DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-10004-UC-001

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protects patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/.

STATISTICAL ANALYSIS PLAN

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

STUDY DRUG: Apremilast

PROTOCOL NUMBER: CC-10004-UC-001

DATE FINAL: 29 Sep 2017

Prepared by:

on behalf of

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	CC-10004-UC-001 Statistical Analysis Plan
SAP VERSION, DATE	Version 1.0, 29 Sep 2017
SAP AUTHOR	Printed Name and Title / Signature and Date
PROTOCOL TITLE	A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS
INVESTIGATIONAL PRODUCT	Apremilast (CC-10004)
PROTOCOL NUMBER	CC-10004-UC-001
PROTOCOL VERSION, DATE	Amendment 3, 20 Jul 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Celgene Lead Stati	
Signature	
Printed Name	
Celgene Statistical	
Signature	
Printed Name	
Celgene Lead Clini	
Signature	
Printed Name	

Celgene Lead Product Safety Physician

Signature _____

Printed Name _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Meaning
AE	Adverse event
ANCOVA	Analysis of covariance
APR 30 BID, APR 40 BID	Apremilast 30 mg twice daily, Apremilast 40 mg twice daily
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
ECG	Electrocardiograms
GI	Gastrointestinal
HRQoL	Health-related quality of life
IP	Investigational product
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Modified Mayo score
PGA	Physician's global assessment
PMS	Partial Mayo score

Abbreviation	Meaning
PP	Per-protocol
PT	Preferred term
RBS	Rectal bleeding subscore
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-12v2	The Medical Outcomes Study Short Form 12-item Health Survey, version 2 (SF-12v2)
SFS	Stool frequency subscore
SOC	System organ class
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TMS	Total Mayo score
UC	Ulcerative colitis
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-10004-UC-001 "A Phase 2, Randomized, Placebo-Controlled, Multicenter Study to Investigate the Efficacy and Safety of Apremilast (CC-10004) for Treatment of Subjects with Active Ulcerative Colitis" as amended on 20 Jul 2016. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

Planned data analyses include 1) an analysis at the completion of the 12-week Placebo-controlled Phase for all subjects (referred to as the Double-blind Placebo-controlled Phase analysis hereafter), 2) an analysis at the completion of the Active-treatment Phase (through Week 52) for all subjects, and 3) the final analysis at the completion of the entire study.

In this SAP, apremilast 30 mg twice daily (BID) and apremilast 40 mg BID are referred to as APR 30 BID and APR 40 BID, respectively. Investigational product (IP) refers to placebo, APR 30 BID, or APR 40 BID.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active ulcerative colitis (UC).

3.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of apremilast (30 mg BID and 40 mg BID), compared with placebo, in subjects with active UC
- To evaluate the long-term safety in subjects with active UC, receiving apremilast (30 mg BID or 40 mg BID)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of 2 doses of apremilast in subjects with active UC (defined as a total Mayo score [TMS] of ≥ 6 to ≤ 11, with an endoscopic subscore ≥ 2).

Approximately 165 subjects (55 subjects per arm) will be randomized in a 1:1:1 ratio using an Interactive Voice Response system (IVRS) or an Interactive Web Response System (IWRS) to receive oral apremilast (30 mg BID or 40 mg BID), or identically appearing placebo BID for up to 12 weeks, followed by 40 weeks of blinded treatment with apremilast (30 mg BID or 40 mg BID). At the end of 52 weeks in the study, subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase and will continue to receive the same treatment assigned during the Blinded Active-treatment Phase for an additional 52 weeks.

Treatment assignment will be stratified via IVRS/IWRS based on concomitant use of oral corticosteroids and previous exposure to immunosuppressants (eg, 6-MP, AZA, or MTX). The number of subjects with previous exposure to immunosuppressants is targeted to comprise, no more than 50% of the subjects enrolled, and no less than 30%.

The study will consist of 5 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Weeks 0 to 12
- Blinded Active-treatment Phase – Weeks 12 to 52
- Extension Phase – Weeks 52 to 104
    - The 52-week extension is a blinded, active treatment phase and henceforth will be referred to as the Extension Phase for the remainder of the document.
- Post-treatment Observational Follow-up Phase – The 4-week period after the last dose of investigational product (IP).

Double-blind Placebo-controlled Phase

Eligible subjects will enter the Double-blind Placebo-controlled Phase for 12 weeks, at the Baseline Visit (Week 0, Visit 2). Subjects will be randomly assigned to study treatment as described above. With the aim to mitigate potential dose-related side effects associated with apremilast, such as headache and gastrointestinal (GI) disturbances, apremilast-treated subjects will be dose-titrated in 10-mg/day increments over the first 8 days of treatment. All subjects will receive blister cards of identical appearance to maintain blinding. Subjects will continue to receive the treatment assigned at baseline for 12 weeks.

Blinded Active-treatment Phase

Following 12 weeks of treatment, subjects will enter the Blinded Active-treatment Phase for 40 weeks. At the Week 12 visit, subjects will be evaluated for clinical improvement based on the

TMS. The endoscopy subscore assessed by the investigator will be used for the calculation of the Week 12 TMS.

Subjects who achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP between the Week 12 Visit and the Week 52 Visit:

- Subjects who were randomized to apremilast (30 mg BID or 40 mg BID) at baseline will continue to receive the treatment assigned at baseline.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment.

Subjects who do not achieve at least a 20% decrease from baseline in the TMS at Week 12 will receive the following IP until the Week 52 Visit:

- Subjects who were randomized to apremilast 30 mg BID at baseline will be re-assigned apremilast 40 mg BID, with no dose titration.
- Subjects who were randomized to apremilast 40 mg BID at baseline will continue to receive apremilast 40 mg BID.
- Subjects who were randomized to placebo at baseline will be re-randomized to receive apremilast (30 mg BID or 40 mg BID) and will be dose-titrated in 10-mg/day increments over the first 8 days of treatment.

In order to maintain the blind for the treatment assigned at baseline, all subjects will receive blister cards of identical appearance during the titration period beginning at Week 12. However, for subjects continuing on the dosage of apremilast assigned at baseline, and for subjects who are not undergoing dose titration (as noted above), the IP included in the "titration" portion of the blister card will include the total daily dose of apremilast (30 or 40 mg BID) and will not include the dose titration.

Extension Phase

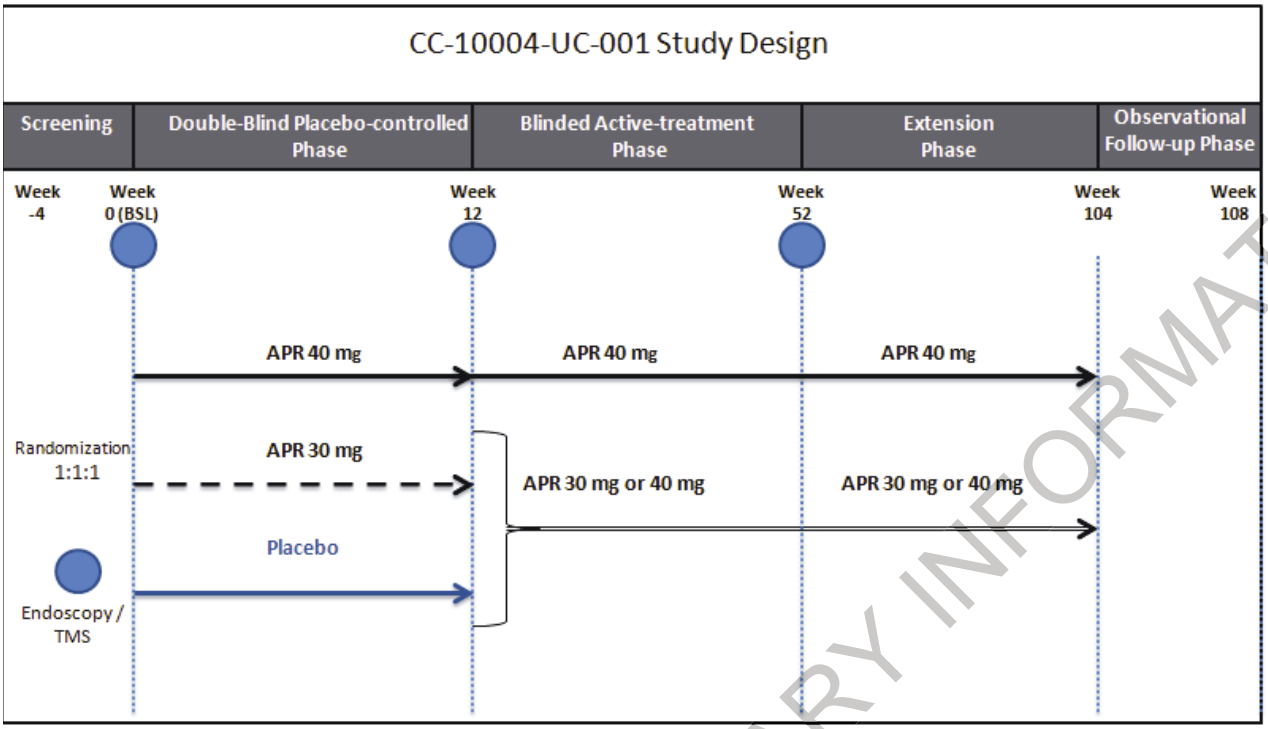
At the end of the Blinded Active-treatment Phase (Week 52), subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase. Subjects participating in the Extension Phase will continue to receive the same treatment assigned during the Blinded Active-treatment Phase for an additional 52 weeks (ie, Weeks 52 to 104).

Post-treatment Observational Follow-up Phase

All subjects are required to spend 4 weeks in the Post-treatment Observational Follow-up Phase following the last dose of IP.

The study schematic is presented in Figure 1 below.

Figure 1: Overall Study Design



4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects achieving a clinical remission in the TMS at Week 12, defined as a TMS of ≤ 2, with no individual subscore > 1.

4.2.2. Secondary Efficacy Endpoints

- The proportion of subjects achieving clinical response at Week 12, defined as a decrease from baseline in the TMS of at least 3 points and at least 30%, along with a reduction in the rectal bleeding subscore (RBS) of at least 1 point or an absolute RBS of ≤ 1
- The proportion of subjects achieving endoscopic remission at Week 12, defined as a Mayo endoscopic subscore of 0
- The proportion of subjects achieving endoscopic response at Week 12, defined as a decrease from baseline of at least 1 point in the Mayo endoscopic subscore
- The proportion of subjects achieving a RBS ≤ 1 at Week 12
- The proportion of subjects achieving clinical remission in the modified Mayo Score (MMS) (range: 0 to 9, based on stool frequency (SFS), RBS and endoscopy) at Week 12, defined as a score of 2 points or lower, with no individual subscore exceeding 1 point
- The proportion of subjects achieving clinical response in the MMS at Week 12, defined as a decrease from baseline at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1 point

- The proportion of subjects achieving clinical remission at Week 8, defined as a partial Mayo score (PMS) of ≤ 2, with no individual subscore > 1
- The proportion of subjects achieving clinical response at Week 8, defined as a decrease from baseline in the PMS of at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1 point

4.2.3. Secondary Safety Endpoints

- Type, frequency, severity, and relationship of AEs to IP
- Number of subjects who discontinue IP due to any AE
- Frequency of clinically significant changes in physical examination, vital signs, and/or laboratory findings

[redacted]

4.3. Stratification, Randomization, and Blinding

Approximately 165 subjects (55 subjects per arm) will be randomized in a 1:1:1 ratio using an IVRS/IWRS to receive oral apremilast (30 mg BID or 40 mg BID), or identically appearing placebo BID for up to 12 weeks, followed by 40 weeks of blinded treatment with apremilast (30 mg BID or 40 mg BID). At the end of 52 weeks in the study, subjects who have a Mayo endoscopy score ≤ 1 will have the opportunity to participate in the Extension Phase and will continue to receive the same treatment assigned during the Blinded Active-treatment Phase for an additional 52 weeks.

Treatment assignment will be stratified via IVRS/IWRS based on concomitant use of oral corticosteroids and previous exposure to immunosuppressants (eg, 6-MP, AZA, or MTX). The number of subjects with previous exposure to immunosuppressants is targeted to comprise, no more than 50% of the subjects enrolled, and no less than 30%.

4.4. Sample Size Determination

A 2-group chi-square test with a 0.1 two-sided significance level will have approximately 80% power to detect a true 20% absolute difference (30% versus 10%) between a dose of apremilast and placebo, for the proportion of subjects achieving a clinical remission at Week 12 when the sample size in each group is 49. Assuming a dropout rate of 10% prior to Week 12, approximately 165 subjects (approximately 55 subjects per group) are planned to be randomized in this study.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

The following reporting conventions apply generally to tables, listings, and figures:

- Treatment comparisons between each apremilast group and the placebo group will be made for the efficacy analyses.
- Stratified analyses will use the 2 randomization stratification factors (concomitant use of oral corticosteroids [yes/no] and previous exposure to immunosuppressants [yes/no]), unless otherwise specified.
- Stratified analyses and subgroup analyses with respect to the 2 randomization stratification factors will be based on each subject's actual strata according to the clinical database of prior/concomitant medications, rather than the strata as randomized in the IVRS/IWRS.
- P-values will be 2-sided and presented with 4 decimal places. P-values that are rounded to 0.0000 will be presented as "< 0.0001" and p-values that are rounded to 1 "> 0.9999".
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, standard deviation (SD), median, minimum, 25th percentile (Q1), 75th percentile (Q3), and maximum for continuous variables.
- All mean, median, Q1, Q3, and CI values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.
- Change from baseline is calculated as the post-baseline value minus the baseline value.
- All laboratory data will be reported using standard international units.
- All analysis and summary tables will include the analysis population sample size (ie, number of subjects) in the column headings.
- Listings will include both the randomized treatment and actual treatment.

5.2. Safety Analysis Periods

For the safety analysis, the following analysis periods for post-baseline data are defined. Safety data in these periods are considered treatment-emergent.

- Weeks 0-12 placebo-controlled phase: This period encompasses data through Week 12. It starts on the date of the first dose of IP in the study, and ends on the date before IP dispensing at Week 12 for subjects who receive at least 1 dose of IP after Week 12 (defined as the date of the last dose of IP in the study no earlier than the date of IP dispensing at Week 12), or 28 days after the last dose of IP in the study or on the date of the actual last follow-up in the study, whichever comes first, for subjects who discontinue at or prior to Week 12.

  Of note, this period is exclusive of the date of the first dose of IP in the study and inclusive of the date of IP dispensing at Week 12 for the analyses of the lab, vital signs, weight, and ECG data.

  The safety analysis tables for the placebo-controlled phase will be presented by the following 4 groups: placebo, APR 30 BID, APR 40 BID, and APR total.

- Weeks 0-52 apremilast-exposure period: This period encompasses all apremilast-exposure data through Week 52, irrespective of when the apremilast exposure starts (at Week 0 or 12) in the study. It starts on the date of the first dose of apremilast in the study, and ends on the date before IP dispensing at Week 52 for subjects who receive at least 1 dose of apremilast after Week 52 (defined as the date of the last dose of apremilast in the study no earlier than the date of IP dispensing at Week 52), or 28 days after the last dose of apremilast in the study or on the date of the actual last follow-up in the study, whichever comes first, for subjects who discontinue at or prior to Week 52.

  Of note, this period is exclusive of the date of the first dose of apremilast in the study and inclusive of the date of IP dispensing at Week 52 for the analyses of the lab, vital signs, weight, and ECG data.

  The safety analysis tables, with an exception for the summaries of labs, vital signs, and body weight by time point, for the apremilast-exposure period during Weeks 0-52 will be presented by the following 4 groups: APR 30 BID, APR 40 BID, APR 30 BID/APR 40 BID, and APR total, as follows:

  - The APR 30 BID group includes the data during the APR 30 BID treatment for subjects who receive APR 30 BID only in the study, subjects who initially receive APR 30 BID and switch to APR 40 BID at Week 12, and subjects who initially receive placebo and switch to APR 30 BID at Week 12.
  - The APR 40 BID group includes the data during the APR 40 BID treatment for subject who receive APR 40 BID only in the study and subjects who initially receive placebo and switch to APR 40 BID at Week 12.
  - The APR 30 BID/APR 40 BID group includes the data during the APR 40 BID treatment for subjects who initially receive APR 30 BID and switch to APR 40 BID at Week 12.
  - The APR total group combines all the data of all the groups.

  For the summaries of labs, vital signs, and body weight by time point, the data during the APR 30 BID and APR 40 BID treatments after Week 12 for subjects who initially receive

placebo and switch to APR 30 BID and APR 40 BID, respectively, at Week 12 will be summarized in the placebo/APR 30 BID and placebo/APR 40 BID groups, respectively.

- Weeks 0-104 apremilast-exposure period: This period encompasses all apremilast-exposure data through Week 104, irrespective of when the apremilast exposure starts (at Week 0 or 12) in the study. It starts on the date of the first dose of apremilast in the study, and ends 28 days after the last dose of apremilast in the study or on the date of the actual last follow-up in the study, whichever comes first.

  Of note, this period is exclusive of the date of the first dose of apremilast in the study for the analyses of the lab, vital signs, weight, and ECG data.

  The treatment groups presented in the safety analysis tables for the apremilast-exposure period during Weeks 0-104 will be the same as those for the apremilast-exposure period during Weeks 0-52.

- Weeks 52-104 apremilast-exposure period: This period encompasses the apremilast-exposure data during Weeks 52-104 and is to be summarized for subjects who receive at least 1 dose of apremilast after Week 52 (defined as the date of the last dose of apremilast in the study no earlier than the date of IP dispensing at Week 52). It starts on the date of IP dispensing at Week 52, and ends 28 days after the last dose of apremilast in the study or on the date of the actual last follow-up in the study, whichever comes first.

  Of note, this period is exclusive of the date of IP dispensing at Week 52 for the analyses of the lab, vital signs, weight, and ECG data.

  The safety analysis tables for the apremilast-exposure period during Weeks 52-104 will be presented by the following 3 groups: APR 30 BID, APR 40 BID, and APR total.

In the analyses of the lab, vital signs, weight, and ECG data, the value at the end of an analysis period is determined as the last post-baseline value among scheduled, unscheduled, and ET visits (excluding the follow-up visit) in the analysis period, whereas the worst value of an analysis period is determined among all visits (including the follow-up visit) in the analysis period.

5.3. Time Points

5.3.1. Analysis Time Point Assignments

The designation of time points used for analysis (analysis time points) will be based on the actual day of assessment relative to the date of the first dose of IP in the study (relative day, ie, date of assessment – date of the first dose of IP in the study + 1), rather than the nominal visit recorded. Visits to be assigned with this method include the screening, Week 0 through Week 104, unscheduled, and early termination visits. The only exception is the assessments recorded at the post-treatment observational follow-up visit, which will be assigned to the follow-up visit.

All assessments performed prior to the date of the first dose of IP in the study will be assigned to the screening analysis time point. All assessments performed on the date of the first dose of IP in the study will be assigned to the Week 0 analysis time point.

The analysis time point assignments for the post-baseline visits (excluding the post-treatment observational follow-up visit) will be based on the relative day windows. These relative day windows are continuous, mutually exclusive, stretch from the date after the first dose of IP in the

study to the midpoint between the first 2 scheduled visits, from midpoint to midpoint between each successive pair of scheduled visits, and from the last midpoint onward for the last scheduled visit. If data are available on multiple days within a relative day window, then the assessment closest to the visit's target day (ie, study week × 7 + 1) will be used for that analysis time point. 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 time point. If multiple assessments are available on the same relative day, then the average of these assessments will be used for that relative day, except for the lab and ECG data for which the assessment at a later time of the same day will be used.

For efficacy analyses, the data after the date of treatment failure (Section 11.2) will be set to missing prior to the assignments of analysis time points.

5.3.2. Screening and Baseline Definitions

The screening SFS and RBS (involving the subject diary data) will be derived from the 3 earliest days with a non-missing value within a 7-day window that is allowed to be rolling within the 14 days of the screening visit, whereas the screening PGA is defined as the first assessment on or before the date of the first dose of IP in the study.

Unless otherwise specified, the baseline value is defined as the last assessment on or before the date of the first dose of IP in the study. The baseline SFS and RBS will be derived from the 3 most recent days (or as few as 2 days) with a non-missing value within the 7 days prior to the day before the screening endoscopy. In case of insufficient diary data during this period, the baseline value will be set to the screening value. The baseline TMS is calculated using the baseline SFS, RBS, PGA, and endoscopy subscores that are identified separately. The baseline PMS and MMS are calculated similarly.

For the safety analysis, the baseline value is defined as the last assessment on or before the date of the first dose of IP in the study for the analysis of the placebo-controlled phase, and the last assessment on or before the date of the first dose of apremilast for the analysis of an apremilast-exposure period.

5.4. Analysis Populations

5.4.1. Intent-to-treat Population

The intent-to-treat (ITT) population will be the primary population for the efficacy analysis. The ITT population will consist of all subjects who are randomized as specified in the protocol and receive at least 1 dose of IP. To assess change from baseline, a baseline value and at least 1 post-baseline value are also required. Subjects will be included in the treatment group to which they were randomized, irrespective of the treatments actually received.

5.4.2. Per-protocol Population

A supportive analysis using the per-protocol (PP) population will be performed for the primary efficacy endpoint (clinical remission defined in the TMS) and the first secondary efficacy endpoint (clinical response defined in the TMS). The PP population will consist of all subjects included in the ITT population who have no protocol violations that may substantially affect the efficacy results. These protocol violations could include, but are not limited to, not meeting key

inclusion/exclusion criteria, gross IP non-compliance, receiving incorrect IP, treatment unblinding by the investigator, concomitant use of protocol-prohibited medications that are potentially effective for UC for an unrelated comorbid condition, not having the required assessment at the designated time point for reasons other than experiencing a treatment failure, or discontinuing due to lack of efficacy or a drug-related AE prior to the time point. The final determination on protocol violations, and thereby the composition of the PP population, will be made prior to the unblinding of the database for the Double-blind Placebo-controlled Phase analysis and will be separately documented. Subjects will be included in the treatment group to which they were randomized, irrespective of the treatments actually received.

5.4.3. Safety Population

The safety analysis for the placebo-controlled phase will be based on the safety population, which will consist of all subjects who are randomized and receive at least 1 dose of IP. At least 1 post-baseline assessment is required for inclusion in the analysis of each specific laboratory, vital sign, weight, or ECG parameter. To assess change from baseline, a baseline measurement is also required. Subjects will be included in the treatment group corresponding to the IP they actually received.

5.4.4. Apremilast Subjects as Randomized Population

The efficacy analysis during Weeks 12-104 will be based on the apremilast subjects as randomized population, which will include all subjects who are randomized (at Week 0) or re-randomized (at Week 12) to an apremilast dose group and receive at least 1 dose of apremilast. To assess change from baseline, a baseline value and at least 1 post-baseline value are also required. Subjects will be included in the apremilast dose group to which they were randomized or re-randomized.

5.4.5. Apremilast Subjects as Treated Population

The safety analysis for an apremilast-exposure period will be based on the apremilast subjects as treated population, which will include all subjects who are randomized (at Week 0) or assigned (at Week 12) to an apremilast dose group, and receive at least 1 dose of apremilast. At least 1 post-baseline assessment is required for inclusion in the analysis of each specific laboratory, vital sign, weight, or ECG parameter. To assess change from baseline, a baseline measurement is also required. Subjects will be included in the apremilast dose group corresponding to the apremilast dose they actually received.

6. SUBJECT DISPOSITION

The number of subjects screened, the numbers and percentages of subjects randomized and not randomized, and of the eligibility criteria failed will be summarized based on all subjects screened.

The number and percentage of subjects included in the analysis populations will be summarized based on all subjects randomized.

Subject disposition (entered, completed, discontinued, along with primary reason for discontinuation) will be summarized based on all subjects randomized, unless otherwise specified below, for

- Weeks 0-12
- Weeks 0-52
- Weeks 12-52 (based on subjects who complete Week 12)
- Weeks 52-104 (based on subjects who enter the Extension Phase)
- Post-treatment observational follow-up phase (entered and completed only) within each of the above periods (based on subjects who enter the respective period)

The definitions of entry and completion in the above disposition summaries are given in Table 2.

Table 2: Definitions of Entry and Completion in Disposition Summaries

Disposition Category	Weeks 0-12	Weeks 0-52	Weeks 12-52	Weeks 52-104	Follow-up Phase
Entered	Randomized	Randomized	Completed Week 12/Visit 6	Completed Week 52/Visit 11 and indicated continuation into Extension Phase in eCRF	Indicated continuation into Follow-up Phase in eCRF and had data after the last non-follow-up visit (Week 104/Visit 14 or ET visit, excluding any unscheduled visits associated with Week 104/Visit 14 and ET visit)
Completed	Completed Week 12/Visit 6	Completed Week 52/Visit 11	Completed Week 52/Visit 11	Completed Week 104/Visit 14	Completed the follow-up visit

A listing of discontinued subjects with reason for discontinuation will be provided.

The number and percentage of subjects by region, country, and site will be provided based on all subjects randomized.

7. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol violations and deviations will be summarized for the Screening Phase and Weeks 0-12 using the ITT population, for Weeks 12-52 for subjects who complete Week 12, and for Weeks 52-104 for subjects who enter the Extension Phase.

A listing of all protocol violations and deviations in the study will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized descriptively using the ITT population. The comparability of the treatment groups for each relevant characteristic will be assessed descriptively in table format; no statistical hypothesis tests will be performed on these characteristics. Subject data listings will be provided.

8.1. Demographics and Baseline Characteristics

The following characteristics will be summarized as continuous variables:

- Age (years)
- Baseline body weight (kg)
- Baseline body mass index (BMI; kg/m^2)

The following characteristics will be summarized as categorical variables:

- Age (< 65, ≥ 65 years; < 40, 40 – < 65, 65 – < 75, 75 – < 85, ≥ 85 years)
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other, not collected or reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, unknown)
- Region (North America, Western Europe, Eastern Europe/Russia, Australia/New Zealand)
- Baseline body weight (< 55, 55 – < 70, 70 – < 85, 85 – < 100, ≥ 100 kg)
- Baseline BMI (< 18.5, 18.5 – < 25, 25 – < 30, 30 – < 35, 35 – < 40, and ≥ 40 kg/m^2)
- Alcoholic beverages (yes [< 1 drink per week, 1 – 14 drinks per week, > 14 drinks per week], no)
- Tobacco history (never smoked, past smoker, current smoker)

Age will be calculated as (date of informed consent – date of birth + 1) / 365.25 when the full date of birth is collected; otherwise, the age recorded will be used.

8.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized as continuous variables:

- Duration of UC (years)
- Screening TMS
- Baseline TMS
- Baseline PMS
- Baseline MMS

- Baseline SFS
- Baseline RBS
- Baseline PGA subscore
- Baseline endoscopy subscore
- Baseline SF-12v2 Physical Component Summary (PCS) score
- Baseline SF-12v2 Mental Component Summary (MCS) score

The following baseline disease characteristics will be summarized as categorical variables:

- Duration of UC (< 2, 2 – < 5, 5 – < 10, ≥ 10 years)
- Disease localization (Rectum and sigmoid colon only, left side of colon)
- Baseline extraintestinal manifestations (yes [peripheral arthropathy, axial arthropathies, pyoderma gangrenosum, erythema nodosum, episcleritis, uveitis, primary sclerosing cholangitis, other], no)
- Therapeutic failure with or intolerance to UC medications (yes [never responded, loss of response, partial response, intolerance], no)
- Therapeutic failure with or intolerance to oral aminosalicylates (yes [never responded, loss of response, partial response, intolerance], no)
- Therapeutic failure with or intolerance to budesonide (yes [never responded, loss of response, partial response, intolerance], no)
- Therapeutic failure with or intolerance to systemic corticosteroids (yes [never responded, loss of response, partial response, intolerance], no)
- Therapeutic failure with or intolerance to immunosuppressants (yes [never responded, loss of response, partial response, intolerance], no)
- Contraindication to UC medications (yes [oral aminosalicylates, budesonide, systemic corticosteroids, immunosuppressants], no)
- Concomitant use of oral corticosteroids (as randomized) (yes, no)
- Concomitant use of oral corticosteroids (per clinical database) (yes, no)
- Previous exposure to immunosuppressants (as randomized) (yes, no)
- Previous exposure to immunosuppressants (per clinical database) (yes, no)
- Screening TMS (< 6, 6 – 8, 9 – 11, 12)
- Baseline TMS (< 6, 6 – 8, 9 – 11, 12)
- Baseline endoscopy subscore (0 – 1, 2, 3)

Duration of UC will be calculated as (date of informed consent – date of diagnosis + 1) / 365.25.

8.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized based on the ITT population by system organ class (SOC) and preferred term (PT), with SOCs sorted in the standard international order and PTs within each SOC in descending order of frequency, and by PT only in descending order of frequency.

8.4. Prior Medications/Procedures

Prior medications are defined as medications with a start date before the date of the first dose of IP in the study (whether or not the end date is before the date of the first dose of IP). Prior medications that continue on or after the date of the first dose of IP will be also reported as concomitant medications. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHODD) will be used to group medications into relevant categories. Prior medications will be summarized based on the ITT population by ATC2 level and standardized medication name, with ATC2 levels and standardized medication names within each ATC2 level sorted in descending order of frequency.

Prior procedures are similarly defined. Prior procedures will be coded according to the MedDRA, and summarized based on the ITT population by SOC and PT, with SOCs sorted in the standard international order and PTs within each SOC in descending order of frequency.

9. EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

9.1. Treatment Duration

Treatment duration will be summarized for the Weeks 0-12 placebo-controlled phase using the safety population, for the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods using the apremilast subjects as treated population, and for the Weeks 52-104 apremilast-exposure period for subjects who receive at least 1 dose of apremilast after Week 52.

Treatment duration (in weeks) is calculated as (the date of the last dose of IP in the period – the date of the first dose of IP in the period + 1) / 7 and rounded to one decimal place. The date of the last dose of IP in the Weeks 0-12 placebo-controlled phase is defined as the date before IP dispensing at Week 12. The date of the last dose of IP in the Weeks 0-52 apremilast-exposure period and the date of the first dose of IP in the Weeks 52-104 apremilast-exposure period are defined as the date before and the date of, respectively, IP dispensing at Week 52.

Treatment duration will be summarized as a continuous variable, and as a categorical variable with the following exposure intervals:

- Weeks 0-12 placebo-controlled phase: ≤ 4, > 4 – 8, > 8 – 12, > 12 weeks
- Weeks 0-52 apremilast-exposure period: ≤ 4, > 4 – 8, > 8 – 12, > 12 – 20, > 20 – 28, > 28 – 36, > 36 – 44, > 44 – 52, and > 52 weeks
- Weeks 0-104 apremilast-exposure period: ≤ 4, > 4 – 8, > 8 – 12, > 12 – 20, > 20 – 28, > 28 – 36, > 36 – 44, > 44 – 52, > 52 – 68, > 68 – 86, > 86 – 104, > 104 weeks
- Weeks 52-104 apremilast-exposure period (intervals denote the number of weeks relative to the date of the first dose of IP in the Weeks 52-104 apremilast-exposure period as defined above): ≤ 16, > 16 – 34, > 34 – 52, > 52 weeks

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

9.2. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and returned will be recorded at each visit. These records will be used to calculate treatment compliance. Treatment compliance will be summarized for the Weeks 0-12 placebo-controlled phase using the ITT population, for Weeks 12-52 for subjects who receive at least 1 dose of apremilast after Week 12 (defined as the date of the last dose of apremilast in the study no earlier than the date of IP dispensing at Week 12), and for Weeks 52-104 for subjects who receive at least 1 dose of apremilast after Week 52.

The compliance rate (%) 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 period divided by the intended total number of tablets that should have been taken over the same period (defined by the first and last IP dose dates in the period). The date of the last dose of IP in the Weeks 0-12 placebo-controlled phase and the date of the first dose of IP in Weeks 12-52 are defined as the date before and the date of, respectively, IP dispensing at Week

12. The date of the last dose of IP in Weeks 12-52 and the date of the first dose of IP in Weeks 52-104 are defined as the date before and the date of, respectively, IP dispensing at Week 52.

Treatment compliance rate will be summarized as a continuous variable, and as a categorical variable with the following categories: < 75%, 75% – 120%, and > 120%.

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

10. CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medications and procedures will be summarized for the Weeks 0-12 placebo-controlled phase using the safety population, for the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods using the apremilast subjects as treated population, and for the Weeks 52-104 apremilast-exposure period for subjects who receive at least 1 dose of apremilast after Week 52.

10.1. Concomitant Medications

A concomitant medication in each of the above periods is defined as a non-study medication with any amount taken during the period as defined in Section 5.2.

The ATC coding scheme of the WHODD will be used to group medications into relevant categories. Concomitant medications will be summarized by ATC2 level and standardized medication name, with ATC2 levels and standardized medication names within each ATC2 level sorted in descending order of frequency.

10.2. Concomitant Procedures

Concomitant procedures are defined similarly to concomitant medications. Concomitant procedures will be coded according to the MedDRA, and summarized by SOC and PT, with SOCs sorted in the standard international order and PTs within each SOC in descending order of frequency.

11. EFFICACY ANALYSIS

11.1. Multiplicity

Formal statistical tests, conducted at a 2-sided significance level of 0.1, are planned between APR 40 BID and placebo and between APR 30 BID and placebo for the primary efficacy endpoint. To control the family-wise Type 1 error rate at the 0.1 level, these 2 formal statistical tests will be carried out by using a fixed sequence testing procedure, with the comparison between APR 40 BID and placebo tested first. The comparison between APR 30 BID and placebo will be tested only if the comparison between APR 40 BID and placebo is statistically significant. If any of the 2 apremilast dose groups is discontinued prior to the end of the study, the treatment comparison will be conducted for the comparison between the retained apremilast dose and placebo at a 2-sided significance level of 0.1.

For formal statistical tests that are planned but not performed as a result of the aforementioned multiplicity adjustment strategy, as well as for any other comparisons that are not subjected to multiplicity adjustment, nominal 2-sided p-values (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

11.2. Missing Data Handling

11.2.1. Treatment Failures

Subjects who have (1) protocol-prohibited initiation or dose increase of concomitant UC medications, or (2) a colectomy (partial or total) or an ostomy will be considered treatment failures after the date of the event. Use of antidiarrheals or dose increase of oral corticosteroids back to the baseline dose for subjects undergoing corticosteroid tapering will not be considered a treatment failure.

Efficacy data after the date of treatment failure will be considered missing. Of note, for efficacy analyses, the data after the date of treatment failure will be set to missing prior to the assignments of analysis time points as described in Section 5.3.1.

11.2.2. Binary Efficacy Endpoints

11.2.2.1. Primary Approach for Analysis

For binary efficacy endpoints, the primary approach to handling missing data will be nonresponder imputation (NRI), where subjects who have insufficient data for response determination for the time point under consideration will be considered nonresponders for that time point. Insufficient data, including missing data at baseline (if the binary endpoint assesses change from baseline) or a post-baseline time point, will be determined after the handling of time points as described in Sections 5.3.

11.2.2.2. Sensitivity Analyses

Sensitivity analyses using different missing data handling approaches (data as observed [DAO] and last observation carried forward [LOCF]) will be performed for the primary efficacy endpoint (clinical remission defined in the TMS) and the first secondary efficacy endpoint (clinical response defined in the TMS).

In the DAO analyses, only subjects with sufficient data for response determination at the time point under consideration will be included.

In the LOCF analyses, missing data at the time point under consideration will be imputed by the last post-baseline observation. For the TMS which consists of 4 individual subscores, the LOCF method will be applied to the individual subscores rather than directly to the TMS, and then the TMS will be calculated based on the observed or imputed subscores. Subjects who still have insufficient data for response determination at the time point under consideration despite the application of LOCF (eg, no post-baseline data) will be considered nonresponders for that time point.

11.2.2.3. Approach for Descriptive Summary

Binary endpoints by time point will also be summarized based on DAO, where only subjects with sufficient data for response determination at the time point under consideration will be included in the summary of that time point.

11.2.3. Continuous Efficacy Endpoints

11.2.3.1. Primary Approach for Analysis

For continuous efficacy endpoints, the primary missing data handling approach will be last observation carried forwarded (LOCF). For subjects who initially receive placebo and switch to an apremilast dose at Week 12 and subjects who initially receive APR 30 BID and switch to APR 40 BID at Week 12, the values on or before the date of IP dispensing at Week 12 will not be carried over beyond Week 12. For the TMS, PMS, and MMS, which are composite scores derived from individual subscores, the LOCF method will be applied to the individual subscores rather than to the composite score.

11.2.3.2. Approach for Descriptive Summary

Continuous endpoints by time point will also be summarized based on DAO, where only subjects with sufficient data at the time point under consideration will be included in the summary of that time point.

11.3. Analysis of Primary Endpoint

11.3.1. Primary Analysis of Primary Endpoint

The primary objective of the study will be evaluated by testing the superiority of each of the 2 apremilast doses over placebo with respect to the proportion of subjects achieving a clinical remission in the TMS, defined as a TMS of ≤ 2, with no individual subscore > 1, at Week 12 based on the ITT population and the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. Within-group proportions, 2-sided 95% CIs (based on the

Wilson score method) for the within-group proportions, unstratified treatment differences in proportions, stratified treatment differences in proportions using the weighted average of the treatment differences across the strata with the CMH weights, stratified 2-sided 95% CIs (based on the stratified Newcombe method [Yan, 2010]) for the treatment differences in proportions, and the 2-sided p-values from the CMH tests, will be provided. Missing data will be handled by the NRI approach.

11.3.2. Sensitivity Analyses of Primary Endpoint

The following sensitivity analyses will be performed for the primary endpoint: 1) using the PP population and the NRI method for missing data; 2) using DAO (Section 11.2.2.2); 3) using the ITT population and the LOCF method for missing data (Section 11.2.2.2). The statistical methods adopted for the primary analysis will also be used for these sensitivity analyses.

11.4. Analyses of Secondary Efficacy Endpoints

The analyses of secondary efficacy endpoints will be performed identically to the primary analysis of the primary endpoint. In addition, the sensitivity analyses of the primary endpoint will also be performed for the first secondary efficacy endpoint (clinical response defined in the TMS).

11.7. Assessing Study Center Effect and Treatment-by-center Interaction

This study is a multicenter study. The limited sample size of the study relative to the number of study sites does not allow for a meaningful assessment of study center effect.

12. SAFETY ANALYSIS

Safety will be evaluated via descriptive statistics and point estimates. No inferential testing for statistical significance will be performed.

The safety analyses will be based on the safety population for the Weeks 0-12 placebo-controlled phase, the apremilast subjects as treated population for the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods, and subjects who receive at least 1 dose of apremilast after Week 52 for the Weeks 52-104 apremilast-exposure period. The treatment groups presented for these analysis periods are described in Section 5.2.

12.1. Adverse Events

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

For the analyses of AEs, the following point estimates are provided, unless otherwise specified:

- 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 person-years: The EAIR per 100 person-years is defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) to the event 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 duration of the specific analysis period as described in Section 5.2, whereas the exposure time for a subject with the specific event is the duration of the specific analysis period 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 person-years is interpreted as the expected number of subjects with at least 1 occurrence of the specific event per 100 person-years of exposure to the event.

A subject data listing of all AEs (including treatment-emergent AEs [TEAEs] and non-TEAEs) will be provided.

12.1.1. Overall Summary of TEAEs

An overall summary of the following TEAE categories will be provided for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods:

- Any TEAE
- Any drug-related TEAE

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

In addition, the overall summary of TEAE categories will be provided by age category (< 65, ≥ 65), race (white, non-white), and region (North America, Western Europe, Eastern Europe/Russia, Australia/New Zealand) for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period.

12.1.2. All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence) for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods.

All TEAEs by exposure interval will be summarized for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period. The exposure intervals are ≤ 2, > 2 – 4, > 4 – 8, > 8 weeks for the Weeks 0-12 placebo-controlled phase, and ≤ 2, > 2 – 4, > 4 – 12, > 12 – 20, > 20 – 28, > 28 – 36, > 36 – 44, > 44 – 52, > 52 – 68, > 68 – 86, > 86 weeks for the Weeks 0-104 apremilast-exposure period. 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 starts. The denominator of a subject incidence is the number of subjects with the exposure time reaching the lower bound of the particular exposure interval, and the denominator of an EAIR is the sum of the exposure time during the exposure interval (up to the start date [inclusive] of the first occurrence of the specific event for each subject reporting the event in the interval) among the same number of subjects as in the denominator of the corresponding subject incidence.

All TEAEs will be summarized by sex and concomitant use of oral corticosteroids for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period.

All TEAEs starting after the date of the last dose of IP and up to 28 days after the last dose of IP will be summarized for subjects who enter the observational follow-up phase during the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period. The EAIR will not be provided in this summary.

12.1.3. Common TEAEs

Any TEAEs with subject incidence ≥ 5% (or another cutoff if justified) in any treatment group and any non-serious TEAEs with subject incidence ≥ 5% (or another cutoff if justified) in any treatment group will be summarized for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period.

Onset day and duration will be summarized for any TEAEs with subject incidence ≥ 5% (or another cutoff if justified) in any treatment group for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period. Multiple occurrences of a specific event for

the same subject will all be counted in the summaries of onset day and duration. For subjects who initially receive placebo and switch to an apremilast dose at Week 12, AEs with start dates in the placebo-controlled phase and end dates in the apremilast-exposure period will be summarized as ongoing for the summary of duration in the placebo-controlled phase, whereas for all other subjects, the actual AE end dates regardless of being in the placebo-controlled phase or apremilast-exposure period will be used for calculating duration. Duration will not be calculated for AEs reported as ongoing.

12.1.4. Drug-related TEAEs

Drug-related TEAEs will be summarized for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods.

12.1.5. TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing) for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods. If a subject reports multiple occurrences of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the "missing" category of severity.

12.1.6. Serious TEAEs

Serious TEAEs will be summarized for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods.

Serious TEAEs will also be summarized by sex and concomitant use of oral corticosteroids for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period.

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

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

TEAEs leading to drug interruption will be summarized for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods.

TEAEs leading to drug withdrawal will be summarized for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52, Weeks 0-104, and Weeks 52-104 apremilast-exposure periods.

TEAEs leading to drug withdrawal will also be summarized by sex and concomitant use of oral corticosteroids for the Weeks 0-12 placebo-controlled phase and the Weeks 0-104 apremilast-exposure period.

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

12.1.8. Deaths

TEAEs leading to death will be summarized for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. A subject data listing of all deaths will be provided.

12.2. Clinical Laboratory Evaluations

The following protocol-specified hematologic and serum chemistry parameters from the central laboratory will be summarized:

- Hematology: complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count)
- Serum chemistries: total protein, albumin, calcium, phosphorous, glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), magnesium

For the above hematologic and serum chemistry parameters, summary statistics of observed values and changes from baseline will be provided by time point (including the end of period and the post-treatment observational follow-up visit) for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points (including shifts to the end of period value and to the worst value) by category of low/normal/high/both low and high (the last category for the shift to the worst value only) will be provided for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods.

Frequency summaries of the shift from baseline to the worst value by folds of ULN (<= 1xULN, > 1 to 2xULN, > 2 to 3xULN, > 3 to 5xULN, > 5 to 8xULN, > 8xULN) will be provided for ALT, AST, total bilirubin, and alkaline phosphatase for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods.

Summaries of laboratory marked abnormalities as defined in Section 17.1 will be provided for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. Subject incidence for each abnormality will be calculated based on subjects with a baseline value and at least 1 post-baseline value in the period under consideration for criteria requiring baseline, or subjects with at least 1 post-baseline value in the period under consideration for criteria not requiring baseline. Separate summaries of laboratory marked abnormalities will also be presented by normal baseline and abnormal baseline. For the purpose of these summaries, abnormal (normal) baseline is defined as a baseline value that is low (normal or high) for criteria concerning low values and as a baseline value that is high (normal or low) for criteria concerning high values; both low and high are relative to the laboratory normal range.

A subject data listing including all values of a subject's laboratory parameter(s) that have any marked abnormality will be provided. A subject data listing of all laboratory data (including urinalysis) will be provided.

12.3. Vital Signs and Body Weight

For vital signs and body weight, summary statistics of observed values and changes from baseline (also percent change from baseline for body weight) will be provided by time point (including the end of period and the post-treatment observational follow-up visit) for the Weeks

0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points (including shifts to the end of period value and to the worst value) by category of low/normal/high/both low and high (the last category for the shift to the worst value only) will be provided for pulse, systolic and diastolic blood pressures (SBP and DBP) for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. The 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.

Frequency summaries of change and percent change in body weight from baseline to the end of the respective analysis period for all subjects with a baseline value and at least 1 post-baseline value, as well as by baseline BMI category (< 18.5, 18.5 to < 25, 25 to < 30, 30 to < 35, 35 to < 40, and ≥ 40 kg/m^2) and by baseline weight category (< 70, ≥ 70 to < 85, ≥ 85 to < 100, and ≥ 100 kg) will be provided for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods. 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. The end of period value is the last post-baseline value in the respective analysis period (excluding the value obtained at the post-treatment observational follow-up visit, if applicable).

A subject data listing of all vital signs and body weight will be provided, with subjects with body weight loss of ≥ 7.5% from baseline flagged.

12.4. Electrocardiogram

Frequency summaries (shift tables) of the shift from baseline to the end of period in investigator clinical interpretation of ECG (normal; abnormal, not clinically significant; and abnormal, clinically significant) will be provided for the Weeks 0-12 placebo-controlled phase, the Weeks 0-52 and Weeks 0-104 apremilast-exposure periods.

A subject data listing including all of a subject's ECG interpretations will be provided for subjects who have any clinically significant abnormal interpretation by the investigator.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

Not applicable.

16. REFERENCES

Yan X, Su XG. Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Statistics in Biopharmaceutical Research 2010;2:329-335.

17. APPENDICES

17.1. Laboratory Marked Abnormalities Criteria

Table 5: Laboratory 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
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
Triglycerides	mmol/L	> 3.4
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