disease
BDCAF	Behçet's disease Current Activity Form
BID	Twice daily
BMI	Body mass index
BSAS	Behçet's Syndrome Activity Score
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel (test or weights)
CRF	Case report form
DMC	Data Monitoring Committee
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
ET	Early termination
GI	Gastrointestinal
IL	Interleukin
IP	Investigational product

IRT	Interactive Response Technology
ITT	Intent-to-Treat
LOCF	Last observation carried forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
PCS	Physical Component Summary
PGA	Physician's Global Assessment
PP	Per Protocol
PRO	Patient Reported Outcome
PT	Preferred term
QOL	Quality-of-life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SI	Standard international (unit)
SOC	System organ class
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum observed plasma concentration
ULN	Upper limit of normal
VAS	Visual analog scale
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-BCT-002 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Study, followed by an Active-Treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects with Active Behçet's Disease," Amendment 1 and Amendment 1.1 DE, which were issued on 02 FEB 2016 and 05 JUL 2017 (for German sites only), respectively. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

Throughout this SAP, the treatment arms will be referred to as the 30 mg twice daily (BID) group and the placebo group. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches for the analyses of study data prior to database lock and the data analyses. This SAP will be finalized and signed prior to the clinical database lock for the first analysis (at 12 weeks).

These analyses include:

- Week 12 data analyses: clinical efficacy and safety analyses on a database cut at Week 12/Visit 9 after all subjects have completed Week 12/Visit 9 or have discontinued early at or prior to Week 12, including Early Termination and Observational Follow-up visits (referred as the 12-week database). The treatment comparisons during Placebo-controlled Treatment Phase and the safety analysis for the Placebo-controlled period will be based on this database lock;

- Analyses of efficacy up to Week 28 and safety with at least 100 subjects with at least 1 year of apremilast exposure (referred as the second database);

- Week 68 analyses: clinical efficacy and safety analyses when all subjects have completed the Active Treatment Phase and/or 4-week Posttreatment Observational Follow-up Phase or have discontinued early;

In addition, for German sites only:

- Analyses for the optional Open-label Extension Phase for subjects from German sites who choose to enter the optional Open-label Extension Phase after completing the Active Treatment Phase.

All statistical analyses detailed in this SAP will be conducted using *SAS*® 9.2 or higher.

3.   STUDY OBJECTIVES

3.1.   Primary Objective

The primary objective is to evaluate the efficacy of apremilast in the treatment of oral ulcers in active Behçet's disease.

3.2.   Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of apremilast in subjects with active Behçet's disease
- To evaluate the effect of apremilast on Patient Reported Outcomes (PROs) in subjects with active Behçet's disease

3.3.   Safety Objective

- To evaluate the safety and tolerability of apremilast in subjects with active Behçet's disease

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study, followed by an active-treatment extension phase to evaluate the efficacy and safety of apremilast (CC-10004) in the treatment of subjects with active Behçet's disease (BD). Approximately 204 eligible subjects will be randomized 1:1 (102 subjects per group) to receive apremilast 30 mg BID (APR 30 BID), or identically-appearing placebo tablets BID for the 12-week Placebo-controlled Treatment Phase.

Upon completion of the Week 12 visit, subjects initially randomized to placebo will transition to APR 30 BID, while subjects initially randomized to APR 30 BID will continue on the same treatment during the 52-week Active Treatment Phase.

Subjects from German sites who complete Visit 14 of the 52-week Active Treatment Phase will have an opportunity to continue to receive APR 30 BID in an optional Open-label Extension Phase. Subjects who choose not to enter the optional Open-label Extension Phase will complete the 4-week Posttreatment Observational Follow-up Phase.

Subjects who discontinue at any time from the study for any reason are to enter the 4-week Posttreatment Observational Follow-up Phase.

The study will include the following:

- Screening Phase: up to 6 weeks

- Double-blind, Placebo-controlled Treatment Phase: 12 weeks

    - APR 30 BID

    - Placebo

- Active Treatment Phase: 52 weeks

    - APR 30 BID

- Optional Open-label Extension Phase for German Sites until apremilast is commercially available for BD or until the benefit/risk of apremilast is found not to be acceptable for BD, according to either the sponsor or health authority.

    - APR 30 BID

- Posttreatment Observational Follow-up Phase: – 4 weeks after the last dose (if a subject early terminates or, for subjects from German sites, choose not to enter the optional Open-label Extension Phase). Subjects from German sites who complete the optional Open-label Extension Phase do not need to complete the Observational Follow-up Visit.

Screening Phase

Screening procedures must be performed no more than 6 weeks prior to the start of study investigational product (IP) at Visit 2 (Day 1).

Treatment Phase

Subjects who qualify for enrollment will be randomized 1:1 to receive APR 30 BID or identically-appearing placebo tablets BID for the 12-week Placebo-controlled Treatment Phase. To mitigate potential gastrointestinal (GI) side effects dose titration will be implemented in the first week of this study. For dose titration, 10 mg, 20 mg and 30 mg apremilast tablets, or identically appearing placebo tablets, will be dispensed in dose titration cards at Week 0.

Active Treatment Phase

All subjects who complete the Placebo-controlled Treatment Phase will be eligible to enter the Active Treatment Phase. Subjects initially randomized to placebo will transition to APR 30 BID, while subjects initially randomized to APR 30 BID will continue on the same treatment during the 52-week Active Treatment Phase. To maintain the blind regarding the initial treatment assignment, all subjects will receive dose titration cards at Visit 9 (Week 12). Although only subjects initially randomized to placebo will be dose titrated during their first week of the Active Treatment Phase, all subjects entering the Active Treatment Phase will receive identically-appearing titration/treatment cards.

Posttreatment Observational Follow-up Phase

Subjects who discontinue at any time from the study for any reason are to enter the 4-week Posttreatment Observational Follow-up Phase to monitor changes in disease activity or safety parameters.

Optional Open-label Extension Phase

Subjects from German sites who complete Visit 14 of the 52-week Active Treatment Phase will have an opportunity to continue to receive APR 30 BID in an optional Open-label Extension Phase.

End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary   analysis, as pre-specified in the protocol and/or the SAP, whichever is the later date.

4.2.   Study Endpoints

Study endpoints are described below, and the timing of when each assessment is to be collected is described in the protocol.

4.2.1.   Efficacy Endpoints

4.2.1.1.   Primary Efficacy Endpoint

The primary endpoint is area under the curve (AUC) for the number of oral ulcers from baseline through Week 12.

4.2.1.2.   Secondary Efficacy Endpoints

- Complete response rate for oral ulcers at Week 12

- A complete response is defined as the proportion of subjects who are oral ulcer-free.

- Change from baseline in the pain of oral ulcers as measured by visual analog scale (VAS) at Week 12

- Complete response rate for genital ulcers at Week 12 for subjects who had genital ulcers at baseline

  - A complete response is defined as the proportion of subjects who are genital ulcer-free.

- Change from baseline in the pain of genital ulcers, as measured by VAS at Week 12 in subjects who had genital ulcers at baseline

- Change from baseline in disease activity as measured by Behçet's Disease Current Activity scores (BD Current Activity Form [BDCAF]) at Week 12

- Change from baseline in the BD Quality-of-Life (QoL) score at Week 12

- Change from baseline in Behçet's Syndrome Activity Score (BSAS) at Week 12

- Time to oral ulcer resolution (complete response), ie, the first instance when a subject has a complete response, during the Placebo-controlled Treatment Phase

- Proportion of subjects with no oral ulcers following complete response, ie, the first time when a subject has a complete response, during the Placebo-controlled Phase (Note: this will be the proportion of subjects with no oral ulcers following subject's first complete response during the Placebo-controlled Phase.)

- Number of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase (Note: this will be the number of oral ulcers reported at the time of the first loss of complete response during the Placebo-controlled Phase.)

- Time to recurrence of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase

- Change from baseline in the total score of the Static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis and erythema nodosum) of BD at Week 12 in subjects who had BD skin lesions at baseline

- Proportion of subjects achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after start of dosing, and who remain oral ulcer free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase

4.2.2.   Safety Endpoints

Safety and tolerability as defined by the following:

- Type, frequency, severity, and relationship of the AEs to apremilast
- Number of subjects who prematurely discontinue IP due to any AE
- Frequency of clinically significant changes in vital signs, and/or laboratory findings
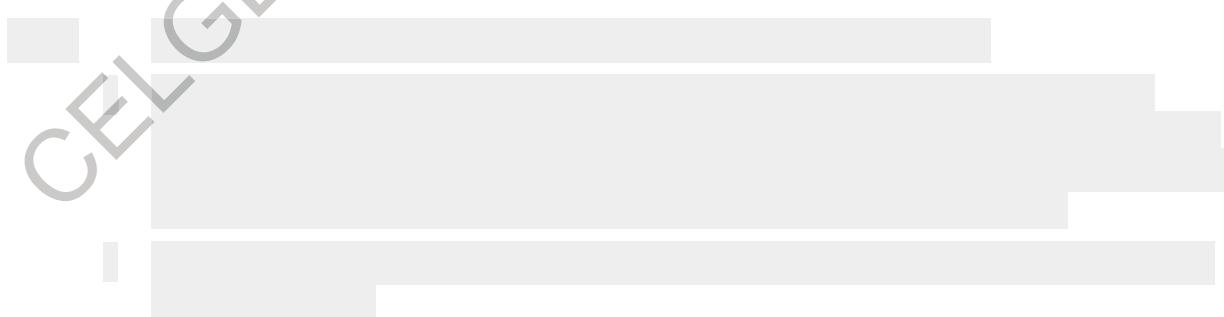
4.2.5.   Derivations of Efficacy Endpoints

Efficacy assessments, as detailed in the following section, will be done at the intervals specified in the Table of Events, Table 1 in the protocol.

- The number of oral ulcers and genital ulcers will be counted at each study visit, at ET and Observational Follow-up visits following the Placebo-controlled or Active Treatment Phase. For females, both vulvar and vaginal ulcers will be considered for genital ulcers.

- The AUC from baseline to Week 12/Day 85 (AUC_{85}) is the sum of the AUCs in each time interval specified by the dates of the visits. The individual AUC for any given time interval is calculated based on the linear trapezoidal method, which uses linear interpolation between data points to calculate the AUC. The AUC_{85} can be calculated as follows:

$$AUC = p * \sum_{k=2}^{8} \frac{1}{2} (C_k + C_{k+1})(t_{k+1} - t_k), \ k = 2, 3, \cdots, 8,$$

and

$$p = \frac{(85-1)}{(t_9-t_2)} = \frac{84}{(t_9-t_2)} p = \frac{(85-1)}{(t_9-t_2)} = \frac{84}{(t_9-t_2)}.$$

where C2, C3, …, C9 are the number of ulcers at each visit from Visit 2/Baseline to Visit 9/Week 12, and t2, t3, …, t9 are the ulcer assessment dates for Visit 2/Baseline to Visit 9/Week 12. When Visit 9/Week 12 does not exactly coincide with Day 85, the AUC through Week 12 will be adjusted for the actual study duration by dividing the total AUC by total study duration (in days) and multiplying this quantity by 84 days.

  – The multiple imputation method will be used to impute missing oral ulcer counts when deriving the primary efficacy endpoint of AUC for the number of oral ulcers.

- – AUC using a last observation carried forward (LOCF) approach to impute missing assessments at Week 12 will be used as a sensitivity analysis. If a subject has no post baseline ulcer assessment excluding the value obtained at the Observational Follow-up Visit, the baseline value will be carried forward for calculation. If there is a missing oral ulcer assessment between two visits or time points with assessments within a period, the AUC will be calculated based on the preceding and subsequent ulcers count.

- The LOCF approach will also be used for all other efficacy endpoints based on oral or genital ulcers count including calculating the cumulative number of oral ulcers per subject at all scheduled visits from baseline to Week 12. Of note, the cumulative count does not distinguish new occurrence of ulcers or the same ulcers appeared previously.

- The number of subjects who are oral ulcer-free (complete response) at Week 12 will be determined. Similarly, the complete response for genital ulcers at Week 12 will be determined for subjects who had genital ulcers at baseline. Subjects with missing data at Week 12 will be classified as non-responders. A sensitivity analysis with LOCF approach will also be conducted.

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- The time to oral ulcer resolution is defined as the time interval in weeks from the date of first dose of IP to the date of first complete response with oral ulcer-free during the Placebo-controlled Treatment Phase. For subjects without any post-baseline oral ulcer assessment, the time to oral ulcer resolution will be censored to Day 1 of the placebo-controlled period; for the rest of the subjects who have a post-baseline assessment but have not achieved the complete response during Placebo-controlled Treatment Phase, the time to event will be censored at the last oral ulcer assessment date during the Placebo-controlled Treatment Phase

- Time to oral ulcer recurrence is defined as the time interval in weeks from the date of first complete response to the first reappearance of oral ulcers during the Placebo-controlled Treatment Phase. This analysis will only be conducted for subjects who are complete responders prior to Week 12. For subjects without ulcers recurrence following a complete response during the Placebo-controlled Treatment Phase, the time to event will be censored to the last oral ulcer assessment date during the Placebo-controlled Treatment Phase; for subjects without any ulcer assessment following the first complete response, the time to event will be censored to the first complete response date.

- For continuous endpoints including pain of ulcers as measured by VAS, BDCAF scores, total scores of PGA, BD QoL scores, and BSAS scores, the LOCF imputation approach will be used for subjects whose Week 12 assessment is unavailable. Similar to number of ulcers, if a subject has no post baseline assessment of endpoints above

excluding the value obtained at the Observational Follow-up Visit, the baseline value will be carried forward for calculation.

- Additional derivations including 3 patient reported outcome (PRO) endpoints are provided below:

  – Two separate pain VAS scales (100 mm) for oral and for genital ulcers will be completed by the subject and recorded on a secure, validated hand-held device. Subjects will be asked to click on the VAS line at the point that represents the severity of their pain during the previous week, with zero (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst possible. The change from baseline will be determined. A negative change from baseline indicates improvement.

  – Behçet's Disease Current Activity Form (BDCAF) was developed for the International Scientific Committee on Behçet's Disease for routine monitoring of subjects, as well as for clinical studies (Lawton, 2004). The questionnaire is administered to the subjects by the investigator (Investigator will complete the form on a secure, validated hand-held device), and disease manifestations over the previous 4 weeks are quantified on a 12-point scale, with a higher score indicating higher level of activity, which is the sum score of 12 questions. A negative change from baseline indicates improvement.

  – Physician's global assessment (PGA) of BD related skin lesions (on skin lesions except oral/genital ulcers) will be completed by the investigators.

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  – The Behçet's Disease Quality of Life (BD QoL) questionnaire was developed to measure the influence of BD on a subject's life (Gilworth, 2004). It consists of 30 self-completed items that measure disease-related restrictions on the subject's activities and the subject's emotional response to these restrictions. The BD QoL measure will be completed by the subject on a secure, validated hand-held device. The total score will be the summary of all 30 items (each yes scores 1 and each no scores 0). For possible missed items collected on the paper, the total score will be calculated using the following formula: [(sum of score of nonmissing items)/(total number of nonmissing items)]*total number of items on questionnaire. The total score ranges from 0-30, with zero representing no influence of BD on a subject's quality of life, and 30 representing the most severe influence. A negative change from baseline indicates improvement.

  – The Behçet's Syndrome Activity Score (BSAS) (Forbess, 2008) contains 10 questions, including assessments of the number of new oral and genital ulcers and skin lesions; assessment of the GI, CNS, vascular, and ocular involvement; and the assessment of the subject's current level of discomfort. The item scores are

totaled to create a score ranging from 0 to 100, with a higher score indicating higher level of activity; a negative change from baseline indicates improvement. The BSAS will be completed by the subject on a secure, validated hand-held device. If any BSAS question has the missing answer, the total score will be calculated based on the same formula used for BD QoL.

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4.2.6. Derivations of Safety Endpoints

Baseline definition for all safety endpoints is given in Section 5.3. Change from baseline is calculated as on-treatment value minus the baseline value. Handling of time points is described in Section 5.4.

4.2.6.1. Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any AE that begins or worsens on or after the date of the first dose of IP through 28 days after the last dose of IP for subjects who have completed the study or have discontinued early by the time of database cut, or on or after the date of the first dose of IP for subjects who are ongoing at the time of database cut.

If the treatment-emergent status of an AE is unclear due to a missing/incomplete start date, it will be defined as a TEAE, unless shown otherwise by data. Date imputation rules for partially missing AE start dates are described in Section 16.2.

Relationship to IP is based on the investigator's causality judgment; that is, a drug-related AE is an AE indicated by the investigator to have a suspected relationship to IP.

4.3. Stratification, Randomization, and Blinding

At Visit 2, subjects who meet entry criteria will be randomized using a permuted block randomization in parallel 1:1 (102 subjects per group) to receive either APR 30 BID or identically-appearing placebo BID for the 12-week Placebo-controlled Treatment Phase, using a centralized Interactive Response Technology (IRT). Eligible subjects will be stratified according to sex, history of uveitis, and region (Japan and Other).

This study will be conducted as a double-blind study for the Placebo-controlled Treatment Phase. During the Active Treatment Phase (Weeks 12 to 64), the IP will remain blinded, to prevent study personnel and subjects from knowing the IP assignment in the Placebo-controlled Phase.

To maintain the blind regarding the initial treatment assignment, all subjects will receive dose titration cards at Visit 9. Although only subjects initially randomized to placebo will be dose titrated during their first week of the Active Treatment Phase, all subjects entering the Active Treatment Phase will receive identically-appearing titration/treatment cards.

Data analyses and reporting will be performed after all subjects have completed Week 12/Visit 9 or have discontinued early (the 12-week database). After medical/scientific review has been completed, protocol violations/deviations have been identified, and the data have been declared final and complete, the 12-week database will be extracted and restricted with the corresponding external data files in the appropriate location in the data repository. For 12-week database lock, Celgene personnel who have access to the unblinded data are not to discuss or make materials available that would unblind individual subjects data to the personnel involved in the study conduct. Blinding to treatment assignment will be maintained at all study sites prior to the Week 68 database lock.

4.4.   Sample Size Determination

The sample size estimation is based on the consideration from the results of the Phase 2 study CC-10004-BCT-001. A 2-sided t-test at a 0.05 significance level will have 90% power to detect a treatment difference of 66 in the AUC of oral ulcer counts from Day 1 through Week 12 (AUC_{85} of placebo – drug = 66), the primary efficacy endpoint, when the sample size in each group is 102, assuming a common standard deviation of 144.

5.   GENERAL STATISTICAL CONSIDERATIONS

5.1.   Reporting Conventions

Summary statistics for continuous variables include sample size (n), mean, standard deviation (SD), median, minimum, the 25th (Q1) and 75th (Q3) percentiles, and maximum. All mean and median values will be formatted to one more decimal place than the measured value. SD 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 treatment group in the column heading. P-values (2-sided) will be presented with 4 decimal places. All laboratory data will be reported using standard international (SI) units.

5.2.   Analysis Periods

For the purposes of data analysis and reporting, 2 analysis periods are defined as follows, unless otherwise defined for a specific tabulation. Data analysis and reporting for a specific analysis period will include all data measured or collected (based on date of measurement or date of specimen collection, as appropriate) during that analysis period.

- Placebo-controlled period:

This period starts on the date of the first dose of IP, and stops

  - on the date the first dose of apremilast is administered at the Week 12 visit (Visit 9), or

  - on the date of the last study visit (including the ET Visit and the Observational Follow-up Visit; i.e., all data after the start date will be included) for efficacy analyses, or 28 days after the last dose of IP or the date of death (if applicable), whichever comes first, for safety analyses, for whom IP is not dispensed at Week 12

The start day is exclusive and the stop day is inclusive for efficacy, and safety analyses based on laboratory, vital signs, and weight. For AE analyses, the start day is inclusive, and the stop day under the first bullet is exclusive and the stop day under the second bullet is inclusive.

- Apremilast-exposure period:

This period starts

  - on the date the first dose of apremilast is administered for subjects who are randomized to an apremilast dose group, or

  - on the date the first dose of apremilast is administered at the Week 12 (Visit 9) for subjects who were originally randomized to placebo and switched to the APR 30 BID group,

and this period stops

– For efficacy analyses, on the date of the last study visit (including the ET visit and the Observational Follow-up Visit; i.e., all data after the start date of the apremilast-exposure period will be included), or

– For safety analysis, 28 days after the last dose of apremilast for subjects who have completed the study or have discontinued early, or the date of death (if applicable), whichever comes first.

The start day is exclusive and stop date is inclusive for efficacy analyses, and safety analyses of laboratory, vital signs, and weight. For AE analyses, both the start date and stop date are inclusive.

5.3.   Baseline Definitions

For all efficacy analyses and the data tabulation of baseline disease characteristics, baseline is defined as the last value measured on or before the day of the first dose of IP. For the summaries of laboratory parameters, vital signs, and weight, baseline is defined as the last value measured on or before the day of the first dose of IP in the summaries for the placebo-controlled period, and defined as the last value measured on or before the start day (defined in Section 5.2) of the apremilast-exposure period in the summaries for the apremilast-exposure period.

5.4.   Time points

Assessments will be done at the intervals specified in the Table of Events, Section 5 in protocol. During the trial, assessments can occur outside protocol specified intervals (i.e., Early Termination Visit or unscheduled visits). For the purpose of data analysis and reporting, all assessments will be assigned to analysis visits according to a visit window schema (See Table 2 and Table 3), which is defined as the study day ranges relative to either the date of first dose of IP or apremilast 30 mg for placebo subjects who switch to the APR 30 BID group at Week 12.

If more than one assessment of a particular efficacy or safety variable occurs in the same study visit window (due to unscheduled visits or Early Termination visit), the assessment within given visit window that is closest to the target Study Day will be used for the analysis; in the case of ties, the later assessment will be used.

Table 2:   Definition of Visit Window for Study Visit

Visit Number	Week	Analysis Time Point	Target Study Day	Start (Study Day)	End (Study Day)
Visit 2	Week 0	Baseline	1		1
Visit 3	Week 1	Week 1	8	2	11
Visit 4	Week 2	Week 2	15	12	22
Visit 5	Week 4	Week 4	29	23	36
Visit 6	Week 6	Week 6	43	37	50
Visit 7	Week 8	Week 8	57	51	64
Visit 8	Week 10	Week 10	71	65	78
Visit 9	Week 12	Week 12	85	79	1) Last measure on or prior to first APR dose date on Visit 9 or 2) 1 day prior to date of Follow-up Visit if subjects discontinue study prior to Visit 9 and complete Follow-up visits or 3) ET visit if performed or date of treatment discontinuation if subjects discontinue study and have no Observational Follow-up Visits, whichever is later.
Visit 10	Week 16	Week 16	113	First APR dose date on Visit 9 + 1	155
Visit 11	Week 28	Week 28	197	156	239
Visit 12	Week 40	Week 40	281	240	323
Visit 13	Week 52	Week 52	365	324	407

Visit Number	Week	Analysis Time Point	Target Study Day	Start (Study Day)	End (Study Day)
Visit 14	Week 64	Week 64	449	408	For subjects entering Active Treatment Phase but not entering optional Open-label Extension Phase: 1) 1 day prior to date of Observational Follow-up Visit if Observational Follow-up Visit performed or 2) ET visit if performed or 3) Date of APR treatment discontinuation if subjects discontinue study and have no Observational Follow-up visits, whichever is later. For subjects from German sites entering the optional Open-label Extension Phase, the end day is when the IP is administered at Visit 14

APR = Apremilast; ET = Early termination.

The time points for analyses of efficacy data will be assigned according to visit window scheme in Table 2 which are set up as the continuous and mutually exclusive, from midpoint to midpoint between each successive part of scheduled visits or otherwise specified.

The time points for summaries of safety data (laboratory parameters, vital signs, and weight) will be assigned as defined above for both placebo-controlled and apremilast-exposure period for subjects who are randomized as APR30 BID; and for placebo-control period only (through Week 12) for placebo subjects. For all placebo subjects who switch to the APR 30 BID group at Week 12, safety data within apremilast-exposure period will be mapped to reflect the Study Days relative to the first dose of apremilast (see Table 3 below). In addition, safety analysis on the end of treatment will be included, which is defined as the last visit among all the scheduled and unscheduled visits and, if applicable, the Early Termination visit, all within the same analysis period. The baseline visit and the Observational Follow-up Visit are not included in the derivation of the end-of-treatment value.

Table 3: **Mapping of Study Weeks for Placebo Subjects who Switched Treatment in Summary of Safety Data over Time**

Visit	Week	Mapped Analysis Time Point	Target APR Day	Start (APR Day)	End (APR Day)
Visit 9	Week 12	Baseline	1		Last measure prior to First **APR** Dose Date(≤ 1 APR day)
Visit 10	Week 16	Week 4	29	2	71
Visit 11	Week 28	Week 16	113	72	155
Visit 12	Week 40	Week 28	197	156	239
Visit 13	Week 52	Week 40	281	240	323
Visit 14	Week 64	Week 52	365	324	407
Note: APR Day is the study day relative to the first apremilast dose date on Visit 9.					

5.5.   Analysis Populations

5.5.1.   Intent-to-Treat Population

The intent-to-treat (ITT) population will be defined as all randomized subjects who received at least one dose of IP. This ITT population will be used for the primary efficacy analysis. Subjects will be included in the treatment group to which they are randomized.

5.5.2.   Safety Population

The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment group to which they actually received.

5.5.3.   Per-Protocol Population

The per protocol (PP) population will include all randomized subjects who received at least one dose of IP, have a baseline and at least one post-baseline oral ulcer evaluation, and have no important protocol violations during the 12-week Placebo-controlled Treatment Phase. The final determination of important protocol violation criteria will be made prior to the unblinding of the database and will be documented separately.

5.5.4.   Apremilast Subjects as Treated Population

Safety analyses for the apremilast-exposure period will be based on the apremilast subjects as treated population, which will include all subjects who actually receive 30 mg BID at the randomization visit or switched (at the Week 12 visit) to the APR 30 BID. Subjects will be included in the treatment sequence they actually received.

6.   SUBJECT DISPOSITION

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

The number and percentage of subjects who entered, completed, and discontinued each study phase (Placebo-controlled Treatment Phase, Active Treatment Phase, and Observational Follow-up Phase), and the number and percentage of primary reasons for discontinuation of each study phase (except for the Observational Follow-up Phase) will be summarized by treatment group at randomization. For the Placebo-controlled Treatment Phase, the summary of the number and percentage of subjects who completed and entered or completed but did not enter the Active Treatment Phase will be provided separately.

The primary reasons for discontinuation are collected in the Discontinuation eCRF and will be summarized with the following categories:

- Adverse event
- Lack of efficacy
- Non-compliance with IP
- Withdrew by subject
- Death
- Lost to follow-up
- Study terminated by sponsor
- Protocol violation
- Pregnancy
- Other

The number of subjects randomized, and the number and percentage of subjects included in the ITT, PP, Safety and Apremilast as Treated analysis populations will be summarized by treatment group (placebo and 30 mg BID) at randomization. The percentages will be based on the number of subjects randomized. A listing of subject eligibility/analysis population and a listing of subjects who discontinue the study early and reasons for discontinuation will be provided. A listing of subjects excluded from the per protocol population, with the reasons for exclusions, will also be provided.

The number and percentage of subjects by region, country, study site and treatment group will be tabulated based on the ITT population.

Subject disposition for the optional Open-label Extension Phase will be presented in a separate listing.

7.   PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by clinical research physician or designee following company standard operational procedure.

The number and percentage of protocol violations and deviations will be summarized for the ITT population from Weeks 0 to 12 by treatment group at randomization, and after Week 12 by treatment sequence and the total for subjects who enter the Active Treatment Phase.

A listing of subjects with protocol deviations/violations in the ITT population will be provided.

8.   DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT population. The demographics and baseline clinical characteristics will also be summarized for subjects who discontinued study early within the ITT population. Individual subject listings will be provided to support the summary tables.

8.1.   Demographics

Summary statistics will be provided by treatment group for the following continuous variables:

- Age (years)

- Weight (kg)

- Height (cm)

- Body mass index (BMI; kg/m^2)

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

- Age category (< 65, ≥ 65 years; < 40, ≥ 40 to < 65, ≥ 65 years)

- Sex (female, male)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other)

- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

- Region (Japan, Other; Europe, North America, Asia, Rest of the World)

- Weight category (< 50, ≥ 50 to 60, ≥ 60 to 70, ≥ 70 to < 85, ≥ 85 kg)

- BMI category (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30 kg/m^2)

  The body mass index (BMI) will be calculated as

  BMI (kg/m^2) = baseline weight (in kilograms) / height^2 (in meters).

- Alcoholic beverage intake (yes [<1 drink per week, 1-14 drinks per week, >14 drinks per week], no)

- Tobacco use (current user, past user, non-user).

8.2.   Baseline Disease Characteristics

Variables indicated below will be summarized descriptively:

- Duration of disease (time [in years] from first diagnosis to the informed consent date)

- Duration of disease (≤ 2, > 2 to ≤ 6, > 6 to ≤ 10, > 10 years)

- History of uveitis from IRT data

- History of uveitis from clinical data, defined as having a history of 'Anterior uveitis, iridocyclitis', 'Cells in vitreous', 'Chorioretinitis, retinovasculitis', and/or 'Posterior uveitis', which are collected on screening and randomization visit BD manifestation activity history

- Behçet's syndrome diagnostic criteria

- Ophthalmologic examination for presence of uveitis

- Chest Radiograph (Normal, Abnormal [Not Clinically Significant, Clinically Significant])

- Electrocardiogram (ECG) (Normal, Abnormal [Not Clinically Significant, Clinically Significant])

- Baseline BD activities as measured by number of oral ulcers, number of genital ulcers (non-zero for subjects who had genital ulcers at baseline), pain of oral ulcers as measured by VAS , pain of genital ulcers as measured by VAS (non-zero), BD Current Activity Index score, BD QOL total score, BSAS score, total score of PGA of BD skin lesions (non-zero),
.

- Baseline oral ulcers category (≥ 2 to ≤ 5, > 5 to ≤ 10, > 10)

- Prior use of immunosuppressants (Yes, No)

- Prior use of colchicines (Yes, No)

- Prior use of oral corticosteroids (Yes, No)

- Prior use of topical corticosteroids (Yes, No)

- Prior use of biologics (Yes, No)

- Prior use of NSAIDs (Yes, No)

- Prior use of analgesics/anesthetics (Different from NSAIDs) (Yes, No)

8.3.   Medical History

Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA). A frequency summary table of medical history will be presented by treatment group, system organ class (SOC) and preferred term (PT).

8.4.   Prior Therapy

Prior medications are defined as therapies that were started before the start of the study treatment (whether or not ended before the start of the study treatment). Prior therapies that continue into study treatment period(s) will be also reported as concomitant medications. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHODD) will be used to group medications into relevant categories. A frequency summary of prior medications will be provided by treatment group, ATC1 level, and standardized medication name.

8.5.   Concomitant Medications and Procedures

Concomitant medications/procedures are defined as non-study medications or procedures that are started after the start but before the end of the study treatment (of each study period), or started before the start of the study treatment and ended or remain ongoing during the study treatment.

All concomitant treatments documented during the placebo-controlled period and apremilast-exposure period will be summarized respectively in frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the WHODD will be used to group medications into relevant categories. A frequency summary of concomitant medications for each analysis period will be provided by treatment group, ATC1 level, and standardized medication name. Concomitant medications in the Posttreatment Observational Follow-up Phase will be summarized for all subjects who enter the phase. In addition, concomitant medications initiated in the Posttreatment Observational Follow-up Phase will be summarized separately and a corresponding listing will be provided.

A frequency summary table for concomitant procedures will be presented for each analysis period by presented by treatment group, MedDRA SOC, and PT.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

Treatment duration will be summarized by treatment group for the placebo-controlled period using the safety population, and for the apremilast-exposure period using the apremilast subjects as treated population. Subjects whose treatments are switched to active therapy will have the following treatment group designation: Placebo/APR 30 BID in the apremilast-exposure period. A subject data listing of study drug administration will be provided.

Treatment duration (in weeks) is calculated as (the date of the last dose of IP – the date of the first dose of IP + 1) / 7 during each period and rounded to one decimal place. Summary statistics for subject years, treatment duration (in weeks), as well as a frequency summary of treatment duration categories (e.g., ≥ 1 day, < 2 weeks, ≥ 2 to < 6 weeks, etc.), will be provided.

The specific definitions of the first and last dose dates for the Placebo-controlled and Apremilast-exposure periods are given below:

- Placebo-controlled period:
    - First dose date: The date of the first dose of IP.
    - Last dose date:
        o 1 day before the date of first dose of apremilast administered at the Week 12/Visit 9, or
        o The date of the last dose of IP in the study for subjects who discontinue the study on or prior to Week 12/Visit 9.
- Apremilast-exposure period:
    - First dose date:
        o The date the first dose of apremilast is administered for subjects who receive apremilast at randomization, or
        o The date the first dose of apremilast is administered at the Week 12 (Visit 9) for subjects who originally received placebo during the Placebo-controlled Treatment Phase and switched to the APR 30 BID group when entering Active Treatment Phase.
    - Last dose date:
        o The date of the last dose of apremilast during Active Treatment Phase for subjects who have either completed or discontinued Active Treatment Phase by the time of database lock or study close, or
        o The latest date out of scheduled visit dates, AE event dates or study drug administration dates for treatment ongoing subjects at time of database lock (ie, the second database in Section 2).

9.2.   Treatment Compliance

Subjects are instructed to return the IP blister cards, including any unused IP, to the study site at each post-baseline visit for pill counts and reconciliation. The number of tablets dispensed and returned will be recorded at visits specified in the Table of Events, Table 1 in the protocol.

The compliance rate (%) will be calculated for each subject as 100 times the total number of tablets taken (total number of tablets dispensed minus the total number of tablets returned) over the period divided by the intended total number of tablets that should have been taken over the same period.

It is assumed that from the first dose date through the last dose date, a subject takes the first 3 rows of tablets (6 tablets per row/day) on each complete blister card before taking the remaining rows (4 tablets per row/day), and completes all 33 rows and then starts a new blister card if multiple cards are dispensed. It is also assumed that a subject takes the full day's tablets from a new blister card on a study drug dispense date.

The intended total number of tablets is calculated as follows. First order the first dose date, the second dispense date, the third dispense date, etc., and the last dose date. The first and last dose dates are defined in the same way as those defined for treatment duration calculations. The intended number of tablets between any 2 consecutive dates is calculated as

$$4 \times n + 2 \times \text{int}[(n + 32) / 33] + 2 \times \text{int}[(n + 31) / 33] + 2 \times \text{int}[(n + 30) / 33],$$

where n denotes the number of days between the 2 consecutive dates (i.e., the second date minus the first date for all pairs of consecutive dates, and the second date minus the first date plus 1 for the last pair), and "int" denotes the integer part of the result. Then the intended total number of tablets is the sum of all intended numbers of tablets as calculated above from the first dose date through the last dose date.

Of note, compliance rate will not be calculated for subjects (if existent) who have only the dispense record at Week 0/Visit 2 and no other drug accountability records.

Compliance will be summarized using descriptive statistics for the placebo-controlled period and apremilast-exposure period. The acceptable range for compliance is defined as between 75%-120%. The number and percentage of subjects will be summarized by category < 75%, ≥ 75% to ≤ 120%, and > 120%.

A subject data listing of drug accountability records will be provided.

10.   EFFICACY ANALYSIS

10.1.   General Approaches to Efficacy Analyses

The efficacy analyses will be based on the ITT population, and analyses of the primary efficacy endpoint will also be provided using the PP population. Statistical comparisons will be made between the apremilast group and the placebo group using 2-sided tests and the overall significance level will be maintained at 0.05.

All efficacy endpoints will be summarized by time points per the report conventions in Section 5.1. Analyses of the primary endpoint, secondary   endpoints assessed during the Placebo-controlled Period will be presented by randomized treatment group, Placebo and 30 mg BID. During the Active Treatment Phase, data will be presented by treatment sequence, i.e., Placebo/30 mg BID, or 30 mg BID/30 mg BID.

Efficacy results that will be considered statistically significant are described in Section 10.2.1. All statistical tests will be conducted at the $\alpha = 0.05$ (2-sided) level, and 2-sided p-values will be reported.

10.2.   Efficacy Evaluation for the Double-blind, Placebo-controlled Treatment Phase

10.2.1.   Multiplicity

Planned statistical tests will be conducted between APR 30 BID and placebo for the primary endpoint, and selected secondary endpoints evaluated at Week 12.

The multiplicity of the analyses of the primary and selected secondary efficacy endpoints will be adjusted using a gatekeeping Procedure. This procedure will preserve the Family Wise Error Rate of the multiple analyses. The analyses will be performed in sequence until one of the analyses has failed to show the significant difference or all analyses have been completed at a significance level of 0.05. The sequence of the analyses for the selected secondary efficacy endpoints are listed below:

Table 4:   Rank of the Endpoints (Including Primary Efficacy Endpoint) in the Hierarchy of Multiplicity Adjustment

Endpoints	Rank of Endpoints in Multiple Testing Sequence
AUC for the number of oral ulcers from baseline through Week 12	1
Change from baseline in the pain of oral ulcers as measured by VAS at Week 12	2
Change from baseline in Behçet's Syndrome Activity Score (BSAS) at Week 12	3
Change from baseline in disease activity as measured by Behçet's Disease Current Activity scores (BD Current Activity Form) at Week 12	4
Proportion of subjects achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after start of dosing, and who remain oral ulcer free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase	5
Time to oral ulcer resolution (complete response), ie, the first instance when a subject has a complete response, during the Placebo-controlled Treatment Phase	6
Complete response rate for oral ulcers at Week 12	7
Change from baseline in the BD QoL score at Week 12	8
Complete response rate for genital ulcers at Week 12 for subjects who had genital ulcers at baseline	9
Proportion of subjects with no oral ulcers following complete response, ie, the first time when a subject has a complete response, during the Placebo-controlled Treatment Phase	10
Time to recurrence of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase	11
Number of oral ulcers following loss of complete response, ie, the first instance when a subject has a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase	12
Change from baseline in the total score of the Static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis and erythema nodosum) of BD at Week 12 in subjects who had BD skin lesions at baseline	13
Change from baseline in the pain of genital ulcers as measured by VAS at Week 12 in subjects who had genital ulcers at baseline	14

For example, formal comparison with respect to the first secondary endpoint to be tested (Change from baseline in the pain of oral ulcers as measured by VAS at Week 12) will be conducted conditional on the test results for primary efficacy endpoint. If the test of AUC is

statistically significant, (i.e., two sided p-value ≤ 0.05), then the comparison for change from baseline in the pain of oral ulcers as measured by VAS at Week 12 will be performed at $\alpha = 0.05$. If the test result of AUC is not statistically significant, the formal statistical tests will not be performed for change from baseline in the pain of oral ulcers as measured by VAS at Week 12 and for the remaining of secondary/   endpoints.

For planned statistical tests that are not formally performed as a result of aforementioned multiplicity adjustment strategy, nominal 2-sided p-values (without adjustment for multiplicity) will still be computed as a measure of the strength of the association between the endpoints and the treatment effect rather than formal test of hypotheses. In addition, nominal 2-sided p-values may also be computed for other efficacy analysis.

10.2.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the AUC for the number of oral ulcers from Day 1 through Week 12/Day 85 (AUC_{85}). The AUC_{85} will be compared between the placebo and APR 30 BID groups using a two-tailed parametric ANCOVA test at the 0.05 level. The model will include AUC_{85} as the response variable; treatment, sex and region as factors; and the number of oral ulcers at baseline as a covariate. Within-group least-squares (LS) means, the associated standard errors (SE), and treatment differences in LS means, the associated SE, and associated 2-sided 95% CIs and 2-sided p-values will be derived from the model. The primary efficacy analysis will be performed using the ITT and PP population.

To derive AUC_{85}, the multiple imputation (MI) method will be used to impute missing oral ulcer counts on study visits from Day 1 through Week 12 with 3 steps:

- Check missing data patterns;

- If there are non-monotone patterns, then use the Markov Chain Monte Carlo (MCMC) with a single chain method to impute sufficient missing oral ulcer counts by treatment to make 25 data sets having monotone patterns only. The seed will be set to 37851. When the imputed oral ulcer count post-baseline is negative, the value of 0 will be assigned.

- For the monotone datasets, use the predictive mean matching method with treatment, sex, region, and oral ulcer counts from previous visits as covariate to impute the remaining missing oral ulcer counts to make datasets complete. The MONOTONE REGPMM statement will be used with a seed of 37951.

In this MI approach, instead of filling in a single value for each missing value, SAS® procedure PROC MI performs MI by replacing each missing value with a set of plausible values. The missing data will be filled in multiple times to generate multiple complete data sets. A supportive analysis based on PP population will be performed using MI approach with the same seed number on PP population.

Missing data patterns will be provided in a separate table. The results obtained from parametric ANCOVA models (one for each imputation) will then be combined to derive valid statistical inference through the SAS® procedure PROC MIANALYZE. The complete-data degrees of freedom for parameter estimate specified in the PROC MIANALYZE option will be pulled from degree of freedom from parametric ANCOVA models.

Parametric ANCOVA modeling AUC_{85} will also be performed for ITT and PP populations using an LOCF approach, and for subjects who complete Week 12 assessment based on observed data as sensitivity analyses.

Additional sensitivity analyses for AUC_{85} will be conducted for ITT population for subjects who complete each scheduled assessment from baseline through Week 12 based on observed data and for subjects who missed at most 2 scheduled oral ulcer assessments from baseline through Week 12 based on MI imputed data.

10.2.3.   Analyses of Secondary Efficacy Endpoints

Frequency counts and percentages will be provided for categorical variables including oral ulcer complete responders at Week 12, and genital ulcer complete responders at Week 12 for subjects who had genital ulcers at baseline. The proportions of complete responders in the two study treatment groups will be compared using a 2-sided Cochran-Mantel-Haenszel (CMH) test with significance level of 0.05, controlling for stratification factors including sex (male, female) and region (Japan, Other). Subjects who have discontinued early prior to Week 12 or who do not have data at Week 12 will be regarded as non-responders at Week 12. A sensitivity analysis using LOCF approach will be performed. The complete response rate based on the approach of NRI, or LOCF or the observed data will be provided for each time point during Placebo-controlled Treatment Phase.

Similarly, the proportion of subjects with no oral ulcers or no genital ulcers following subject's first complete response during Placebo-controlled Treatment Phase will be analyzed. The subjects who have a complete response prior to Week 12 but have no oral ulcers or genital ulcers assessment following subject's first complete response through Week 12 assessment will be excluded when summarizing each endpoint. The treatment comparison will only be conducted if appropriate.

The proportion of subjects achieving an oral ulcer complete response (oral ulcer-free) by Week 6, after the start of dosing, and who remain oral ulcer free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase will be analyzed similarly as the complete response rate as described above. Only those subjects who are oral ulcer-free by Week 6 and remain oral ulcer free for at least 6 consecutive weeks during the 12-week Placebo-controlled Treatment Phase will be considered as a responder; otherwise, subjects will be considered as non-responders. In case an oral ulcer assessment is missing at a visit, the LOCF approach will be used to impute missing assessments up to the ET visit or the last scheduled visit on or prior to date of treatment discontinuation, whichever is later.

The number of oral ulcers following subject's first loss of a complete response will be summarized for subjects who have a complete response prior to Week 12. The number of oral ulcers will be summarized as zero for subjects who had no reappearance of oral ulcers following a complete response prior to Week 12. The comparison between two treatment groups will be performed using ANCOVA model with the treatment, sex and region as factors and baseline number of oral ulcers as a covariate. Within-group LS means, the associated SEs, and treatment differences in LS means, the associated SE, and associated 2-sided 95% CIs and 2-sided p-values will be derived from the model. The treatment comparison will only be conducted if appropriate.

The summary tables with descriptive statistics for number of oral ulcers and general ulcers will be presented by treatment group at all applicable analysis visits.

Summary tables for change from baseline with descriptive statistics will be presented for continuous variables including pain VAS of oral ulcers, pain VAS of genital ulcers, BD Current Activity Form Scores, BD QoL scores, BSAS scores,   , and total score of the Static PGA of skin lesions by treatment group at all applicable visits per study period. For the PGA, only subjects who had BD skin lesions at baseline will be included. For the pain VAS of genital ulcers, only subjects who had genital ulcers at baseline will be included.

The LOCF approach will be used to impute the missing assessment at Week 12 for the following endpoints: pain VAS of oral ulcers, pain VAS of genital ulcers, BD Current Activity Form Scores, BD QoL, and BSAS. The change from baseline at Week 12 (LOCF approach) will be compared between the placebo and the APR 30 BID group using ANCOVA model with change from baseline at Week 12 as the response variable, treatment, sex and region as factors and baseline value as a covariate. Within-group LS means, the associated SEs, and treatment differences in LS means, the associated SE, and associated 2-sided 95% CIs and 2-sided p-values will be derived from the model. A sensitivity analysis for change from baseline in the pain VAS of oral ulcers at Week 12 will be conducted using mixed-effects model for repeated measures (MMRM) with treatment, visit, treatment-by-visit interaction, sex and region as factors and baseline value as a covariate. An unstructured covariance matrix that is homogeneous across treatment groups is to be used.

The frequency distributions for categorical changes from baseline for VAS (-100 to 100 inclusive in 25 increment for each interval) , BD QoL (< -20 to ≥ 10 in 5 increment for each interval), BD BSAS (< -60 to ≥ 40 in 20 increment for each interval)   will be summarized by time point A shift table from baseline to applicable analysis visits will be provided for number of oral ulcers, genital ulcers, the Behçet's disease activity index (0 to 3, 4 to 8 and 9 to 12), and PGA of skin lesions scales components (None, Mild, Moderate, and Severe).

Analyses of time to oral ulcer resolution and time to recurrence of oral ulcers following the first complete response during the Placebo-controlled Treatment Phase will use Kaplan-Meier method to estimate the median resolution/ recurrence time and its 2-sided 95% CIs. The stratified log-rank test will be used for calculating 2-sided p-values for treatment comparison. The hazard ratio and 2-sided 95% CIs will be estimated using a stratified Cox model. For the time to oral ulcer resolution, the baseline number of oral ulcers will be included as covariate in the Cox model. The treatment comparison will only be conducted if appropriate.

Kaplan-Meier curves for time to event endpoints will be provided by treatment group.

10.3. Efficacy Evaluation for the Active Treatment Phase in the Final Analysis

All subjects entering into the Active Treatment Phase of the study will be included in the analysis. Descriptive summaries for the endpoints as listed below will be performed at each applicable study visits based on the observed data by treatment sequence.

- Complete response   rate for oral ulcers

- Complete response rate for genital ulcers for subjects who had genital ulcers at baseline

- Number of oral ulcers

- Number of genital ulcers

- Change from baseline in the pain of oral ulcers as measured by VAS

- Change from baseline in the pain of genital ulcers, as measured by VAS in subjects who had genital ulcers at baseline

- Change from baseline in disease activity as measured by BD Current Activity scores (BD Current Activity Form)

- Change from baseline in the BD QoL score

- Change from baseline in Behçet's Syndrome Activity Score (BSAS)

- Change from baseline in the total score of the Static Physician's Global Assessment (PGA) of skin lesions (acne-like lesions, folliculitis and erythema nodosum) of BD in subjects who had BD skin lesions at baseline

10.4. Subgroup Analysis

The focus of subgroup analyses will be limited to the stratification factor and baseline characteristics as listed below and will be conducted on the ITT population for AUC_{85}:

- Sex (male, female)

- Race (White, non-White)

- Age (< 40, ≥ 40 to < 65, ≥ 65 years years)

- Region (Japan, Other; Europe, North America, Asia, Rest of the World)

- Baseline weight category (< 50, ≥ 50 to < 60, ≥ 60 to < 70, ≥ 70 to < 85, ≥ 85 kg)

- Baseline BMI category (< 18.5, ≥ 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2)

- Alcoholic beverage intake (yes, no)

- Tobacco use (current user, past user, never user).

- Duration of disease (≤ 2, > 2 to ≤ 6, > 6 to ≤ 10, > 10 years)

- Baseline oral ulcers category (≥ 2 to ≤ 5, > 5 to ≤ 10, ≥ 10)

- Prior use of colchicines (Yes, No)

- Prior use of oral corticosteroids (Yes, No)

The consistency of the treatment effect across subgroups will be assessed in the context of the primary methods used for the analyses. For AUC_{85}, sex or region will not be included as a factor for the sex or region subgroup analysis, respectively, in the ANCOVA model.

Forest plots will be provided based on the treatment differences for each subgroup estimated as described above for AUC_{85}.

10.5.   Assessing Study Center Effect and Treatment-by-Center Interaction

This study is a multicenter study. As site enrollment caps are imposed in this study, no single site will have a sufficient number of subjects felt to allow a meaningful within-site analysis of treatment differences in AUC_{85} stratified by sex, therefore, study site effects will be assessed by pooling sites on a geographic basis to help interpret the results should potential site effects be suspected. In pooling sites for analysis purposes, values around 5 are often chosen as the minimum cell size in models containing interaction terms for a continuous endpoint. In this study, a minimum of 5 ITT subjects per treatment group per stratum of sex is chosen. The detailed pooling strategy for the stratified analyses is described in 4 steps as follows:

- Sites will first be pooled within each country according to their rank based on site-specific sample size, starting with the smallest sites; i.e., within a country, the smallest sites will first be pooled until the pooled site has a minimum cell size of 5.

- The remaining unpooled sites will then be pooled within a region (as defined in the subgroup analysis by region) in a similar fashion.

- The remaining unpooled sites will then be pooled across regions in a similar fashion.

- The remaining unpooled sites will finally be pooled with the smallest pooled site.

Study site effects will be assessed for the primary efficacy endpoint by stratifying the analysis based on both sex and pooled sites and examining whether the treatment differences, adjusted for pooled site, are consistent with those from the primary analysis.

In addition, the consistency of the treatment effect across pooled sites will also be assessed by performing a subgroup-type analysis with respect to the primary endpoint, with pooled sites treated as subgroups (see Section 10.4). A table summarizing AUC_{85} values by multiple imputation approach will be provided by individual study site and treatment group.

11.   SAFETY ANALYSES

11.1.   General Approaches to Safety Analyses

Safety analyses will be performed for both the placebo-controlled and apremilast-exposure periods (see Section 5.2), based on the safety population and the apremilast subjects as treated population respectively. Summary tables during the placebo-controlled period are presented by treatment group, Placebo and 30 mg BID. During the apremilast-exposure period, data are presented by treatment sequence, i.e., Placebo/30 mg BID, 30 mg BID as Initiated, and a total column of 30 mg BID as Treated.

Unless otherwise specified, the analyses of AEs and marked abnormalities (laboratory parameters and vital signs) for both the placebo-controlled and apremilast-exposure periods will include the subject incidence rate (i.e. percentage [%] used in a frequency summary), which 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.

To account for the different exposure to the IP, AEs and laboratory marked abnormalities will also be analyzed using exposure-adjusted incidence rate (EAIR) per 100 subject-years as defined below:

- 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.

Summaries of vital signs, weight, and laboratory parameters over time (e.g., summary statistics of observed value and changes from baseline and shifts from baseline to post-baseline time points in terms of normal/abnormal or grade) will be provided. In summaries for a post-baseline time point, subjects who have both values at baseline and at the time point will be included; for end of period and shifts from baseline to the end of period and to the worst post-baseline value, subjects who have a baseline value and at least one post-baseline value will be included.

Safety data collected during the optional Open-Label Extension Phase will be listed.

11.2.   Adverse Events

AEs will be classified using the MedDRA. Unless otherwise specified, AEs will be summarized by system organ class (SOC) and preferred term (PT), with SOCs presented in the standard international order and PTs within each SOC in descending order of subject incidence.

A subject data listing of all AEs (including TEAEs and non-TEAEs) sorted by subject ID and AE start date will be provided based on the safety population, irrespective of analysis periods; this listing will include a "non-treatment-emergent" flag and the date of the last IP dose. Only TEAEs will be included in the AE summaries as described below.

11.2.1.   Overall Summary of Adverse Events

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

- Subjects with any TEAE

- Subjects with any drug-related TEAE

- Subjects with any severe TEAE

- Subjects with any serious TEAE

- Subjects with any serious drug-related TEAE

- Subjects with any TEAE leading to drug interruption

- Subjects with any TEAE leading to drug withdrawal

- Subjects with any TEAE leading to death

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

11.2.2.   All TEAEs

All TEAEs will be summarized by

- SOC and PT

- PT only (in descending order of subject incidence)

New events of all TEAEs by exposure interval (≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12 and > 12 weeks) will be summarized for the placebo-controlled period and for the apremilast-exposure period (≤ 1, > 1 to ≤ 2, > 2 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12, > 12 to ≤ 16, > 16 to ≤ 28, > 28 to ≤ 40, > 40 to ≤ 52, > 52 to ≤ 64 and > 64 weeks); an event with a start date falling within an exposure interval is considered a new event for that interval. Each subject is counted once in the numerator of a subject incidence or EAIR for each applicable specific TEAE in each exposure interval where an event started. The denominator of a subject incidence is the number of subjects with treatment duration exceeding the lower bound of the particular exposure interval, while the denominator of an EAIR is the sum of the exposure time during the exposure interval (up to the first event start date subjects with at least one event starting in the interval) among the same number of subjects as in the denominator of the responding subject incidence.

11.2.3.   Common TEAEs

TEAEs with subject incidence $\geq 5\%$ in any treatment group will be summarized by SOC and PT as well as by PT only in descending order of subject incidence.

Summaries about the most frequent TEAEs will include onset day of the most frequent TEAE, and the duration of those most frequent TEAE. The most frequent TEAEs will be those identified in the $\geq 5\%$ summaries noted above.

11.2.4.   Drug-related TEAEs

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

11.2.5.   TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, and severe). 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.

11.2.6.   Serious TEAEs

Serious TEAEs and serious drug-related TEAEs will be summarized by SOC and PT. Serious TEAEs will also be summarized by PT only (in descending order of subject incidence).

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

11.2.7.   Severe TEAEs

Severe TEAEs will be summarized by SOC and PT.

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

11.2.8.   TEAEs Leading to Drug Withdrawal

All TEAEs leading to drug withdrawal will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence).

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

11.2.9.   TEAEs Leading to Drug Interruption

All TEAEs leading to drug interruption will be summarized by SOC and PT.

11.2.10.   TEAEs of Special (Specific) Interests

The diarrhea characterization CRF collects information at each visit: what event occurred, if the event meets protocol definition (yes or no), and frequency of watery/liquid stools (Daily, 5 – 6 days per week, 2 – 4 days per week, Once every other week to once a week, Once a month or less). Protocol-defined diarrhea refers to diarrhea adverse events that have two or more watery or liquid stools in a day.

Summarization will include:

- Subject incidence of protocol-defined diarrhea TEAE;
- Total number of diarrhea event and protocol-defined diarrhea TEAE;
- Protocol-defined diarrhea TEAE characteristics of highest frequency of watery/liquid stools, duration and onset day of the event,

The summaries will be provided for the placebo-controlled period, and for the apremilast-exposure period.

A listing for diarrhea events will be provided.

11.2.11. TEAEs and Serious TEAEs by Subgroups

All TEAEs and serious TEAEs will be summarized by sex (male, female), age category (< 65, ≥ 65 years), race (White, non-White), and region (Japan, other; Europe, North America, Asia, and Rest of the World), provided sufficient subjects are enrolled into these categories.

11.2.12. TEAEs Leading to Drug Withdrawal by Subgroups

All TEAEs leading to drug withdrawal will be summarized by sex (male, female), age category (< 65, ≥ 65 years), race (White, non-White), and region (Japan, other; Europe, North America, Asia, and Rest of the World)), provided sufficient subjects are enrolled into these categories.

11.2.13. Deaths

All TEAEs leading to death will be summarized by SOC and PT. A subject data listing of deaths will be provided.

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. The EAIR will not be provided in this summary.

11.3. Clinical Laboratory Evaluations

Laboratory parameters as specified in protocol 6.6.7 will be included.

Laboratory marked abnormalities (see Section 16.3) will be summarized using subject incidence and EAIR for each marked abnormality 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. Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and subjects with abnormal values at baseline separately. For the purposes of these summaries, subjects with abnormal (normal) values at baseline are defined as those whose baseline value is low (not low) for criteria concerning low values and those whose baseline value is high (not high) for criteria concerning high values; both low and high are relative to the laboratory normal range.

Summary statistics of observed values and changes from baseline in continuous laboratory parameters will be provided by time points. Numeric values reported as less than (<) or greater than (>) a laboratory-defined limit will be included with the "<" or ">" signs ignored. Frequency summaries of shifts from baseline category to the category of post-baseline time points, the end of treatment and to the worst post-baseline category in terms of normal/abnormal (low or high) or grade will be provided in the above hematology and serum chemistry parameters.

A subject data listing of all laboratory data sorted by subject ID and date of sample collection will be provided based on the safety population, irrespective of analysis periods.

11.4. Vital Signs and Weight

Summary statistics of observed values and changes from baseline in vital signs (including weight, for which percent change from baseline will also be summarized) will be provided over time. 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,

respiratory rate and blood pressure. The normal ranges are defined as: 60-100 beats/minute for pulse, 12 to 16 breaths/minutes for respiratory rate, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure).

Vital sign abnormalities will be summarized in a manner similar to laboratory marked abnormalities. A subject data listing of vital sign abnormalities will be provided. Frequency summaries of change and percent change in weight from baseline to the end of the period will be provided by baseline BMI category ($< 18.5, \geq 18.5$ to $< 25, \geq 25$ to $< 30, \geq 30$ kg/m^2) and by baseline weight category ($<50, \geq 50$ to $60, \geq 60$ to $< 70, \geq 70$ to $< 85, \geq 85$ kg). The categories of weight change (kg) and percent change (%) are $< -20, \geq -20$ to $< -10, \geq -10$ to $< -5, \geq -5$ to $< 0, 0, > 0$ to $\leq 5, > 5$ to $\leq 10, > 10$ to ≤ 20, and > 20. The end-of-period value is the last post-baseline value in the analysis period (excluding the value obtained at the follow-up visit, if applicable) up to 28 days after the last dose of IP in the study.

A subject data listing of all vital signs and weight data sorted by subject ID and date of measurement will be provided based on the safety population, irrespective of analysis periods.

11.5.   Physical Examination

Physical examination results will not be summarized.

11.6.   Electrocardiogram

A 12-lead ECG will be performed during the Screening Phase. The site will use its own, local ECG machines for the study. ECG reading will be interpreted by the investigator and recorded as: normal; abnormal, not clinically significant; or abnormal, clinically significant.

A subject data listing of all ECG data sorted by subject ID and date of measurement will be provided based on the safety population, irrespective of analysis periods.

12.   INTERIM ANALYSIS

No interim analysis is planned prior to the analysis of the primary efficacy endpoint and the planned analyses are stated in Section 2.

14.   CHANGES TO THE STATISTICAL SECTION OF THE PROTOCOL
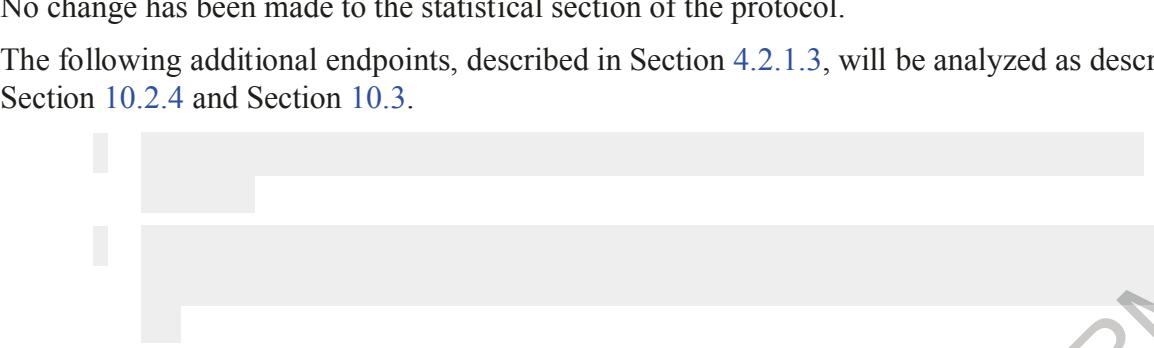
No change has been made to the statistical section of the protocol.

The following additional endpoints, described in Section 4.2.1.3, will be analyzed as described in Section 10.2.4 and Section 10.3.

15.   REFERENCES

Forbess C, Swearingen C, Yazici Y. Behçet's syndrome activity score (BSAS): A new disease activity assessment tool, composed of patient-derived measures only, is strongly correlated with the Behçet's disease current activity form (BDCAF). Presented at the Annual European Congress of Rheumatology, Paris, 11-14 June 2008; Abstract D 14.

Gilworth G, Chamberlain MA, Bhatia B, Haskard D, Silman A, Tennant A. Development of the DB-QoL; A quality of life measure specific to Behçet's disease. J Rheumatol. 2004;31:931- 937.

Lawton G, Bhakta BB, Chamberlain MA, Tennant A. The Behçet's disease activity index. Rheumatol. 2004;43:73-78.

Stokes, Davis, Koch (2000) Categorical Data Analysis Using the SAS Program, Page 174-179.

16.   APPENDICES

16.1.   Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.

- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (ie, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.

- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.

- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.

- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

16.1.1.   Calculation Using Dates

Calculations using dates (ie, 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 (e.g, lenalidomide) plus 1 day. The generalized calculation algorithm for relative day is the following:

  o If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE –
     DSTART) + 1;

  o Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug. Negative study days
are reflective of observations obtained during the baseline/screening period. 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 (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In
  practice, age will be transformed to years by dividing the difference by 365.25 days,
  then truncating.

  – Preference is for using calculated age from clinical database. When not available,
    calculated age from CRF or IVRS may be used

  – Partial birth date: impute missing day as 15th of the month; impute missing month
    as July; set missing age for missing year

- 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

16.2.   Date Imputation Guideline

16.2.1.   Impute Missing Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of
  the first doing date will be assigned to the missing fields.

- If the year is **prior to** the year of first dosing date, then December 31 will be assigned
  to the missing fields.

- If the year is **after** the year of first dosing, then January 1 will be assigned to the
  missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the
  first doing date will be assigned to the missing day.

- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.

- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

16.2.2.   Impute Missing Diagnosis Date for Behçet's Disease

Partial missing BD diagnosis date will be imputed in the ADaM dataset for the purpose of calculating duration of BD history. The 16th of the month will be used to impute a partially missed diagnosis date that has only the day missing, that July 1st will be used to impute a partially missed diagnosis date that has both the month and day missing. If the above imputation

inappropriately results in a diagnosis date on or after the informed consent date, then the
incomplete date will be assigned to the day prior to the informed consent date.

16.3.   Marked (Atypical) Abnormalities Criteria

Table 5:   Marked Abnormalities Criteria

Category / Analyte	SI Units	Criteria
Chemistry /		
Alanine Aminotransferase (SGPT)	U/L	> 3 xULN
Albumin	Kg/m^3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 3 x ULN
Total Bilirubin	μmol/L	> 1.8 x ULN
Blood Urea Nitrogen	mmol/L	> 15
Calcium	mmol/L	< 1.8 > 3.0
Creatinine	μmol/L	> 1.7 x ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 9
Lactate Dehydrogenase	U/L	> 3 x ULN
Magnesium	mmol/L	> 1.2
Phosphate	mmol/L	< 0.64 > 1.60
Potassium	mmol/L	< 3.0 > 5.5
Sodium	mmol/L	< 130 > 150
Urate	μmol/L	Male: > 590; Female: > 480
Hematology /		
Hemoglobin	g/L	Male: < 105, Female: < 85 Male: > 185, Female: > 170
Leukocytes	10^9/L	< 1.5
Lymphocytes	10^9/L	< 0.8
Neutrophils	10^9/L	< 1.0
Platelets	10^9/L	< 75 > 600
Vital Signs /		
Systolic Blood Pressure	mmHg	Increase > 10 but ≤ 15 (mild) Increase > 15 but ≤ 20 (moderate) Increase > 20 (severe)
Diastolic Blood Pressure	mmHg	Increase > 5 but ≤ 10 (mild) Increase > 10 but ≤ 15 (moderate) Increase > 15 (severe)