STATISTICAL ANALYSIS PLAN

SERES-101

A Multiple Dose Study to Evaluate the Safety, Tolerability and Microbiome Dynamics of SER-287 in Subjects with Mild-to-Moderate Ulcerative Colitis

Version: Final 2.0

Date: 21 August 2017

REVISION HISTORY

Final SAP 1.0: 11 Apr 2017

SAP Amendment Final 2.0 21 Aug 2017

CHANGES FROM THE FINAL SAP VERSION 1.0, 11 APRIL 2017

Section 2.2, Secondary Objective
Changed the endpoint from "complete" remission to "clinical" remission.

Section 6.4, Breaking the Study Blind at the End of the Short-term Safety Follow-up Period
Added language for an independent and unblinded team including a clinical data programmer, biostatistician, and statistical programmer to produce unblinded study results after all subjects complete Visit 13, Day 92. This is referred to as "Efficacy" analysis. A complete CSR will be written based on these results.

Section 7.1.1.1, Demographic and Baseline Variables
Removed variables for "Active UC disease (Histopathology)" and "Active UC disease (Mucosal appearance)"

Section 7.1.3.1, Secondary Endpoints
Defined "clinical remission" as "TMMS $\leq$ 2 and an endoscopic subscore of 0 or 1."

Section 7.1.4, Exploratory Endpoints
Removed histological remission endpoint (Geboes score $\leq$ 2B.0) and Mucosal Histopathology Robarts Histopathologic Index (RHI) endpoint.

Section 7.3.6.3 Demographic Variables
Remove Active UC at Baseline.

Section 7.3.7.2, Clinical Efficacy Response
Updated to reflect changes to endpoints.

SIGNATURE PAGE - SERES THERAPEUTICS, INC.

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

Jeff Zhao

21 Aug 2017

Jeff Zhao, Ph.D. **Date (DD Mmm YY)**

Director, Biostatistics

Michele Trucksis

23 Aug 2017

Michele Trucksis, MD, Ph.D. **Date (DD Mmm YY)**

Executive Vice President and Chief Medical Officer

SIGNATURE PAGE - PAREXEL

Declaration
The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

Beth Wilson Margaret Connolly signing for	23 Aug 17
Principal Biostatistician	**Date (DD Mmm YY)**

TABLE OF CONTENTS

REVISION HISTORY 2
CHANGES FROM THE FINAL SAP VERSION 1.0, 11 APRIL 2017 3
SIGNATURE PAGE - SERES THERAPEUTICS, INC. 4
SIGNATURE PAGE - PAREXEL 5
TABLE OF CONTENTS 6
ABBREVIATION AND ACRONYM LIST FROM PROTOCOL 8
1. STATISTICAL ANALYSIS PLAN 10
2. STUDY OBJECTIVES 11
2.1 Primary Objectives 11
2.2 Secondary Objectives 11
2.3 Exploratory Objectives 11
3. STUDY DESIGN 12
4. STUDY POPULATION 14
5. STATISTICAL BASIS FOR SAMPLE SIZE 15
6. SUBJECT IDENTIFICATION AND RANDOMIZATION 16
6.1 Subject Identification 16
6.2 Methods of Assigning Patients to Study Treatment 16
6.3 Maintaining the Randomization Codes and Breaking the Study Blind 16
6.4 Breaking the Study Blind at the End of the Short-term Safety Follow-up Period 17
6.5 Subject Replacement 17
7. STATISTICAL ANALYSIS CONVENTIONS 19
7.1 Analysis Variables 19
7.1.1 Study Subjects 19
7.1.1.1 Demographic and Baseline Variables 19
7.1.1.2 General Medical and Surgical History 20
7.1.1.3 Prior and Concomitant Medications 20
7.1.1.4 Diet Inventory 20
7.1.2 Microbiome Alterations and Engraftment Primary Endpoints 20
7.1.3 Secondary Endpoints 21
7.1.3.1 Clinical Response, Clinical Remission, and Endoscopic Improvement 21
7.1.3.2 Biomarkers 22
7.1.4 Exploratory Endpoints 22
7.1.5 Safety Variables 23
7.1.5.1 Adverse Events 23
7.1.5.2 Clinical Laboratory Tests 23

7.1.5.3 Vital Signs 24
7.1.5.4 Electrocardiograms 24
7.1.5.5 Physical Examination 24
7.2 Analysis Populations 25
7.2.1 Safety Population 25
7.2.2 Intent-to-Treat (ITT) Population 25
7.2.3 Sensitivity Analysis Population – 1 (without replacement) 25
7.2.4 Sensitivity Analysis Population – 2 (with replacements only) 25
7.3 Statistical Analysis Methods 25
7.3.1 Listings and Descriptive Statistics 25
7.3.2 Statistical Analysis and Significance Level 26
7.3.3 Software 26
7.3.4 Missing or Spurious Data 26
7.3.5 Interim Analysis and Safety Halting Rules 28
7.3.6 Study Subjects 28
7.3.6.1 Disposition of Subjects 28
7.3.6.2 Protocol Deviations 28
7.3.6.3 Demographic Data 29
7.3.6.4 Medical and Surgical History 29
7.3.6.5 Prior and Concomitant Medication 29
7.3.6.6 Diet Inventory Log 30
7.3.6.7 Exposure to the Investigational Medicinal Product 30
7.3.7 Endpoints for Analysis 30
7.3.7.1 Microbiome Alterations and Engraftment Primary Endpoints 30
7.3.7.2 Clinical Efficacy Response 30
7.3.7.3 Serum Biomarkers 31
7.3.7.4 Fecal Biomarkers 31
7.3.7.5 Exploratory Endpoints 32
7.3.8 Safety Analysis 33
7.3.8.1 Adverse Events 33
7.3.8.2 Clinical Safety Laboratory Tests (Chemistry, Hematology, Liver and Urinalysis) 34
7.3.8.3 Vital Signs 35
7.3.8.4 Twelve-Lead Electrocardiogram 35
8. CHANGE FROM PROTOCOL 36
9. REFERENCES 37
10. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT 38
11. FIGURES TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT 43
12. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT 44
13. DOCUMENTATION OF STATISTICAL METHODS 47

ABBREVIATION AND ACRONYM LIST FROM PROTOCOL

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATC	Anatomical therapeutic chemical
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence interval
CMV	Cytomegalovirus
CRP	C-reactive protein
CSP	Clinical Study Protocol
CS	Clinically significant
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
DSMC	Data safety monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IBD	Inflammatory bowel disease
ITT	Intent to treat
IxRS	Interactive voice/web response system
LFT	Liver function test
MCH	Mean corpuscular hemoglobin

Abbreviation / Acronym	Definition / Expansion
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NCS	Not clinically significant
NK	Not known
PCR	Polymerase chain reaction
RHI	Robarts Histopathologic Index
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SI	Standard international
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TMMS	Total modified Mayo score
UC	Ulcerative Colitis
ULN	Upper limit of normal
WHO-DDE	World Health Organization - Drug Dictionary Enhanced

1. STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing safety and clinical efficacy study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). This SAP addresses planned analysis and presentation of safety and clinical efficacy to be conducted by PAREXEL as described in the protocol, and as collected in the source data. The planned analysis of microbiome alterations is described in a separate document.

The analyses described are based on the final CSP Amendment 3, dated 10 Oct 2016 and on the Blank CRF Casebook (Study Published Date: 08-Jun-2016 08:43 GMT).

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability of SER-287 vs. placebo in adult subjects ≥18 years of age with mild-to-moderate ulcerative colitis
- To compare the baseline composition of the intestinal microbiome to the post-baseline composition after initiation of SER-287 or placebo
- To determine the engraftment of SER-287 bacteria into the intestinal microbial community in each of the SER-287 arms compared to the placebo arm

2.2 Secondary Objectives

- To determine the proportion of subjects in each of the treatment arms who, at 8 weeks post initiation of treatment, achieve a clinical response, clinical remission, and endoscopic improvement
- To assess changes in serum and fecal biomarkers from baseline throughout treatment

2.3 Exploratory Objectives

- To compare the changes in exploratory biomarkers from mucosal biopsies and stool samples in each of the treatment arms from baseline throughout treatment.
- To determine the complement of metabolic pathways from stool in each of the treatment arms from baseline throughout treatment.

3. STUDY DESIGN

This is a Phase 1b multicenter, randomized, double-blind, placebo-controlled multiple dose study designed to evaluate the safety and tolerability of SER-287 and to evaluate the microbiome alterations and pharmacodynamics associated with two dosing regimens of SER-287 in adult subjects with mild-to-moderate ulcerative colitis (UC). Subjects will be randomized to one of 4 study arms:

A) Pre-treatment of placebo, followed by once weekly dosing of SER- 287 for 8 weeks;

B) Pre-treatment of placebo, followed by once daily dosing of placebo for 8 weeks;

C) Pre-treatment of vancomycin, followed by once daily dosing of SER-287 for 8 weeks;

D) Pre-treatment of vancomycin, followed by once weekly dosing of SER-287 for 8 weeks.

The doses, route, and schedule of study drug administration are shown below:

Group	Pre--treatment: Vanco or Pbo				Treatment Period: SER---287 or Pbo			
	Vanco or Pbo	Regimen	Admin	Duration	SER--287 or Pbo	Regimen	Admin	Duration
A	Pbo	Pbo	One capsule four times daily orally	6 days	SER-287 + Pbo	SER-287 Weekly ($1x10^8$ SporQs) +Pbo 6d/wk	Four capsules once daily orally	8 wks
B	Pbo	Pbo	One capsule four times daily orally	6 days	Pbo	Placebo Daily	Four capsules once daily orally	8 wks
C	Vanco	Vanco 125 mg qid	One capsule four times daily orally	6 days	SER-287	SER-287 Daily ($1x10^8$ SporQs)	Four capsules once daily orally	8 wks
D	Vanco	Vanco 125 mg qid	One capsule four times daily orally	6 days	SER-287 + Pbo	SER-287 Weekly ($1x10^8$ SporQs)+Pbo 6d/wk	Four capsules once daily orally	8 wks

The study has 5 study periods: Screening (Day-14 to Day-1), Pre-treatment, Treatment, a 4-Week Short Term Safety Follow-up and a Long Term Safety Follow-up. The Schedule of Events is presented in Table 3 of the CSP.

The Pre-Treatment Period (Day 1 to Day 7) includes administration of either oral vancomycin 125 mg four times a day for 6 days or matching placebo.

The Treatment Period (8 weeks, Day 8-63) includes administration of 4 capsules taken orally once a day of SER-287 or placebo according to the treatment group to which they have been

assigned: SER-287 once daily, SER-287 once weekly with matching placebo on other days, or placebo daily.

4. STUDY POPULATION

The study population will consist of adult subjects with active mild-to-moderate ulcerative colitis.

Detailed lists of inclusion and exclusion criteria are shown in Sections 4.1 and 4.2 of the CSP.

5. STATISTICAL BASIS FOR SAMPLE SIZE

No formal sample size calculation was performed. A sample size of approximately 55 subjects with 15 subjects randomized to each of the active arms (Treatment Groups A, C and D) and 10 subjects in the placebo arm (Treatment Group B) is considered sufficient to evaluate the safety, microbiome alterations, clinical response and exploratory objectives of the study.

6. SUBJECT IDENTIFICATION AND RANDOMIZATION

6.1 Subject Identification

All screened subjects will be assigned a unique subject identification (SID) number that will be used through screening, pre-treatment and treatment periods and safety follow-up period.

6.2 Methods of Assigning Patients to Study Treatment

Randomization will be used to avoid bias in the assignment of subjects to double-blind treatment (SER-287 or placebo) and to increase the likelihood that known and unknown subject characteristics will be evenly distributed between the treatment groups.

Eligible subjects are to be randomized at Visit 3 (Day 1) after all screening procedures have been performed and eligibility for the study confirmed. Subjects will be randomized via interactive voice/web response system (IxRS) to one of 4 study arms: A) Pre- treatment of placebo, followed by weekly dosing of SER-287 for 8 weeks; B) Pre- treatment of placebo, followed by daily dosing of placebo for 8 weeks; C) Pre-treatment of vancomycin, followed by daily dosing of SER-287 for 8 weeks; D) Pre-treatment of vancomycin, followed by weekly dosing of SER-287 for 8 weeks. The randomization scheme was also designed to facilitate balance across the 3 donor lots manufactured for SER-287.

Once a randomization number has been assigned to a subject, the number cannot be reused even if the subject discontinues from the study early or withdraws before receiving any study drug. Subjects who discontinue from the study or who have been previously randomized in the study will not be permitted to re-enter.

During the double-blind period, subjects, the investigators, other study site personnel and clinical staff will remain blinded to the treatment assignment. The medical monitor, study site monitors, and other sponsor representatives involved in the clinical aspects of study conduct also will remain blinded to the treatment assignment.

6.3 Maintaining the Randomization Codes and Breaking the Study Blind

A designated randomization administrator from an external, independent vendor will maintain the randomization codes in accordance with standard operating procedures to ensure that the blind is properly maintained and that only sponsor personnel who require knowledge of

treatment assignments will be unblinded [e.g., staff involved in serious adverse event (SAE) reporting].

Investigators are not to break the study treatment blind except when information concerning the study drug is necessary for the medical treatment of the subject.

A record of any unblinding event will be captured in the database including information of who made the unblinding decision (sponsor, medical monitor, investigator, other), reason, date, time and unblinded personnel names and roles.

6.4 Breaking the Study Blind at the End of the Short-term Safety Follow-up Period

The primary study period will be conducted as a double-blind study. The database will remain blinded until all data collected through Visit 13 (Day 92 ± 2days) have been entered, cleaned and declared complete and final. After finalization, an "efficacy" database lock will occur. An independent, unblinded team, comprised of a clinical data programmer, biostatistician, and statistical programmer, will access the randomization codes, merge the codes into the SDTM datasets, and produce the complete set of analysis datasets, tables, figures, and listings for the CSR. Only data from pre-study up to and including Visit 13/Day 92 will be included in the CSR with the exception of deaths. All available data on deaths reported at the time the CSR is being written, regardless of timepoint in the study, will be reported.

The blinded study team will not be involved in any unblinded analyses and will not have access to the data nor the results until all subjects have completed the study at Day 246 or discontinued from the study.

Study subjects will continue to be monitored through Day 246. Results of the long-term safety period (through Day 246) will be presented in a separate report.

6.5 Subject Replacement

Subjects who meet the following criteria may be replaced.

- Subject withdrew from treatment before Study Day 48 (less than 6-week treatment); or
- Subject didn't have the post-treatment endoscopy procedure performed;

A treatment-specific replacement method will be implemented, i.e. replacement subjects will be randomized to receive the treatment to which discontinued subjects were randomized. Only the first 55 enrolled subjects are eligible to be replaced. The number of subjects who can be replaced will depend on the drug availability.

7. STATISTICAL ANALYSIS CONVENTIONS

7.1 Analysis Variables

7.1.1 Study Subjects

7.1.1.1 Demographic and Baseline Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Age at screening (years)
- Sex
- Height (cm) at screening
- Body weight (kg), predose on Day 1
- Body mass index (BMI) kg/m^2
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Ulcerative colitis disease history: date of first diagnosis
  Time since original UC diagnosis will be calculated from date of first diagnosis to date of informed consent (months)
- Type of UC: Montreal classification
- Smoking history (never, current or former with start and end years)
- Modified Mayo score (rectal bleeding, stool frequency, endoscopic score, physician's rating and Total)
- Severity of UC (Mild/Moderate)
    - Mild UC is defined as the total modified Mayo score at Baseline (Visit 2) of 4, 5 or 6
    - Moderate UC is defined as the total modified Mayo score at Baseline (Visit 2) of 7, 8, 9 or 10

- Current UC treatment (Yes/No)
  Subjects with any ongoing oral medications for the UC indication(s) will be considered as Yes. Subjects taking multiple UC concomitant medications will be counted in each concomitant medication category:
    - Oral 5-ASA
    - Immunomodulator
    - Steroid
    - Other.

7.1.1.2 General Medical and Surgical History

The medical history will include the question whether subject has any vancomycin allergy and will also collect records of any medical/surgical history apart from IBD. Medical history items include medical condition or event, year of diagnosis, outcome (resolved or ongoing) and whether the patient is currently being treated for the condition. Medical history will be collected during screening and medical condition terms will be coded using MedDRA 18.1.

7.1.1.3 Prior and Concomitant Medications

At Screening, subjects will be asked what medications they have taken during the last 6 months. Prior and concomitant medication other than the study drug (vancomycin and SER-287), including herbal and other non-traditional remedies will be documented from screening through Visit 13. Medications used to treat inflammatory bowel disease (IBD) will be flagged and also medications used to treat an AE. Prior and concomitant medications will be coded using the WHO Drug Dictionary (WHO-DDE, September 1st 2015).

7.1.1.4 Diet Inventory

Diet inventory log (CSP Appendix 2) responses will be collected at Screening Visit 1, treatment period Visit 6 (Day 22) and follow-up Visit 12 (Day 64) or early term (ET).

7.1.2 Microbiome Alterations and Engraftment Primary Endpoints

The record of stool samples collected at Visit 1, Visit 4, Visit 5, Visit 6, Visit 12 and Visit 13 or the Early Termination Visit (if applicable), and any Unscheduled Visit will include record of date and time produced, refrigerated (Yes/No), status (frozen, ambient or cooled) and *Clostridium difficile* result.

Genomic sequence results for assessment of microbiome alterations, composition of the intestinal microbiome and engraftment of SER-287 bacteria will be presented in a separate report.

Presentation and analysis of these endpoints/results will be discussed in a separate SAP and are not part of the work order with PAREXEL.

7.1.3 Secondary Endpoints

7.1.3.1 Clinical Response, Clinical Remission, and Endoscopic Improvement

The total modified Mayo score (TMMS, CSP Appendix 1) is a composite score, including the modified Mayo endoscopic subscore, the patient report outcome (stool frequency and rectal bleeding) as well as physician's rating. Only the modified Mayo endoscopic subscore is determined by the central reader and provided to the clinical site.

Total modified Mayo score items scored on a 4 point scale from 0 = none or normal to 3 = most severe symptom category are stool frequency, rectal bleeding, mucosal appearance at endoscopy and physician rating of disease activity.

Partial Mayo score, which is the TMMS without the endoscopic subscore, will be assessed at each visit and the TMMS will be assessed at baseline (Visit 2) and at Visit 12 (or early termination). The primary efficacy analysis time point is Visit 12, after 8-week treatment period.

Baseline scores for the TMMS and for the partial Mayo are calculated using the Screening Visit 2 assessments. If the partial Mayo score changes from Visit 1 to Visit 2, the Visit 2 score should be used in computing the TMMS at Baseline and when assessing the subject for the safety stopping rules.

Clinical response is defined as:

- A decrease of ≥3 points in TMMS from baseline, along with EITHER a decrease of ≥1 point in rectal bleeding subscore OR absolute rectal bleeding subscore of 0 or 1

Clinical remission is defined as:

- A TMMS ≤2 and an endoscopic subscore of 0 or 1

Endoscopic improvement is defined as:

- a decrease in the endoscopic subscore ≥1

Details of each flexible sigmoidoscopy procedure will be recorded to the electronic case report form (eCRF) including date and time, verify preparation and sample collection: biopsy samples for mucosal transcriptomics, mucosal microbiome sample, histopathology with cytomegalovirus (CMV) stain sample, video for central reading.

7.1.3.2 Biomarkers

The following biomarkers will be evaluated at Visit 1, Visit 4, Visit 6, Visit 8 (CRP only), Visit 12 and Visit 13:

- Serum biomarkers (C-reactive protein, CRP)
- Fecal biomarkers (fecal calprotectin) levels

7.1.4 Exploratory Endpoints

The following exploratory endpoints may be evaluated:

- Stool and blood metabolic pathways
- Serum cytokine profile
- Mucosal microbiome
- Mucosal transcriptomic profile
- Mucosal Histopathology, including CMV Immunohistology stains
- Microbial Culture Endpoints: *Candida* titer and diversity

One exploratory endpoint is included in this SAP and will be analyzed by PAREXEL; other exploratory endpoints will be discussed and presented in a separate SAP and are not part of the work order with PAREXEL.

- Microbial Culture Endpoints:
    - *Candida albicans* titer

Candida *albicans* will be analyzed first for the samples from the first 28 subjects at Visit 1, 4 and 12. All the samples collected in other visits for the first 28 subjects, and all the samples for the rest of subjects may be analyzed based on the observations from the analysis results of the first 28 subjects at Visit 1, 4 and 12.

    - *Candida species* titer

Analyses for *Candida species* may be conducted in the same manner as described above in *Candida albicans*.

7.1.5 Safety Variables

Safety evaluations include assessment of AEs, clinical laboratory tests (chemistry, hematology, liver function and urinalysis), physical examination, vital signs and electrocardiograms (ECGs).

7.1.5.1 Adverse Events

Adverse events including local and systemic reactions not considered medically serious, will be recorded from screening through Visit 13. Serious adverse events will be recorded from screening through Day 246.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1).

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug (including pre-treatment) has been administered.

Incidence of TEAE will be summarized by number of subjects and by therapy day. For each subject completing therapy, the total therapy days will be calculated including both the pre-treatment and treatment periods as the end date of treatment minus start date of pre-treatment therapy plus one (1). For each subject who is discontinued from treatment, total therapy days will be calculated up to the day when therapy was discontinued.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

7.1.5.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured:

- Hematology: erythrocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin and hematocrit
- Chemistry: creatinine, glucose, triglycerides, urea, uric acid, cholesterol, albumin, sodium and potassium
- Liver enzymes: alkaline phosphatase (ALP) aspartate aminotransferase (AST), alanine aminotransaminase (ALT), γ-glutamyl transferase (GGT), direct and indirect bilirubin, total bilirubin
- Urinalysis: pH, protein, glucose, ketone, bilirubin, blood, nitrite and leukocyte esterase. If nitrates or leukocytes are positive, a microscopic examination will be performed.
- Pregnancy test, serum and urine, for women of childbearing potential (WOCBP)

7.1.5.3 Vital Signs

The following vital signs measurements will be obtained:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Heart rate (bpm)
- Body temperature (oral) [°C]
- Respiratory rate (breaths per minute)
- Weight (kg)

7.1.5.4 Electrocardiograms

Standard safety 12-lead ECGs (single reading) will be performed at Day 8 (before dosing), and at Follow-Up on Day 92 and will be recorded to the eCRF as: Normal; Abnormal, Not Clinically Significant (NCS); and Abnormal, Clinically Significant (CS).

7.1.5.5 Physical Examination

Physical examinations will be performed in accordance with the Schedule of Events CSP Table 3. Abnormal findings determined by the Investigator to be clinically significant will be reported as medical history if observed prior to randomization to study drug (including pre-treatment therapy), or AEs if observed post-randomization during the study period.

7.2 Analysis Populations

7.2.1 Safety Population

The Safety Population will consist of all subjects who receive any amount of study drug. Subjects will be analyzed according to the treatment they actually received, rather than the treatment to which they were randomly assigned.

All safety analyses including descriptive summaries will be conducted based on the Safety Population.

7.2.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will consist of all subjects who were randomly assigned, including those who were not exposed to any study drug, and will be analyzed based on the treatment to which they were randomized.

All clinical efficacy analyses will be conducted in the ITT population.

Subject listings will be provided for the ITT population.

7.2.3 Sensitivity Analysis Population – 1 (without replacement)

The Sensitivity Analysis Population – 1 will consist of all randomized subjects, excluding any additional subjects randomized to replace withdrawn subjects as described in Section 6.5. Subjects will be analyzed based on the treatment to which they were randomized.

7.2.4 Sensitivity Analysis Population – 2 (with replacements only)

The Sensitivity Analysis Population – 2 will consist of all randomized subjects, excluding any withdrawn subjects who were replaced as described in Section 6.5. Subjects will be analyzed based on the treatment to which they were randomized.

7.3 Statistical Analysis Methods

7.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation

[SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

Selected clinical response data will be presented in treatment mean (+/- SD) profile plots.

The following rules will apply to any repeated measurements:

- If the repeated measurement occurs prior to the first dose of study drug then the last obtained value of any repeated measurement will be used in the descriptive statistics.
- If the repeated measurement occurs after the first dose of study drug then the first value observed of any repeated measurements will be used in the descriptive statistics.

7.3.2 Statistical Analysis and Significance Level

Statistical significance tests, if reported, will be two-sided and will be presented as relative measures of the strength of association to study arm for comparison among study endpoints. All reported confidence intervals (CIs) will be 95%, two-sided. There will be no adjustment of p-values or CIs for multiple comparisons. P-values and/or CIs generated for this study are not intended to be conclusive, but provided for guidance only.

In general, inferential analysis will be based on pairwise comparisons, A, C and D separately compared to placebo (B), and the comparisons A versus D and C versus D. If there is no trend in the differences between A and D, and C and D, then A, C and D will be pooled together versus B. For continuous data these comparisons will be assessed using CIs estimated by one-way analysis of variance (ANOVA) models fit to the separate results of each visit. For binary data these comparison will be assessed by analysis of two-by- two tables (using Fisher's exact test) and calculation of the risk difference, odds ratio and their corresponding asymptotic CIs.

7.3.3 Software

All statistical analyses will be performed using SAS® Version 9.3 or later.

7.3.4 Missing or Spurious Data

Any AE with incomplete date or time will be evaluated conservatively in the classification of treatment emergent AE.

The following imputation methods will be performed on the secondary and exploratory clinical endpoints, as specified in the succeeding sections on endpoint analyses below:

- Last Observation Carried Forward (LOCF) will be performed on the ITT population. Baseline values will not be carried forward.
- Observed Case analyses will be performed on the ITT population, the Sensitivity Analysis Population – 1 and the Sensitivity Analysis Population – 2.
- Worst Case analyses will be performed on the ITT population, the Sensitivity Analysis Population – 1 and the Sensitivity Analysis Population – 2.

The specifications are as follows:

	Observed Case	Worst Case
Early Termination (ET)	The data observed at ET visit will be used in the analysis; if the clinical endpoint is missing or non-calculable, the subject will not be included in the analysis.	All randomized subjects will be included in the analysis and ET subjects whose endpoints are collected prior to study Day 48, or missing, or non-calculable will be considered as having the worst outcome for the clinical endpoints.
Treatment Failure A subject who is considered as treatment failure is defined per PIs' decisions, this includes subjects who need the addition of UC medications for UC flares during study treatment period (from Visit 4 to Visit 12)	If the clinical endpoint(s) for a subject is available and calculable, the subject will be included in the analysis and the observed values for those endpoints will be used. If the endpoint(s) is missing or non-calculable, the subject will not be included in the analysis.	All randomized subjects will be included and the subjects who are considered as treatment failure will be considered as having the worst outcome for the clinical endpoints.

No other missing data will be imputed. Any apparently spurious data will be verified. No verified data will be excluded from summaries or analysis.

7.3.5 Interim Analysis and Safety Halting Rules

No interim analysis for efficacy is planned for this study.

An independent, unblinded, external Data and Safety Monitoring Committee (DSMC) has been established to perform safety evaluations on an ongoing basis. A DSMC charter, which has been reviewed and approved by the DSMC members, details the review of the safety data. The DSMC will make recommendations to ensure both patient safety and the continued ethical integrity of the study. Specific details regarding the responsibilities and requirements for documentation are described in the DSMC charter.

To ensure subject safety, individual (CSP Section 6.2.2.1) and study-wide (as detailed in the DSMC charter) safety halting rules will be implemented.

7.3.6 Study Subjects

7.3.6.1 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be listed for all randomized subjects and summarized overall and by treatment group for the ITT Population. The coded information of each subject discontinued (adverse event, lost to follow up, at the discretion of the investigator, protocol violation, noncompliance, withdrawal by subject, pregnancy, met individual halting rule: UC Flare, met individual halting rule: SUSAR and Other) will be listed and summarized. Detail will be included in the listing of subjects discontinued due to the following reasons: at the discretion of the investigator, protocol violation or other. The AE numbers will be reported for subjects discontinued for AE.

A record of Study Visits completed will be listed and summarized by treatment for the ITT Population.

7.3.6.2 Protocol Deviations

All protocol deviations, including those recorded by the Investigator or identified by data validation checks and will be recorded to a deviation log. All protocol deviations will be discussed between PAREXEL (Medical Monitory, Data Manager and Biostatistician) and also the Sponsor during the clean file meeting before database lock.

Protocol deviations will be listed and any unblinding event record will be listed for the ITT population. Assignment to analysis populations will be presented for each subject.

7.3.6.3 Demographic Data

The following demographic data and baseline data will be listed: age, sex, height, weight, BMI, ethnic origin, race, date of first UC diagnosis and time since UC diagnosis, UC Montreal classification, severity of UC, smoking history, ongoing UC treatment, medical history vancomycin allergy.

Summary tables by treatment and overall for these demographic and baseline data will be presented for the Safety Population and the ITT Population.

7.3.6.4 Medical and Surgical History

Medical and surgical history will be listed. The listing will include reported term, MedDRA preferred term and system organ class, the year of diagnosis or procedure, outcome (ongoing or resolved) and, if ongoing, is the patient currently being treated (yes or no). The medical history vancomycin allergy item will be listed and summarized with demographic data.

7.3.6.5 Prior and Concomitant Medication

All prior and concomitant medications will be listed. The listing will include generic name, WHO-DDE preferred term, start date (and calculated study day if start date is complete), ongoing or discontinued date (and calculated study day if discontinued date is complete), indication, route of administration, dose and dose unit, frequency and flags of medication to treat UC, medication to treat AE and prohibited medications.

Separate listings, sorted by treatment, subject, WHO-DDE preferred term and start date will be presented of all prior and all concomitant medications for the UC indication. For each UC concomitant medication, the medication category (if available), start date and end date/ongoing will be listed and indicated if it is a stable UC background therapy during 8-week treatment period as defined in protocol. (Note that changing UC background therapy during 8-week treatment period is considered as a major protocol deviation.) Any changes in UC background therapy will be flagged.

All prior medications will be summarized by WHO-DDE preferred term and treatment for the ITT Population. Prior medications with UC indication will be summarized separately by WHO-DDE preferred term and treatment. Concomitant medications will be summarized by WHO-DDE preferred term, treatment and study phase (pretreatment or treatment) for the ITT Population. Separate summaries will be presented of prohibited concomitant medications, all permitted UC

concomitant medications and of prohibited concomitant medications or dose changes to permitted UC concomitant medications for the ITT Population. This summary table will be the basis for sensitivity analyses on the clinical endpoints.

7.3.6.6 Diet Inventory Log

Diet inventory log responses will be presented in a listing.

7.3.6.7 Exposure to the Investigational Medicinal Product

The record of actual treatment or dose received including drug dispensed and returned will be presented in a listing for the ITT population and summarized by treatment for each period (pre-treatment and treatment) in the Safety population. Any subject who was not randomized but received a dose of study medication, or received incorrect treatment, will be flagged in the listing and identified in a table footnote.

7.3.7 Endpoints for Analysis

7.3.7.1 Microbiome Alterations and Engraftment Primary Endpoints

Genomic sequence results of the stool samples and assessment of microbiome alterations, composition of the intestinal microbiome and engraftment of SER-287 bacteria will be presented in a separate report beyond the scope of work conducted by PAREXEL. These data will not be considered in this SAP. The clinical record of stool samples collected will be listed.

7.3.7.2 Clinical Efficacy Response

All TMMS item scores with associated calculations of clinical response, clinical remission, and endoscopic improvement will be listed. All partial Mayo item scores with the Partial Mayo Score (sum) and score change from baseline will be listed by visit. The record of flexible sigmoidoscopy procedures will be listed separately. The Geboes score based on biopsy collected at Baseline and post-treatment visit will be listed.

Descriptive summaries by treatment will be presented for clinical response, clinical remission, and endoscopic improvement at Visit 12/ Early Termination visit for the ITT population, Sensitivity Analysis population – 1 and Sensitivity Analysis population – 2. Each endpoint will be calculated using the Observed Case and Worst Case methods for imputation of missing data (Section 7.3.4).

Efficacy response endpoints comprise clinical response, clinical remission, and endoscopic improvement. The primary time point for analysis is Visit 12. Estimates of the Visit 12 difference of rate (active treatment - placebo), 95% CI and statistical significance will be reported for treatment groups A, C and D separately compared to placebo B (A vs. B; C vs. B: D vs. B), A and D pooled together compared to placebo (A+D vs. B), A, C and D pooled together compared to placebo (A+C+D vs. B) and for A and C separately compared to D (A vs. D; C vs. D) for the ITT population, observed cases and worst case method, the Sensitivity Analysis Population – 1 and the Sensitivity Analysis Population – 2. Corresponding calculations of the odds ratio and relative risk will be also presented in those tables.

The following SAS® code will be applied for each comparison (two-by-two table) to estimate exact 95% CI for the clinical response (CLINRESP) rate in each treatment and asymptotic 95% CI for the risk difference and odds ratio:

```
proc freq;
        table TRT* CLINRESP /nopercent nocol alpha=0.05 chisq riskdiff relrisk exact;
        ods  select CrossTabFreqs RiskDiffCol2 RelativeRisks;
run;
quit;
```

Other efficacy endpoints will be analyzed using similar SAS code.

7.3.7.3 Serum Biomarkers

Serum biomarkers (CRP) observed values and change from baseline at each visit will be listed and summarized by treatment and visit. Mean (+/- SD) profile plots (response versus time point by treatment) of observed and change from baseline will be presented for the ITT population. The summary table and figures will use both observed case and LOCF imputation for missing values.

7.3.7.4 Fecal Biomarkers

Fecal biomarkers (fecal calprotectin) observed values and change from baseline at each visit will be listed and summarized by treatment and visit. Mean [+/ SD] profile plots (response versus timepoint by treatment) of observed and change from baseline will be presented for the ITT population. The summary table and figures will use both observed case and LOCF imputation for missing values.

7.3.7.5 Exploratory Endpoints

Results of the following exploratory endpoints collected at Baseline and post-baseline visits will be listed and presented in descriptive summary tables.

Serum cytokine profiles observed and change from baseline values will be listed and summarized for the ITT population. The summary table will use both observed case and LOCF imputation for missing values.

Mucosal Histopathology with CMV stain Geboes scores will be listed and summarized by treatment and visit for the ITT population. A summary table will include Geboes score frequency tabulated (number and percentage or subjects) at baseline and the post-baseline visits by treatment group for the ITT population.

Descriptive statistics for the titers of *Candida albicans* isolated at Visit 1, Visit 4 and Visit 12 will be presented by treatment group for the ITT population. The fold change from baseline (Visit 1) to each post-baseline visit, and the fold change from Visit 4 to each following visit will be also summarized by treatment group. Only subjects with evaluable samples at baseline/Visit 4 and the specified post-baseline/following visit will be included in the analysis of the fold change from baseline/Visit 4 at that visit.

In addition, the preceding summary tables summarizing titers and fold change from baseline of Candida albicans will be provided for the subset of subjects with a positive titer (>=50 CFU/g) at baseline (Visit 1), Visit 4 or Visit 12 by treatment group in the ITT population. A similar summary table will be provided for the subset of subjects with a positive titer (>=50 CFU/g) at Visit 4 or Visit 12 by treatment group in the ITT population.

Any titer at Baseline or Visit 4 (when calculating change from Visit 4) that has a value of "<50 Colony forming unit (CFU)/g" recorded will be given a value of 49 in the analyses, as the imputation method for the calculation of the fold change from Baseline, or change from Visit 4.

A plot presenting the average fold change from baseline of Candida albicans for subjects with at least 1 positive post-baseline titer by visit and treatment group will be generated for the ITT population. A similar plot presenting the average fold change from Visit 4 will be generated for subjects with at least 1 positive titer at Visit 12 in the ITT population. In the plot, the Y-axis will be the average fold change from baseline and the X-axis will present the visit time points for Visit 1, Visit 4 and Visit 12.

The analyses planned for *Candida albicans* may be repeated for *Candida species*.

As majority of stool samples are handled as refrigerated samples, all the frozen samples will not be used for any of these analyses.

7.3.8 Safety Analysis

The analysis of the safety variables will be based on the Safety Population.

Safety endpoint will be summarized by treatment group and also for the pooled SER-287 treatments (A, C and D). The assessment of safety will be based on descriptive summaries of SER-287 treatment groups and the placebo treatment group.

7.3.8.1 Adverse Events

All AEs from screening to Day 92, and all SAEs from screening to Day 246 will be collected and listed, including those occurring before the start of study drug. Separate listings will be presented for AEs leading to death, SAEs, AEs of special interest (AESI) and AEs leading to study drug discontinuation. The following information will be included in the listings: reported (verbatim) term, MedDRA preferred term, system organ class, start date, end date or ongoing, serious, AESI, action taken (drug withdrawn, dose not changed, not applicable), relationship to study drug (not related, possibly related, related), outcome (fatal, not recovered/ not resolved, recovered/ resolved), severity (mild, moderate, severe) and treatment given (yes, no).

The following additional information will be presented for SAEs: results in death, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, is life threatening, is associated with congenital anomaly or birth defect.

An overall TEAE summary by treatment will include number and percentage of subjects with event counts for SAE, AESI, severe AE, related and possibly related AE, AE leading to discontinuation of study drug and AE leading to death. The number and percentage of subjects with event counts of TEAEs will be tabulated by system organ class (SOC) and preferred term (PT) for each treatment group. The incidence of TEAEs based on the number of days the subjects in each treatment group were on study drug (per subject on therapy day) will also be presented by system organ class and preferred term for each treatment group. For calculation of incidence per subject, each type of event will be counted at most once per subject. For calculation of incidence per subject on therapy days all adverse events will be counted.

The subject incidence and incidence per subject therapy day will also be summarized by severity and by relationship to treatment.

7.3.8.2 Clinical Safety Laboratory Tests (Chemistry, Hematology, Liver and Urinalysis)

Clinical safety laboratory tests will be reported in standard international (SI) units.

All scheduled and unscheduled laboratory results will be presented for each subject, sorted by category, subject, test and sample time for hematology observed and change from baseline, chemistry tests observed and change from baseline, liver function tests observed and change from baseline and urinalysis observed values with change from baseline reported for quantitative assessments. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment of NCS or CS. Listings will include change from baseline, where baseline is the latest scheduled or repeat assessment obtained on Day 1 prior to pre-treatment dosing.

A separate listing of all subjects with any abnormal hematology results will be presented, grouped by test category and ordered by test, subject and sample time. All results, both normal and abnormal, for the subject at the other sample times for this hematology test will also be included in this listing. A similar listing will be created for all abnormal chemistry and liver function test results. The liver function tests ALT, AST, total bilirubin and ALP will be assessed for signs of hepatic impairment and liver injury. These tests will be reported for each scheduled or unscheduled laboratory assessment that had ALT > 3xULN, AST > 3xULN, or total bilirubin ≥ 2xULN. Laboratory results and other laboratory tests for these subjects will be reviewed and evaluated relative to Hy's law (Reference 2):

1. a subject having 3-fold or greater elevations above the ULN of ALT or AST
2. the subject also having total bilirubin >2xULN
3. the subject does not show elevated serum ALP (ALP < 2xULN)

Quantitative hematology, chemistry and liver test observed values and changes from baseline will be summarized descriptively (n, mean, SD, median, minimum, maximum) by treatment and visit. Quantitative urinalysis tests will also be presented in a summary table.

The record of serum and urine pregnancy tests will listed.

The record of biopsy sample collected will be listed.

7.3.8.3 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Baseline is the assessment taken on Day 1 of the pre-treatment period or the latest unscheduled assessment taken predose of the pre-treatment study drug. Descriptive statistics (n, mean, SD, median, minimum, maximum) of the vital signs observed and change from baseline will be presented by treatment group for all scheduled study visits. Baseline is the latest scheduled or unscheduled assessment prior to the first dose of study drug in the pre-treatment period.

7.3.8.4 Twelve-Lead Electrocardiogram

The record of ECG, date, time and overall interpretation will be listed and the overall interpretation summarized by treatment and visit.

8. CHANGE FROM PROTOCOL

In Protocol Amendment 3, 10 Oct 2016	In SAP Amendment
The Modified Intent-to-Treat (mITT) population will consist of all randomized patients with baseline and at least one post-baseline stool sample, who were exposed to any amount of study drug, and will be analyzed based on the treatment to which they were randomized (pages 8, 59).	Deleted: mITT
Complete remission defined as: A Total Modified Mayo Score ≤ 2 and an endoscopic subscore 0 with no erythema, no blood and no evidence of inflammation. (pages 4, 27, 38),	Deleted: Complete remission
	Added: Clinical remission defined as: A Total Modified Mayo Score ≤ 2 and an endoscopic subscore 0 or 1

9. REFERENCES

1. SAS® Version 9.3 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Food and Drug Administration Web site. http://www.fda.gov. Accessed September 15, 2016.

10. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Subject Disposition

Table 14.1.1 Subject Disposition by Treatment (Intent to Treat Population)

Table 14.1.2 Study Visits Completed by Treatment (Intent to Treat Population)

Baseline and Demographic Data

Table 14.1.3.1 Subject Demographics and Baseline Variables (Safety Population)

Table 14.1.3.2.1 Subject Demographics and Baseline Variables (Intent to Treat Population)

Table 14.1.3.2.2 Subject Demographics and Baseline Variables (Sensitivity Analysis Population – 1)

Table 14.1.3.2.3 Subject Demographics and Baseline Variables (Sensitivity Analysis Population – 2)

Table 14.1.4.1.1 All Prior Medications (Intent to Treat Population)

Table 14.1.4.1.2 Prior Medications for Ulcerative Colitis (Intent to Treat Population)

Table 14.1.4.2.1 All Prior and Concomitant Medications (Intent to Treat Population)

Table 14.1.4.2.2 All Prior and Concomitant Medications for UC (Intent to Treat Population)

Table 14.1.4.3.1 All Concomitant Medications (Intent to Treat Population)

Table 14.1.4.3.2 All Concomitant Medications for UC (Intent to Treat Population)

Table 14.1.4.4 All Post-treatment Medications (Intent to Treat Population)

Table 14.1.4.5.1 Record of Prohibited Concomitant Medications for UC Indications Taken During the Study Treatment Period (Intent to Treat Population)

Table 14.1.4.5.2 Record of Prohibited Concomitant Medications for non-UC Indications (Intent to Treat Population)

Table 14.1.4.5.3 Record of Dose Changes During the Study Treatment Period to Permitted Prior and Concomitant Medications for Ulcerative Colitis (Intent to Treat Population)

Table 14.1.4.6 Record of All Permitted Concomitant Medications for Ulcerative Colitis Taken During the Study Treatment Period (Intent to Treat Population)

Study Drug Exposure

Table 14.2.1 Study Drug Compliance Rate by Treatment (Safety Population)

Endpoints for Analysis

Table 14.2.2.1 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Intent to Treat Population, Observed Case)

Table 14.2.2.2 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Intent to Treat Population, Worst Case)

Table 14.2.2.3 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Sensitivity Analysis Population – 1, Observed Case)

Table 14.2.2.4 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Sensitivity Analysis Population – 1, Worst Case)

Table 14.2.2.5 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Sensitivity Analysis Population – 2, Observed Case)

Table 14.2.2.6 Clinical Response, Clinical Remission, and Endoscopic Improvement by Treatment (Sensitivity Analysis Population – 2, Worst Case)

Table 14.2.3.1.1 Serum C-reactive Protein (CRP) Observed and Change from Baseline by Treatment and Visit (Intent to Treat Population)

Table 14.2.3.1.2 Serum C-reactive Protein (CRP) Observed and Change from Baseline by Treatment and Visit (Intent to Treat Population, LOCF)

Table 14.2.3.2.1 Fecal Calprotectin Observed and Change from Baseline by Treatment and Visit (Intent to Treat Population)

Table 14.2.3.2.2 Fecal Calprotectin Observed and Change from Baseline by Treatment and Visit (Intent to Treat Population, LOCF)

Table 14.2.3.3 Serum Cytokine Profile Observed Values and Change from Baseline by Treatment and Visit (Intent to Treat Population)

Table 14.2.3.4.1 Mucosal Histopathology with Cytomegalovirus (CMV) Stain Geboes Scores Summary by Treatment and Visit (Intent to Treat Population)

Table 14.2.3.4.2 Mucosal Histopathology with CMV Stain Geboes Scores Shift from Baseline to Day 64 by Treatment (Intent to Treat Population)

Table 14.2.4.1.1 Titers of Candida *albicans* Observed Values and Fold Change from Baseline by Treatment and Visit (Intent to Treat Population)

Table 14.2.4.1.2 Titers of Candida *albicans* Observed Values and Fold Change from Visit 4 by Treatment and Visit (Intent to Treat Population)

Table 14.2.4.1.3 Titers of Candida *albicans* Observed Values and Fold Change from Baseline by Treatment and Visit (Intent to Treat Population, Positive Titer at Baseline)

Table 14.2.4.1.4 Titers of Candida *albicans* Observed Values and Fold Change from Visit 4 by Treatment and Visit (Intent to Treat Population, Positive Titer at Visit 4)

Table 14.2.4.2.1 Titers of Candida *species* Observed Values and Fold Change from Baseline by Treatment and Visit (Intent to Treat Population)

Table 14.2.4.2.2 Titers of Candida *species* Observed Values and Fold Change from Visit 4 by Treatment and Visit (Intent to Treat Population)

Table 14.2.4.2.3 Titers of Candida *species* Observed Values and Fold Change from Baseline by Treatment and Visit (Intent to Treat Population, Positive Titer at Baseline)

Table 14.2.4.2.4 Titers of Candida *species* Observed Values and Fold Change from Visit 4 by Treatment and Visit (Intent to Treat Population, Positive Titer at Visit 4)

Safety Data

Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events by Treatment (Safety Population)
Table 14.3.1.2.1	Treatment-Emergent Adverse Events Incidence by Subject by Treatment, System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.2.2	Treatment-Emergent Adverse Events Incidence by Subject Therapy Day by Treatment, System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3.1	Treatment-Emergent Adverse Events Incidence by Subject by Treatment, System Organ Class, Preferred Term and Severity (Safety Population)
Table 14.3.1.3.2	Treatment-Emergent Adverse Events Incidence by Subject Therapy Day by Treatment, System Organ Class, Preferred Term and Severity (Safety Population)
Table 14.3.1.4.1	Treatment-Emergent Adverse Events Incidence by Subject by Treatment, System Organ Class, Preferred Term and Causality (Safety Population)
Table 14.3.1.4.2	Treatment-Emergent Adverse Events Incidence by Subject Therapy Day by Treatment, System Organ Class, Preferred Term and Causality (Safety Population)
Listing 14.3.2.1	Subject Listing of Adverse Events Leading to Death (Safety Population)
Listing 14.3.2.2	Subject Listing of Serious Adverse Events (Safety Population)
Listing 14.3.2.3	Subject Listing of Adverse Events of Special Interest (Safety Population)
Listing 14.3.2.4	Subject Listing of Adverse Events Leading to Study Drug Discontinuation (Safety Population)
Listing 14.3.4.1	Abnormal Hematology Laboratory Test Values (Safety Population)
Listing 14.3.4.2	Abnormal Chemistry Laboratory Test Values (Safety Population)
Listing 14.3.4.3	Abnormal Liver Function Test Values (Safety Population)
Listing 14.3.4.4	Liver Safety Monitoring Assessments Listed by Subject Time Point and

Test (Safety Population)

Table 14.3.5.1.1 Hematology Observed and Change from Baseline Summary by Treatment and Visit (Safety Population)

Table 14.3.5.1.2 Chemistry Tests Observed and Change from Baseline Summary by Treatment and Visit (Safety Population)

Table 14.3.5.1.3 Liver Function Tests Observed and Change from Baseline Summary by Treatment and Visit (Safety Population)

Table 14.3.5.1.4 Urinalysis Quantitative Tests Observed and Change from Baseline Summary by Treatment and Visit (Safety Population)

Table 14.3.6.1 Vital Signs Observed Values and Change from Baseline by Treatment and Visit (Safety Population)

Table 14.3.6.2 Electrocardiogram Overall Interpretation by Treatment and Visit (Safety Population)

11. FIGURES TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Figure 14.2.1.1 Serum C-reactive Protein (unit) Mean (+/- Standard Deviation) Profiles versus Study Day (Intent to Treat Population)

Figure 14.2.1.2 Serum C-reactive Protein (unit) Change from Baseline Mean (+/- Standard Deviation) Profiles versus Study Day (Modified Intent to Treat Population)

Figure 14.2.2.1 Fecal Calprotectin (unit) Mean (+/- Standard Deviation) Profiles versus Study Day (Intent to Treat Population)

Figure 14.2.2.2 Fecal Calprotectin (unit) Change from Baseline Mean (+/- Standard Deviation) Profiles versus Study Day (Modified Intent to Treat Population)

12. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Subject Disposition

Listing 16.2.1.1 Subject Disposition and Informed Consent (All Randomized Subjects)

Listing 16.2.1.2 Study Visits Completed (Intent to Treat Population)

Listing 16.2.2.1 Protocol Deviations (Intent to Treat Population)

Listing 16.2.2.2 Subject Unblinding Events (Intent to Treat Population)

Listing 16.2.3 Assignment to Analysis Populations (Intent to Treat Population)

Baseline and Demographic Data

Listing 16.2.4.1.1 Subject Demographics and Baseline Characteristics Subject History (Intent to Treat Population)

Listing 16.2.4.1.2 Subject Demographics and Baseline Characteristics – UC History (Intent to Treat Population)

Listing 16.2.4.2 Medical and Surgical History (Intent to Treat Population)

Concomitant Medication and Diet

Listing 16.2.4.3.1.1 Prior Medication for Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.1.2 Prior Medications for Non-Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.2.1 Prior and Concomitant Medication for Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.2.2 Prior and Concomitant Medication for Non-Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.3.1 Concomitant Medication for Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.3.2 Concomitant Medication for Non-Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.4 Post-treatment Medication (Intent to Treat Population)

Listing 16.2.4.3.5.1 Prior and Concomitant Permitted Medication for Ulcerative Colitis Indication (Intent to Treat Population)

Listing 16.2.4.3.5.2 Prior and Concomitant Prohibited Medications for Ulcerative Colitis (Intent to Treat Population)

Listing 16.2.4.3.5.3 Prohibited Concomitant Medications (Intent to Treat Population)

Listing 16.2.4.6 Diet Inventory Log (Intent to Treat Population)

Study Drug Exposure

Listing 16.2.5 Pre-treatment and Treatment Period Drug Dispensed and Returned (Safety Population)

Endpoints for Analysis

Listing 16.2.6.1.1 Total Modified Mayo Score (TMMS) and Clinical Efficacy Endpoints (Intent to Treat Population)

Listing 16.2.6.1.2 Partial Mayo Score and Change from Baseline (Visit 2) by Visit (Intent to Treat Population)

Listing 16.2.6.1.3 Endoscopy Procedure (Intent to Treat Population)

Listing 16.2.6.2 Serum C-reactive Protein Observed and Change from Baseline (Intent to Treat Population)

Listing 16.2.6.3 Fecal Calprotectin Observed and Change from Baseline (Intent to Treat Population)

Listing 16.2.6.4 Serum Cytokine Profile, Observed and Change from Baseline (Intent to Treat Population)

Listing 16.2.6.5 Mucosal Histopathology with CMV Stain Geboes Scores (Intent to Treat Population)

Listing 16.2.6.6 Stool Sample Collection (Intent to Treat Population)

Listing 16.2.6.7 Candida Albicans, Observed Value by Treatment by Visit (Intent to Treat Population)

Listing 16.2.6.8 Candida Species, Observed Value by Treatment by Visit (Intent to Treat Population)

Safety Variables

Listing 16.2.7 All Adverse Events and Pre-Treatment Adverse Events (Safety Population)

Listing 16.2.8.1 Hematology Observed Values and Change from Baseline (Safety Population)

Listing 16.2.8.2 Chemistry Observed Values and Change from Baseline (Safety Population)

Listing 16.2.8.3 Liver Function Tests Observed Values and Change from Baseline (Safety Population)

Listing 16.2.8.4 Urinalysis Observed Values and Change from Baseline (Safety Population)

Listing 16.2.8.5 Pregnancy Tests (Safety Population)

Listing 16.2.9.1 Vital Signs Observed Values and Change from Baseline (Safety Population)

Listing 16.2.9.2 Electrocardiogram Assessments (Safety Population)

13. DOCUMENTATION OF STATISTICAL METHODS

Appendix 16.1.9.2.1 Statistical Analysis of Study Endpoints