Clinical Study Protocol

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

Sponsor:	Seres Therapeutics, Inc. 200 Sidney Street Cambridge, MA 02139
Clinical Research Organization:	PAREXEL International 195 West Street Waltham, MA 02451
Sponsor Protocol No.:	SERES-101
IND No.:	16689
Study Drug Name:	SER-287
Development Phase:	1b
Date of Protocol Amendment 3:	10 Oct 2016
Date of Previous Protocol:	08 Dec 2015

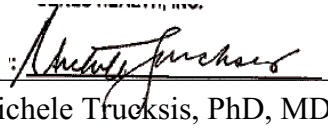
The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

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

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1989, and the guidelines on Good Clinical Practice.



10/10/2016

Michele Trucksis, PhD, MD
Executive Vice President, Chief Medical Officer
Seres Therapeutics, Inc.

Declaration of the Investigator

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

All documentation for this study that is supplied to me, and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic data capture (EDC) system, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

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Name (block letters)

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Title (block letters)

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Institution (block letters)

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Phone number

PROTOCOL SYNOPSIS

Title	A Multiple Dose Study to Evaluate the Safety, Tolerability and Microbiome Dynamics of SER-287 in Subjects with Mild-to-Moderate Ulcerative Colitis
Sponsor Study No.	SERES-101
Phase	1b
Sponsor	Seres Therapeutics, Inc.
Study Centers	Approximately 20 Study Centers in the United States (US)
Objectives	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 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, complete remission, and endoscopic improvement • To assess changes in serum and fecal biomarkers from baseline throughout treatment 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.
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 2 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: Arm A: Placebo pre-treatment, followed by once weekly dosing of SER-287 for 8 weeks Arm B: Placebo pre-treatment, followed by once daily placebo for 8 weeks Arm C: Vancomycin[1] pre-treatment, followed by once daily dosing of SER-287 for 8 weeks Arm D: Vancomycin pre-treatment, followed by once weekly dosing of SER-287 for 8 weeks This study has 5 study periods: **Screening** (Day-17 to Day-1), **Pre-treatment** (Day 1 to Day 7), 8-Week **Treatment** (Day 8-63), 4 Week **Short Term Safety Follow-up** (Day 64-92) and a **Long Term Safety Follow-up** (Day 93-246). Approximately 55 adult subjects with mild-to-moderate ulcerative colitis will be enrolled. **Screening** includes 2 screening visits. At the first Screening **visit,** Visit 1, subjects will be checked for inclusion /exclusion criteria, and medical history and demographic data will be collected. At the second Screening visit, Visit 2, eligible subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsy within 17 days from the first Screening visit and prior to Study Day 1. For Baseline Mayo subscore measurement, the one closest to the randomization, Visit 2 should be used. Subjects will be on a clear liquid diet 1 day before the flexible lower endoscopy (flexible sigmoidoscopy or colonoscopy). On the day of the procedure, the subject

[1] Full name of Vancomycin is Over-encapsulated (OE) Vancomycin HCl 125 mg capsules

will self-administer a bowel prep at the PI discretion (e.g., 2 Fleets enemas) and fast for 6 hours before the procedure.

Endoscopy images will be obtained during each endoscopy and will be sent for independent central reading and determination of the modified Mayo endoscopic subscore. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment to be used for video capture and transmission of endoscopic recordings. For each subject, video recording of the entire endoscopic procedure will be performed using a storage medium provided by the sponsor or designee. The endoscopic recordings will be read centrally in a blinded manner by a qualified gastroenterologist according to the image review charter. The Total modified Mayo score used for clinical endpoints in the trial will use the modified Mayo endoscopic subscore determined by the central reader.

The total modified Mayo score 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. The modified Mayo endoscopic subscore is determined by the central reader and provided to the clinical site. Subjects who meet the inclusion criteria (Total modified Mayo score of 4 to 10, inclusive, and modified Mayo endoscopic subscore of $\geq$ 1, with evidence of mucosal lesions), will be randomized using an interactive web/voice response system (IxRS) to 1 of 4 treatment groups on Study Day 1 and initiate the pre-treatment regimen.

During the **Pre-Treatment** period (Day 1 to Day 7) oral vancomycin 125 mg four times a day (qid) or matching placebo will be administered for 6 days.

Following completion of the Pre-Treatment period, subjects will return to the clinic to begin the 8-Week **Treatment Period** (Day 8-63). On Day 8, subjects will receive 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 the other days, or placebo daily.

During the 8-Week **Treatment Period,** all subjects will come to the clinic weekly for drug dispensing and asked about adverse events (AEs), change in medications and the partial Mayo score assessment (scores should reflect the 24-hour period prior to reporting). All subjects will have a lower endoscopy (flexible sigmoidoscopy or colonoscopy) at Visit 12/Early Termination +/- 3 days to evaluate endoscopic disease activity. Subjects will be on a clear liquid diet the day before the lower endoscopy (flexible sigmoidoscopy or colonoscopy). On the day of the procedure, the subject will self-administer a bowel prep at the PI discretion (e.g., 2 Fleets enemas) and fast for 6 hours before the procedure.
All subjects will have an in-clinic visit at Visit 12/Early Termination +/- 3 days.

Subjects will then enter the **Short-Term Safety Follow-up Period** in which subjects will be contacted by phone on Days 71, 78, 85 +/- 2 days. Subjects will be asked about adverse events (AEs), concomitant medications and will complete disease activity assessment which includes stool frequency and rectal bleeding. All subjects will have an in-clinic safety visit at Visit 13 +/- 2 days.

Subjects will then enter the **Long-Term Safety Follow-up Period** in which subjects will be contacted by phone on Days 246 +/- 3 days. Following Visit 13 through Day 246/ET only SAEs, and concomitant medications associated with SAEs will be collected.

Data and Safety Monitoring Committee

To ensure safe study conduct during the Phase 1b study, an independent, unblinded, external Data and Safety Monitoring Committee (DSMC) will be established to perform safety evaluations on an ongoing basis. A DSMC charter will be developed and will detail the review of the safety data.

Treatment

The **Pre-Treatment Period** includes administration of either oral vancomycin 125 mg four times a day (over encapsulated Vancomycin HCl 125 mg) for 6 days or matching placebo.

The **Treatment Period** includes administration of 4 capsules taken orally once daily 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.

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

	Pre-treatment: Vanco or Pbo				Treatment Period: SER-287 or Pbo			
Group	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

d = day; Pbo = placebo; qid = Four times a day; wk = week; admin= administration; vanco=vancomycin; SporQs= spore equivalents

Number of Subjects

Approximately 55 subjects will be enrolled: 15 subjects in each of the three active arms (Groups A, C and D) and 10 subjects in the placebo arm (Group B).

Population

Male or female subjects with active mild-to-moderate Ulcerative Colitis ≥ 18 years of age.

Criteria for Evaluation of Efficacy

The evaluation of the efficacy data will be performed by comparison of the efficacy endpoints across treatment arms. The following efficacy endpoints will be assessed for the comparison:

Primary Endpoints

- Composition of the intestinal microbiome
- Engraftment of SER-287 bacteria in all treatment arms

Secondary Endpoints

- Clinical response defined as:
  - A decrease of ≥ 3 points in Total Modified Mayo score (TMMS) from baseline, along with **EITHER** a decrease of ≥1 point in rectal bleeding subscore **or** absolute rectal bleeding subscore of 0 or 1
- 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
- Endoscopic improvement, defined as a decrease in endoscopic subscore ≥ 1
- Serum biomarkers [C-reactive protein (CRP)]
- Fecal biomarkers (fecal calprotectin) levels

Exploratory Endpoints

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

Criteria for Evaluation of Safety

The evaluation of the safety data will be performed by comparison of the safety endpoints across treatment arms. The following safety parameters will be assessed for the comparison:

- Incidence of adverse events
- Incidence of adverse events of special interest
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

Statistical Methods

All safety and tolerability, intestinal microbiome, clinical efficacy, and biomarker data will be listed and presented in descriptive summaries by study arm, visit and time point. At a minimum, continuous data will be summarized by study arm using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum). Categorical data will be summarized by study arm using frequency tables (number and percentage).

Analysis Populations

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 will be conducted based on the Safety 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.

The Modified Intent-to-Treat (mITT) Population will consist of all randomized patients with baseline and at least one post-baseline stool sample, including those who were not exposed to any study drug, and will be analysed based on the treatment to which they were randomized.

All analyses on clinical response will be conducted in the ITT population and in the mITT population as sensitivity analyses.

All microbiome alterations analyses will be conducted in the mITT Population.

Analysis of Primary Endpoint

Adverse Events

The percentage of subjects with 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, by severity, and by relationship to treatment. Tables of any TEAEs leading to study drug discontinuation, AESIs and SAEs will also be provided.

Clinical Laboratory Tests

All scheduled and unscheduled laboratory results will be presented for each subject, sorted by category, subject, test and sample time. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. A separate listing of abnormal results will be presented, ordered by test, subject and sample time.

Quantitative chemistry and hematology tests (observed values and change from baseline) will be summarized descriptively in tabular format. A shift table will be presented for chemistry, hematology and urinalysis tests shift from baseline to each post-baseline visit and also the shift from baseline to highest and to lowest post-baseline assessment.

Vital Signs

Vital signs data include measurements of weight (kg), height (cm), blood pressure (mmHg), respiratory rate (breaths/minute), heart rate (bpm), body temperature (Celsius / Fahrenheit), and Body Mass Index (kg/m^2). Descriptive statistics of the

vital signs will be presented by treatment group for all study visits at which they were collected. The change from baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarized by treatment group.

Physical Examination Findings

Abnormal clinically significant physical examination (PE) finding will be reported as Medical History (MH) or as an AE.

Gastrointestinal tract Microbiome

The gastrointestinal (GI) microbiome of subjects will be characterized by using at minimum recombinant deoxyribonucleic acid (rDNA) 16S V4 genomic data sets generated from stool collected for the various endpoints, and may include whole metagenome sequence (WMS) characterization. Genomic data sets will define the microbial composition of the microbiome of a subject at a given time point. Genomic sequence read data sets will be analyzed to assign a taxonomic identity at the resolution of an operational taxonomic unit (OTU) and phylogenetic clade (clade) and, further, to define the relative proportion of each OTU and clade to all other OTUs and clades in a given sample.

Changes in the composition of the microbiome will be measured in terms of both the total number of unique types of bacteria (i.e., α-diversity) and the microbial composition (i.e., β-diversity). Engraftment is defined as the outgrowth of bacteria that comprise the SER-287 spore ecology in a subject's gastrointestinal tract post-treatment. Significant differences between changes in the microbiome across the various treatment arms will be evaluated using both non-parametric tests for α-diversity and multivariate analysis of variances of dissimilarity matrices for β-diversity. Dissimilarity will be defined by using the unweighted Unifrac dissimilarity metric, which evaluates changes in the overall phylogenetic composition between two samples; this method is widely used in the study of microbial communities and represents a balanced approach with minimal bias to the presence of low- and high-abundance bacteria. Additional measures of dissimilarity that are routinely used in the analysis of microbiome data sets will be evaluated.

Determination of 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.

LIST OF STUDY PERSONNEL

Sponsor	Seres Therapeutics, Inc. 200 Sidney Street Cambridge, MA 02139
Contract Research Organization	PAREXEL International 195 West St. Waltham, MA 02451 +1-781-487-9900
Adverse Event Reporting	PAREXEL International 1 Federal Street Billerica, MA 01821 Telephone Phone: +1-781-434-5010 Fax Number: +1-781-434-5957
Central Laboratory	Eurofins Central Laboratory 2430 New Holland Pike Lancaster, PA 17601
Central lower endoscopy (flexible sigmoidoscopy or colonoscopy) **Reader**	**Robarts Clinical Trials** PO Box 5015 100 Perth Drive London, ON CANADA N6A 5K8

Table of Contents

Tables in Text

List of Abbreviations

Abx	Antibiotic
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
5-ASA	Aminosalicylate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical [Classification System]
BP	Blood pressure
Bpm	Beats per minute
CDI	*Clostridium difficile* infection
CFR	Code of Federal Regulations
Cm	Centimeter
CMV	Cytomegalovirus
CS	Clinically significant
Cx	Culture
D	Day
DNA	Deoxyribonucleic acid
DRL	Drug Reference List
DSMC	Data and Safety Monitoring Committee
DSS	Dextran sodium sulfate
ECG	Electrocardiogram
eCRF	Electronic case report form
CRP	C-reactive protein

EDC	Electronic data capture
ESR	Erythrocyte sedimentation rate
FMT	Fecal microbiota transplantation
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HDPE	High density polyethylene
HR	Heart rate
IBD	Inflammatory bowel disease
ICF	Informed consent form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IMP	Investigational medical product
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-treat; intention-to-treat
IVR	Interactive voice response
IxRS	Interactive web/voice response system
Kg	Kilogram
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical history
mL	Milliliter
mmHg	Millimeters of mercury
MMX	Multi-matrix system
NCS	Not clinically significant
NSAID	Non-steroidal anti-inflammatory
OE	Overencapsulated
OTU	Operational taxonomic unit
Pbo	Placebo

PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PE	Physical examination
PI	Principal Investigator
PT	Preferred term
qid	Four times a day
rDNA	Recombinant deoxyribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCFU	Spore Colony Forming Unit
SD	Standard deviation
SID	Subject identification
SOC	System organ class
SPF	Specific Pathogen Free
SporQ	Spore Equivalents, a dosing unit measured by dipicolinic acid content
TEAE	Treatment-emergent adverse event
TMMS	Total modified Mayo score
TNBS	2,4,6-Trinitrobenzenesulfonic acid
Tregs	Regulatory T cells
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
Wk	Week
WHO	World Health Organization
WOCBP	Women of child bearing potential

1 INTRODUCTION

Ulcerative colitis (UC) is a relapsing-remitting chronic inflammatory disorder affecting the mucosal surface of the colon, leading to episodes of bloody diarrhea, urgency and mucosal inflammation.(Danese and Fiocchi, 2011) As the disease mostly affects young and middle-aged individuals, the disease leads to decreased quality of life in those affected by the condition, high morbidity and significant economic burden accounting for nearly four billion health care dollars annually.(Ghosh and Mitchell, 2007; Kappelman et al., 2008; Rubin et al., 2014; Theede et al., 2015) Current medical therapies remain imperfect for the treatment of UC with the focus of drug development on suppressing the immune system rather than reducing the triggers of immune activation. As immunosuppressive agents increase the risk of infectious and oncologic complications, alternative mechanisms of action to decrease immune activation, remain attractive therapeutic goals for UC.

The prevailing model of disease pathogenesis for UC is that in the genetically predisposed host, environmental factors are sufficient to generate an abnormally perpetuated immune response and inflammation.(Xavier and Podolsky, 2007) Alterations in the intestinal microbiota parallel changes in environmental factors with evidence suggesting a role of the intestinal microbiota in immune modulation. (Biedermann et al., 2013, 2014; Leone et al., 2013; Wu et al., 2013) Studies suggest that the intestinal microbiome of UC patients is characterized by a decrease in microbial diversity and richness, with a lower prevalence of organisms within the phylum, Firmicutes. (Frank et al., 2007; Lepage et al., 2011; Machiels et al., 2014; Michail et al., 2012; Morgan et al., 2012; Ott et al., 2004; Papa et al., 2012; Rajilić-Stojanović et al., 2013; Sartor, 2008; Varela et al., 2013; Walujkar et al., 2014; Willing et al., 2010)

Given the dysbiosis seen in UC patients, studies have explored the use of fecal microbial transplantation (FMT) to treat UC. Two randomized, double-blind, placebo-controlled studies suggest a clinical response in mild-to-moderate UC patients by repopulating the intestinal microbial flora via FMT with that of a healthy donor (Moayyedi et al., 2015; Rossen et al., 2015). There was increased microbial diversity and greater similarity to donor microbiota profile noted in subjects with a clinical response to FMT in both studies suggesting that changes in the microbiome due to FMT were responsible for this clinical response. This study will explore microbial therapeutic interventions and the impact on the disease course in UC. The study hypothesis is that SER-287, enriched in spore-forming organisms that are diminished in active UC, can induce remission in mild-to-moderate ulcerative colitis.

SER-287 (Eubacterial Spores, Purified Suspension, Encapsulated) is an ecology of bacterial spores enriched from fecal donations obtained from healthy, screened donors. Bacterial spores are enriched by thorough killing of the vegetative microorganisms with ethanol, and then purifying and formulating the resulting spore population. SER-287 is delivered as oral capsules for administration to patients.

SER-287 for this Phase 1b clinical study was manufactured as SER-109 and then became SER-287 at the time of clinical labeling. SER-109 was administered in a Phase 1b/2

study (SERES-001), and was shown to increase bacterial diversity of the gut microbiota as early as 4 days after dosing in adults with recurrent *Clostridium difficile* infection (CDI). Currently there are no differences in the drug products, SER-109 and SER-287. Seres anticipates that, pending results from this Phase 1b clinical study, there may be future changes in SER-287, with respect to dose, formulation and/or regimen during development.

The patient population targeted for inclusion in this study is adults ≥18 years of age who have mild-to-moderate ulcerative colitis, as defined by a Total Modified Mayo score between 4 and 10, inclusive, with a Modified Mayo endoscopic subscore ≥ 1.

The primary objective of this study is to assess the safety and tolerability of SER-287 in patients with active mild-to-moderate ulcerative colitis. In addition, the study will evaluate the microbiome dynamics throughout treatment and assess preliminary efficacy data.

1.1 Background

1.1.1 Brief Description of the Indication and Existing Practices

The annual incidence rate of UC in Western countries is roughly 9.8/100,000 person-years with increasing incidence observed in developing countries.(Grinspan and Kornbluth, 2015) Approximately 50% of patients experience proctosigmoiditis, 30% have left-sided disease, and 20% have pancolitis. (Kothari et al., 2015) Overall, approximately 50% develop more extensive disease over the first 5 years of disease. There is currently no cure for UC. Therefore, the therapeutic goal is to alleviate and control symptoms (induction of remission) and to promote mucosal healing but also to prevent disease recurrence (maintenance of remission).

Current medical therapies for UC include sulfasalazine, aminosalicylates (5-ASAs), steroids, immunomodulators (azathioprine and 6-mercaptopurine), anti-TNF agents (infliximab, adalimumab, golimumab), anti-integrin agents (vedolizumab), and calcineurin inhibitors (cyclosporine and tacrolimus).(Grinspan and Kornbluth, 2015) As the majority of these medications are immunosuppressant agents targeted for moderate-to-severe disease, there remains an unmet need for safer agents with novel mechanisms of action, especially for patients with mild-to-moderate UC who experience frequent flares on aminosalicylates or as an alternative to aminosalicylate therapy in those intolerant to this class of medication. As alterations in the intestinal microbiome have been identified in UC and preliminary evidence suggests that microbial interventions can affect clinical outcomes, the study will assess whether an ecology of bacterial spores devoid of vegetative organisms in SER-287 can correct the dysbiosis in UC, increase microbial diversity and lead to clinical response in UC patients with active mild-to-moderate disease.

1.1.2 Rationale for the Development of the Compound, and Reasons why the Investigational Product is Applicable for this Disease

The intestinal microbiome is comprised of four principle bacterial phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria. In healthy subjects, the intestinal microbiome is mainly composed of Bacteroidetes and Firmicutes.(Human Microbiome Project Consortium, 2012) Studies have shown that subjects with inflammatory bowel disease, including UC, have a decrease in bacterial diversity and alterations in the intestinal microbiota compared to healthy subjects.(Baumgart et al., 2007; Frank et al., 2007; Gevers et al., 2014; Lepage et al., 2011; Machiels et al., 2014; Michail et al., 2012; Morgan et al., 2012; Ott et al., 2004; Papa et al., 2012; Rajilić-Stojanović et al., 2013; Sartor, 2008; Sokol et al., 2008; Varela et al., 2013; Walujkar et al., 2014; Willing et al., 2010)

The dysbiosis described in UC is characterized by lower microbial diversity and species richness, a greater prevalence of organisms within the phylum, Proteobacteria, and a lower prevalence of commensal bacteria within the phylum, Firmicutes. (Frank et al., 2007; Lepage et al., 2011; Machiels et al., 2014; Michail et al., 2012; Ott et al., 2004; Rajilić-Stojanović et al., 2013; Varela et al., 2013; Walujkar et al., 2014) In particular, Firmicutes within the Clostridiales order are poorly represented in active UC subjects than in age and sex-matched healthy controls with an inverse correlation between disease activity and presence of these organisms.(Michail et al., 2012) This study will test the hypothesis that administering bacterial spores comprised of predominantly Clostridial commensals within SER-287 to UC patients can help correct the dysbiosis and improve clinical outcomes.

1.1.3 Pharmacological Concept for the Treatment

Given the dysbiosis seen in UC patients, studies have explored the use of fecal microbial transplantation to treat UC. (Angelberger et al., 2013; Colman and Rubin, 2014; Kump et al., 2013; Kunde et al., 2013; Moayyedi et al., 2015; Rossen et al., 2015) Fecal microbial transplantation (FMT) is the transfer of stool from a healthy donor to a recipient. FMT has already demonstrated efficacy in preventing recurrent *Clostridium difficile* infection (CDI) with response corresponding to shifts of the recipient's flora towards that of the donor's and increasing microbial diversity in the recipient's microbiome. (van Nood et al., 2013; Youngster et al., 2014a, 2014b)

Most recently, two randomized controlled trials have evaluated the role of FMT in UC. One study administered FMT via enema weekly over 6 weeks (treatment group) versus water enemas (control group) to 75 patients with mild-to-moderate UC with the primary endpoint of clinical remission achieved in 24% of patients in the treatment group and 5% in the control group (p=0.03).(Moayyedi et al., 2015) Clinical remission was defined as a Mayo score < 3 with an endoscopic subscore of 0 at week 7. In a second study, donor FMT (treatment group) or autologous FMT (control group) was administered twice (3 weeks apart) via nasoduodenal tube to 50 UC patients with mild-to-moderate ulcerative colitis. (Rossen et al., 2015) After 12 weeks, while there was no significant difference in clinical remission between groups, there was a trend towards response in the treatment group (30.4% versus 20% control group, p=0.51) and there was increased microbial

diversity noted in responders of both groups with responders in the treatment group developing a similar microbiota profile to the donor. Given these findings of treatment response to FMT in UC patients, this study will explore further if supplementing the microbiome of UC patients with select spore-forming organisms in SER-287, that are underrepresented in subjects with active ulcerative colitis, could alter the microbiome of the recipient and lead to improved clinical outcomes.

1.1.4 Name and Description of Investigational Product

SER-287 (Purified Eubacterial Spores, Encapsulated) is an ecology of bacterial spores enriched from fecal donations obtained from healthy, screened donors, representing approximately 50 commensal bacteria in spore form. The bacterial spores are enriched by thorough killing of the vegetative microorganisms, then fractionating the resulting spore population away from the inactive components and formulating and encapsulating the spores for oral delivery. SER-287 for the proposed Phase 1b clinical study will be manufactured as SER-109. Currently, there are no differences between SER-109 and SER-287. Seres anticipates that, pending results from the Phase 1b clinical study, there may be future changes in SER-287, with respect to dose, formulation and/or regimen during development.

1.1.5 Summary of Findings from Non-Clinical Studies with Potential Clinical Significance

Recent evidence has identified dysbiosis of the intestinal microbiome as a contributing factor to the pathology in UC. Preclinical evidence in mice supports that, more specifically, the spore-forming fraction of both murine and human fecal microbiota is sufficient to drive protection against experimental colitis, in part via the induction of regulatory T cells (Tregs) in the colon (Atarashi et al., 2011, 2013).

In light of these data, efficacy of a research preparation of SER-287, comprised predominantly of Clostridial spore-forming organisms, was evaluated in pilot studies using mouse models of colitis [2,4,6-trinitrobenzenesulfonic acid (TNBS) and dextran sodium sulfate (DSS)]. In these experimental models of colitis, antibiotic pre-treatment with SER-287 (Abx + SER-287) improved clinical outcomes in the DSS model (Further details can be found in the Investigator's Brochure). These data support the hypothesis that SER-287, in combination with antibiotic pre-treatment, may improve symptoms of ulcerative colitis in man.

1.1.6 Summary of Findings from Previous Clinical Studies

SERES-101 will be the first study investigating the use of SER-287 in ulcerative colitis. At this time, there are no differences between SER-109 and SER-287 but SERES anticipates future changes in the dose, frequency and formulation of SER-287 in UC. Data from a SER-109 clinical study (SERES-001) in prevention of recurrent *Clostridium difficile* infection (CDI) provides data on SER-109 safety and post-treatment microbiome dynamics. SERES-001 has been completed and two additional clinical studies are ongoing:

- A Phase 1/2 Study (SERES-001: A Study of Modified Fecal Microbiota Transplant [SER-109] Delivered via Oral Administration for the Treatment of Recurrent *Clostridium difficile)* - completed
- A Phase 2 Study (SERES-004 ECOSPOR: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SER-109 to Prevent Recurrent *Clostridium difficile* Infection) - ongoing
- An Extension Study to the Phase 2 Study (SERES-005 ECOSPOR II: An Open-Labeled Extension of Studies SERES-004/SERES-007 Evaluating SER-109 in Patients with Recurrent *Clostridium difficile* Infection) – ongoing

Further details can be found in the Investigator's Brochure.

SERES-001 was an open-label, single arm, descending-dose study that evaluated the safety and efficacy of SER-109 in prevention of recurrent CDI in adult patients with a history of recurrent CDI episodes, a condition in which the microbiome is characterized as a low diversity state. Thirty patients were enrolled following a therapeutic response to standard of care CDI antibiotics. The primary endpoint of absence of diarrhea with a positive *C. difficile* test up to 8 weeks following dosing was achieved in 26 (87%) patients. Furthermore, evaluation of the microbiome pre- and post-treatment showed SER-109 increased bacterial diversity of the intestinal microbiota as early as 4 days after dosing. SER-109 in SERES-001 was safe and tolerable with no deaths. Seven SAEs were reported in 4 subjects, none considered related to SER-109.

Similar to CDI, UC is characterized by a decrease in microbial diversity and richness, with a lower prevalence of spore-forming organisms within the phylum, Firmicutes. The results from the SERES-001 study in recurrent CDI support exploration of the efficacy of SER-287 in increasing bacterial diversity of the intestinal microbiota in UC patients. The study population in SERES-001 was older (mean age of 62 years) with frequent co-morbid illnesses than what is anticipated for the UC population. Therefore, we anticipate a high safety profile in the UC population. However, as the population will be different for this Phase 1b study (SERES-101) than for SERES-001, SERES-101 will evaluate the safety, tolerability and microbiome dynamics of SER-287 in UC patients.

SERES-101 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 UC. Subjects will be randomized 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. From screening to last follow-up, the study duration will be between 35-37 weeks.

1.2 Rationale

SER-287 (Purified Eubacterial Spores, Encapsulated) is an ecology of bacterial spores enriched from fecal donations obtained from healthy, screened donors, representing approximately 50 commensal bacteria in spore form. As UC is characterized by a decrease in microbial diversity and richness, with a lower prevalence of spore-forming organisms within the phylum, Firmicutes, and preliminary evidence suggests that microbial interventions can affect clinical outcomes in UC, the study will examine whether SER-287 can correct the dysbiosis in UC, increase microbial diversity and lead to clinical response in UC patients with mild-to-moderate disease.

1.2.1 Rationale for Regimen

The inflammatory milieu in UC impacts the microbial composition with animal and human studies showing a greater representation of *Enterobacteriaceae* with a relative depletion of Clostridial organisms. This dysbiosis is seen in patients with recurrent CDI and can be reversed after FMT. While the dysbiosis in *Clostridium difficile* is mainly induced by infection, toxin production and repeated antibiotic usage, the dysbiosis in UC is more complex with host factors and alterations in microbial-host interactions likely contributing to the witnessed microbial changes.

This study will evaluate whether repeated dosing can alter the microbial community in UC, encourage engraftment and, ultimately, decrease mucosal inflammation. This study will test the weekly dosing strategy that was evaluated in the study by Moayyedi et al. and will also evaluate a daily dosing strategy.(Moayyedi et al., 2015) Given that the aim of the study is to induce remission in patients with active mild-to-moderate inflammation, this study will evaluate a higher frequency of dosing from weekly to daily dosing of SER-287 to provide consistent and maximal exposure to SER-287 treatment during a period of active inflammation.

1.2.2 Rationale for dose

The dose selected in this study is supported by the safety and effectiveness of this dose, [1 x 10^8 Spore Equivalents (SporQs)], administered in the SER-109 Phase 1b/2 study for recurrent CDI. The trial explored a range of doses from 3.4×10^7 to 2.3×10^{10} SporQs. The doses evaluated were safe with no deaths in the study and no concerning trends in laboratory values, vital signs or physical examination findings. The SAEs reported were deemed by the investigators to not be related to SER-109.

The dose selected gives a 230-fold margin to the highest dose tested in SERES-001 and a 3-fold margin to the lowest dose shown to be effective in SERES-001. Although the study population for SERES-001 is not the same study population targeted for the current study, the study population in SERES-001 is older (mean age of 62 years) with frequent co-morbid illnesses than the general UC population.

1.2.3 Rationale for Antibiotic Pre-Treatment

Disease states, such as CDI and UC, are characterized by intestinal dysbiosis and a decrease in microbial diversity. Antibiotic treatment prior to administration of a repopulating ecology of spores (SER-287) may allow for engraftment of the spores administered. Data described in the DSS animal colitis models with SER-287

demonstrate a trend toward improvement by the addition of antibiotics prior to SER-287 administration (see Investigator's Brochure).

Data from the SERES-001 study in prevention of recurrent CDI showed engraftment of bacteria from SER-109 as early as 4 days following SER-109 dosing. All the subjects in this study were pre-treated with antibiotics prior to SER-109 dosing, supporting, although not proving, that antibiotic pre-treatment may enhance engraftment. This study will assess whether vancomycin improves engraftment and clinical outcomes through a comparison of outcomes in arms with and without vancomycin pre-treatment.

1.2.4 Rationale for Endpoints

Efficacy endpoints will be measured incorporating an accepted clinical and endoscopic disease activity index in UC, the Total modified Mayo score, with an 8-week treatment period to evaluate induction of remission for UC in keeping with FDA regulatory guidance. The study will also evaluate endoscopic disease activity before and after treatment via central reading. Clinical disease activity throughout the study will be monitored via the partial Mayo score, which is the Mayo Score without the endoscopic subscore. Definitions of disease activity are defined by prior studies for the mild-to-moderate UC population.(Lichtenstein et al., 2015; Moayyedi et al., 2015; Sandborn et al., 2015)

This study is designed to also evaluate microbiome changes in this Phase 1b study. Engraftment is defined as the outgrowth of bacteria that comprise the SER-287 ecology in a patient's gastrointestinal tract post-treatment. This study will evaluate the engraftment of SER-287 bacterial isolates in each treatment arm and determine the overall change in composition of the microbiome both by total number of unique types of bacteria (ie, α-diversity) and by microbial composition (ie, β-diversity). The dysbiosis described in IBD is characterized by lower microbial diversity and species richness, a greater prevalence of pro-inflammatory pathobionts, mainly described within the phylum, Proteobacteria, and a lower prevalence of commensal bacteria within the phylum, Firmicutes, of which the Clostridial organisms within SER-287 belong.

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, complete 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 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

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 UC. Subjects will be randomized 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 study is broken down into 5 study periods: **Screening** (Day-17 to Day-1), **Pre-treatment,** (Day 1 to Day 7), 8-Week **Treatment Period** (Day 8-63), a 4-Week Short Term Safety Follow-up Period (Day 64-92) and a Long Term Safety Follow-up Day 93 - 246). Approximately 55 adult subjects with mild-to-moderate ulcerative colitis will be enrolled.

Screening includes 2 screening visits. At the first **Screening Visit, (V**isit 1), subjects will be checked for inclusion/exclusion criteria, and medical history and demographic data will be collected. At the second Screening Visit, (Visit 2) eligible subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsy within 17 days from the Screening visit and prior to Study Day 1. Subjects will be on a clear liquid diet 1 day before the lower endoscopy (flexible sigmoidoscopy or colonoscopy). On the day of the procedure, the subject will administer a bowel prep at the PI discretion (e.g., 2 Fleets enemas) and fast for 6 hours before the procedure.

Endoscopy images will be obtained during each endoscopy and will be sent for independent central reading and determination of the modified Mayo endoscopic subscore. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment to be used for video capture and transmission of endoscopic recordings. For each subject, video recording of the entire endoscopic procedure will be performed using a storage medium provided by the sponsor or designee. The endoscopic recordings will be read centrally in a blinded manner by a qualified gastroenterologist according to the image review charter. The modified Mayo score used for clinical endpoints in the trial will use the modified Mayo endoscopy subscore determined by the central reader.

The Total modified Mayo score is a composite score. Only the modified Mayo endoscopic subscore is determined by central reader and provided to the clinical site. If the partial Mayo score changes from Visit 1 to Visit 2, the Visit 2 score should be used in computing the Total modified Mayo score at Baseline and when assessing the subject for the safety stopping rules. Subjects who meet the inclusion criteria (Total modified Mayo score of 4 to 10, inclusive and modified Mayo endoscopic subscore of $\geq$ 1, with evidence

of mucosal lesions), will be randomized using an interactive web/voice response system (IxRS) to 1 of 4 treatment groups on Study Day 1 and initiate the pre-treatment regimen.

During the **Pre-Treatment** period (Day 1 to Day 7) oral vancomycin 125 mg four times a day (qid) or matching placebo will be administered for 6 days.

During the 8-Week **Treatment Period,** all subjects will come to the clinic weekly for drug dispensing and asked about adverse events (AEs), change in medications and the partial Mayo score assessment (scores should reflect the 24-hour period prior to reporting. The endoscopy procedure day or preparation day should not be included). All subjects will have a lower endoscopy (flexible sigmoidoscopy or colonoscopy) at Visit 12/Early Termination +/- 3 days to evaluate endoscopic disease activity. Subjects will be on a clear liquid diet the day before the lower endoscopy (flexible sigmoidoscopy or colonoscopy). On the day of the procedure, the subject will self-administer a bowel prep per the PI instructions (e.g., 2 Fleets enemas) and fast for 6 hours before the procedure. All subjects will have an in-clinic visit at Visit 12/Early Termination +/- 3 days.

Subjects will then enter the **Short Term Safety Follow-up Period** in which subjects will be contacted by phone on Days 71, 78, 85 +/- 2 days. Subjects will be asked about adverse events (AEs), concomitant medications and will complete disease activity assessment which includes stool frequency and rectal bleeding, two subscores from the total modified Mayo score. All subjects will have an in-clinic safety visit at Visit 13 +/- 2 days.

Subjects will then enter the **Long Term Safety Follow-up Period** in which subjects will be contacted by phone on Days 246 +/- 3 days. Following Visit 13 through Day 246/ET only SAEs and concomitant medications associated with SAEs will be collected.

To ensure safe study conduct during the Phase 1b study, an independent, unblinded, external Data and Safety Monitoring Committee (DSMC) will be established to perform safety evaluations on an ongoing basis. A DSMC charter will be developed and will detail the review of the safety data.

3.2 Criteria for Evaluation of the Study

The evaluation of the safety data will be performed by comparison of the safety endpoints across the treatment arms. The following safety endpoints will be assessed for the comparison:

- Incidence of adverse events
- Incidence of adverse events of special interest
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

The evaluation of the efficacy data will be performed by comparison of the efficacy endpoints across the treatment arms. The following efficacy endpoints will be assessed across treatment arms at various time points between Visit 1 and Visit 13:

- Composition of the intestinal microbiome
- Engraftment of SER-287 bacteria in all treatment arms
- Clinical response defined as:
    - A decrease of ≥3 points in Total modified Mayo score (TMMS) from baseline, along with **EITHER** a decrease of ≥1 point in rectal bleeding subscore **or** absolute rectal bleeding subscore of 0 or 1
- 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
- Endoscopic improvement, defined as a decrease in endoscopic subscore ≥ 1
- Serum biomarker [C-reactive protein (CRP)]
- Fecal biomarker (fecal calprotectin) levels

The following exploratory endpoints may also be evaluated across the treatment arms at various time points between Visit 1 and Visit 13:

- 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

4 STUDY POPULATION

The study population will consist of adult ≥18 years of age with mild-to-moderate ulcerative colitis. Subjects must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

To be eligible for enrollment, a subject must meet all of the following criteria before undergoing any study-related procedures:

1. Signed informed consent
2. Male or female ≥18 years of age
3. Ulcerative colitis diagnosed by routine clinical, radiographic, endoscopic and pathologic criteria (preferably confirmed by colonoscopy and pathology records within last 2 years or if unavailable, will need approval by medical monitor)
4. Active mild-moderate UC as determined by lower endoscopy (flexible sigmoidoscopy or colonoscopy) within approximately 3 days of randomization to study
    a. Total Modified Mayo score of 4 to 10, inclusive
    b. Modified Mayo endoscopic subscore of ≥ 1, with evidence of mucosal lesions
    c. At least 15 cm of disease from anal verge
5. If female, subject is non-lactating, and is either:
    a. Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy
    b. Of childbearing potential and is practicing at least 1 highly effective method of birth control including the barrier method; oral or parenteral contraceptives; a vasectomized partner; or abstinence from sexual intercourse. The investigator will discuss with the subject the option of practicing more than 1 of the above methods for the duration of the study
6. If male and partner is of childbearing potential, subject agrees to practice at least one highly effective method of birth control for the duration of the study

4.2 Exclusion Criteria

A subject will not be enrolled if the subject meets any of the following criteria:

1. Fever ≥ 38.3°C
2. Known or suspected toxic megacolon and/or known small bowel ileus
3. Known history of Crohn's disease
4. Subjects with serum albumin ≤2.5 g/dL at baseline
5. CMV polymerase chain reaction (PCR) positive from blood plasma at screening
6. Known stool tests positive for ova and/or parasites or stool culture within the 30 days before enrollment
7. Subjects on cyclosporine or triple immunosuppression, Triple immunosuppression will include any three of the following classes of drugs taken in combination: steroids (i.e., prednisone/budesonide/budesonide MMX®),

immunosuppressant (i.e., methotrexate/azathioprine/6-mercaptopurine), and/or other immunosuppressant (i.e., tacrolimus, cellcept).

8. Biologic medication (infliximab/ adalimumab/ golimumab/ certolizumab/vedolizumab/ustekinumab/natalizumab) use within 3 months prior to screening
9. Known active malignancy except for basal cell skin cancer, squamous cell skin cancer
10. Subjects with previous colectomy, ostomy, J-pouch, or previous intestinal surgery (excluding cholecystectomy, appendectomy)
11. Subjects with known history of celiac disease or gluten enteropathy
12. Subjects with *Clostridium difficile* positive stool performed by the Central lab at Screening Visit
13. Antibiotic use within the prior 1 month before randomization
14. Expected to receive antibiotics within 8 weeks of signing the Informed Consent Form (ICF) (i.e., for planned/anticipated procedure)
15. Received an investigational drug within 1 month before study entry
16. Received an investigational antibody or vaccine within 3 months before study entry
17. Previously enrolled in a SER-109/SER-287 study
18. Received an FMT within the last 6 months
19. Poor concurrent medical risks with clinically significant co-morbid disease such that, in the opinion of the investigator, the subject should not be enrolled including:
    a. Subjects with decompensated liver cirrhosis (Child-Pugh Class B or C) or uncontrolled liver disease
    b. Prior history of bone marrow transplant
    c. Known Hypogammaglobulinemia
    d. Known severe immunodeficiency
    e. Underlying liver function test (LFT) [screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] abnormalities greater than 2x upper limit of normal (ULN)
    f. Absolute neutrophil count (ANC) <500
20. Subjects with anatomic or medical contraindications to lower endoscopy (flexible sigmoidoscopy or colonoscopy), including but not necessarily limited to toxic megacolon, gastrointestinal (GI) fistulas, immediate post-operative status from abdominal surgery, severe coagulopathy, large or symptomatic abdominal aortic aneurysm, or any subject where study physician deems subject at significant risk of complications of lower endoscopy (flexible sigmoidoscopy or colonoscopy)
21. Unable to stop steroid enemas or suppositories or mesalamine enemas or suppositories before screening visit
22. Unable to stop opiate treatment unless on a stable dose and no increase in dose planned for the duration of the study
23. Unable to stop probiotics before screening visit
24. Concurrent intensive induction chemotherapy, radiotherapy, or biologic treatment for active malignancy (subjects on maintenance chemotherapy may only be enrolled after consultation with medical monitor)

25. Unable to comply with the protocol requirements
26. Any condition that, in the opinion of the investigator, might interfere with study objectives
27. Known allergy or intolerance to oral vancomycin
28. Known active intravenous drug or alcohol abuse or use of other drugs of abuse

4.3 Subject Withdrawal and Replacement

Subjects should continue to be followed for safety assessments through 24 weeks after treatment, even after being discontinued from study medication. However, a patient may withdraw from the study at any time for any reason, without any consequence.

Subjects may be required to withdraw from study after discussion with the Sponsor and/or Investigator for the following reasons:

- Pregnancy (see Section 6.2.2.4);
- Adverse event(s);
- Met at least one of the safety halting rules (see Section 6.2.2.1)
- At the discretion of the Investigator
- Protocol violation
- Non-compliance

In all cases, the reason(s) for withdrawal will be recorded on the electronic data capture (EDC) system. If a subject is prematurely withdrawn from the study drug for any reason before Visit 12, the Investigator must make every effort to perform the evaluations described for Follow Up Visit 12.

If a subject withdraws consent and still agrees to undergo a final examination, this will be documented on the EDC system and the Investigator's copy of the ICF, which will be countersigned and dated by the subject.

A subject may also be withdrawn from study by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs).

Subjects will also be withdrawn if the entire study is terminated prematurely.

If a subject fails to appear for a follow-up assessment, all attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible (i.e, 3 documented contact attempts via phone calls, e-mail, etc., on separate occasions will be made to locate or contact them, or at least to determine their health status).

Subjects who discontinue from the study after randomization may be replaced.

4.4 Planned Sample Size and Number of Study Centers

Approximately 55 subjects will be enrolled at approximately 20 sites in the United States (US).

4.5 Subject Identification and Randomization

4.5.1 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.

4.5.2 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.

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. Similarly, study drug assigned to a subject may not be re-used, even if the bottle is returned unopened.

During the double-blind period, subjects, the investigators and 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.

4.5.3 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. If a medical emergency requiring unblinding occurs, the investigator (or designated physician) is strongly encouraged to contact the medical or safety monitor to assess the necessity of breaking the study drug blind. If unblinding is warranted, the investigator will obtain the treatment assignment information from the IxRS. Every effort is to be made to limit study site personnel unblinding only to those individuals providing direct care to that subject. Any intentional or unintentional breaking of the blind is to be reported immediately to the sponsor. The other circumstances in which unblinding may be necessary are at the request of a subject who becomes pregnant during the study or for

regulatory reporting purposes.

If the blind is broken, the date, time, and reason must be recorded in the patient's EDC system, and any associated AE report.

If a subject is unblinded, they will not receive any additional study medications.

After the statistical analysis plan (SAP) is final and the primary study period (Visit 1 through Visit 13) data is declared complete and final, the study blind codes will be broken.

5 INVESTIGATIONAL PRODUCT

5.1 SER-287

5.1.1 Donor Screening

Donors undergo a general health examination including GI medical history, familial GI medical history, clinical chemistry, hematology with complete blood count, urinalysis, and blood and fecal viral and bacterial pathogen testing before donating stool. The donor must successfully complete the physical screening and laboratory tests after the donation period before the material can be released for manufacturing. A description of donor screening procedures is provided in the Investigator's Brochure.

5.1.2 SER-287 Manufacturing

SER-287 is manufactured as SER-109 using current Good Manufacturing Practice - compliant processing steps, and is subsequently released using assays for purity, potency, and identity. The manufacturing process inactivates non-spore forms of bacteria, fungi, and other potential components (parasites and some viruses), substantially reduces the amount of undigested food and inactivated vegetative biomass via successive filtration steps, and formulates the drug substance in 92% glycerol and approximately 8% saline solution (0.9% of sodium chloride), containing less than about 30 mg of non-spore solids. The drug substance is filled into capsules, and then over-encapsulated. For each unit-dose bottle, four capsules (1×10^8 SporQs) are packaged in an HDPE container, induction sealed with foil and closed with child resistant closures. At the time of labeling for investigational use the drug product becomes SER-287. SER-287 is odorless and tasteless as prescribed. If chewed or if capsule integrity is compromised, SER-287 has a sweet taste.

Study drug will be packaged by Catalent Pharma Solutions according to all local legal requirements. Study drug will be labeled in accordance with applicable regulatory requirements.

5.2 Over-encapsulated (OE) Vancomycin HCl 125 mg Capsules, Hard Gelatin Capsules ("Vancomycin")

5.2.1 Vancomycin HCl Procurement, Over-encapsulation, Packaging and Storage

Commercially available Vancomycin HCl 125 mg Capsules, USP, in 20-capsule blister packs are de-blistered and over encapsulated in size 00 Swedish Orange Capsules with microcrystalline cellulose backfill. Capsules are filled into 40 mL white high density polyethylene (HDPE) bottles, induction sealed with a foil seal and closed with child resistant closures. Each bottle is filled with 24 capsules. Bottles are stored at ambient temperature.

5.3 SER-287 Placebo Capsules

5.3.1 SER-287 Placebo Manufacturing

Placebo will be identical to the Investigational Product SER-287 but will not contain product spores or non-spore solids. Placebo will consist of 92% glycerol and approximately 8% saline solution (0.9% of sodium chloride). The SER-287 Placebo will be provided in a single-dose container of 4 white, size 00 capsules in a foil-sealed, opaque, 40 mL HDPE bottle with child resistant closures. At the time of labeling for investigational use the placebo becomes SER-287 placebo. The SER-287 placebo is odorless and tasteless as prescribed. If chewed or if capsule integrity is compromised, SER-287 placebo has a sweet taste.

5.4 Vancomycin HCl Placebo Capsules ("Vancomycin Placebo")

5.4.1 Vancomycin HCl Placebo Manufacturing and Storage

Vancomycin HCl placebo is manufactured in size 00 Swedish Orange Capsules. Capsules are filled with microcrystalline cellulose and filled into 40 mL white HDPE bottles. Bottles are induction sealed with a foil seal and closed with child resistant closures. Each bottle is filled with 24 capsules. Bottles are stored at ambient temperature.

5.5 Storage

5.5.1 SER-287 and SER-287 Placebo Storage

SER-287 or placebo bottles are assembled into weekly kits and stored at or below -15°C at the distribution depot. Kits are shipped to the clinical site on dry ice. Kits are stored at or below -15°C at the clinical site until dispensed to the subject. Subjects are instructed to store kits at home in the refrigerator (2°C-8°C). For more information on storage, refer to the Study Manual.

The doses, route, and schedule of study drug administration are shown in Table 1, below:

Table 1: Doses, Route, and Schedule of Study Drug Administration

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

d = day; Pbo = placebo; qid = Four times a day; wk = week; admin= administration; vanco=vancomycin; SporQs= spore equivalents

After the primary study period (Visit 1 to Visit 13) data is declared complete and final, the overall randomization code will be broken only for reporting purposes. The record of randomization will include study arm assignment and also the association of treatment kit number with donor group.

5.6 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

Vancomycin or Vancomycin placebo are provided in sealed bottles containing 24 capsules. The seal on a given bottle should be punctured at the time of subject randomization to perform drug accountability at the capsule level. Each bottle should be stored unopened and intact until dispensed to the subject.

SER-287 or SER-287 placebo are provided in sealed bottles containing four capsules. The seal on a given bottle should only be removed at the time of administration. Each bottle should be stored unopened and intact until time-of-use. Drug accountability at the

clinical site should be done both at the kit level and at the individual unit-dose bottle level.

5.7 Prior and Concomitant Medications

Any medication the subject takes through Visit 13 other than the study drug (vancomycin and SER-287), including herbal and other non-traditional remedies, is considered a concomitant medication. Following Visit 13 through Day 246/ET only concomitant medications associated with SAEs will be collected. All concomitant medications must be recorded in the EDC system. The following information must be recorded in the EDC system for each concomitant medication: generic name (or trade name if generic is not known), route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the EDC system.

At Screening, subjects will be asked about all current and prior IBD medications they have taken and in addition all medications taken during the last 6 months (non-IBD related) At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

Permitted concomitant medications include:

- Oral aminosalicylates (Aminosalicylates taken for at least 6 weeks, with a stable dose for $\geq$ 2 weeks prior to screening)
- Immunomodulator: 6-Mercaptopurine, Azathioprine, Methotrexate (Stable dose for $\geq$ 12 weeks prior to screening)
- Prednisone $\leq$ 15 mg (Stable dose for $\geq$ 2 weeks prior to screening)
- Budesonide $\leq$ 6 mg (Stable dose for $\geq$ 2 weeks prior to screening
- Budesonide MMX® $\leq$ 9 mg (Stable dose for $\geq$ 2 weeks prior to screening)
- Opiate treatment (stable dose)
    - Short term opiate use is permitted
    - Short term use of non-steroidals/NSAIDS, is permitted
    - Low dose aspirin (81mg) is permitted for long-term use

Subjects who are receiving any of the above permitted concomitant medications at the time of study entry must keep their dosage stable throughout the study, unless investigator judgment requires it to be increased, reduced or discontinued for safety concerns or medical necessity. If there is a change in dosage, the subject would then be discontinued from the study.

The following **prohibited concomitant medications may not** be administered at any time through the study period. Subjects who initiate the following treatments will be discontinued from further study agent administration.

- Probiotics
- Loperamide, diphenoxylate/atropine, or bile-salt sequestrant (cholestyramine, colesevelam)
- Cyclosporine or triple immunosuppression
- Biologic medication (infliximab/ adalimumab/ golimumab/ certolizumab/ vedolizumab/ ustekinumab/ natalizumab)

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Microbiome Alterations and Engraftment Primary Endpoints

6.1.1 Microbiome Alterations

Stool samples will be analyzed to characterize changes in the microbiome and associated functional metabolic changes in the gastrointestinal tract at various time points between Visit 1 and Visit 13.

Composition of the intestinal microbiome

Composition of the intestinal microbiome will be assessed at time points between Visit 1 and Visit 13.

Engraftment of SER-287 bacteria

Engraftment is defined as the outgrowth of bacteria that comprise the SER-287 spore ecology in a subject's gastrointestinal tract post-treatment. Engraftment of SER-287 bacteria will be assessed at time points between Visit 4 and 13.

Secondary Endpoints

6.1.2 Clinical Response, Complete Remission, and Endoscopic Improvement

Partial Mayo score, which is the Mayo Score without the endoscopic subscore, will be assessed at each visit and the Total modified Mayo score (TMMS) will be assessed at baseline and at Visit 12 (or early termination)

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

Complete remission is defined as:

- A TMMS ≤2 and an endoscopic subscore of 0 with no erythema, no blood and no evidence of inflammation

Endoscopic improvement is defined as:

- a decrease in the modified Mayo endoscopic subscore ≥ 1

6.1.3 Biomarkers

The following biomarkers will be evaluated at time points between Visit 1 and Visit 13.

- Serum biomarkers (CRP)
- Fecal biomarkers (fecal calprotectin) levels

6.1.4 Exploratory Endpoints

The following exploratory endpoints may be evaluated. Please refer to schedule of assessments for times collected.

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

6.2 Safety Variables

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

6.2.1 The Safety Endpoints

- Incidence of adverse events
- Incidence of adverse events of special interest
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

6.2.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject who was administered study drug, regardless of its causal relationship to the study drug. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be related to the study drug.

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization; hospital admissions and/or surgical operations scheduled to occur during the study period, but planned before study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not worsen in any unexpected manner during the study (e.g., surgery performed earlier than planned).

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a subject's ability to conduct normal life functions.
- Is associated with a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate.

In this protocol, a **UC flare**, as defined in Section 6.2.2.1 below, has been designated as an AESI and as such will be reported and followed in the same manner as a SAE during the course of the study.

All AEs, including SAEs, will be graded for severity by using the following grading system:

- Mild: Events require minimal or no treatment and do not interfere with the subject's daily activities
- Moderate: Events result in a low level of inconvenience or concern and may require treatment; moderate events may cause some interference with functioning
- Severe: Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment; severe events are usually incapacitating

Changes in the severity of an AE will be documented, and documentation will include assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent will be documented based on the severity, onset, and duration of each episode.

An abnormal laboratory test finding that meets any of the criteria below will be considered an AE:

- Is associated with accompanying symptoms
- Requires additional diagnostic testing or medical/surgical intervention
- Leads to a concomitant drug treatment or any change in a concomitant medication or therapy
- Is considered an AE by the Investigator

Laboratory results that fall outside the reference range and do not meet 1 of the criteria above will not be reported as AEs. Repeating a test because of an abnormal result, in the

absence of the above conditions, does not constitute as AE. Any abnormal test result that is determined to be an error will not be reported as an AE.

For all AEs, including SAEs, the Investigator will report on the relationship of the AE to the study drug by using the following definitions:

- Unrelated: There is little or no chance that the study drug caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event
- Related or Possibly Related: The association of the AE with the study drug is unknown; however, the AE is not clearly due to another condition, or a reasonable temporal association exists between the AE and treatment administration and, based on the Investigator's clinical experience, the association of the AE with the study drug seems likely

Adverse events, including local and systemic reactions not considered medically serious, will be recorded. Information to be collected includes event description, time of onset, Investigator assessment of severity, relationship to study drug, date of resolution of the event, seriousness, and outcome.

Any medical condition that is present at the time that the subject is screened will be considered as a baseline condition and not be reported as an AE. However, if it worsens at any time during the study, it should be recorded as an AE.

All AEs, SAEs and AESIs will be collected from Informed Consent up to Visit 13. Following Visit 13 through Day 246, only SAEs will be collected. All AEs, including SAEs and AESIs, will be monitored until resolution or determined by the Investigator to be due to a subject's stable or chronic condition or intercurrent illness.

The Investigator is responsible for:

- Informing the sponsor in the event that a patient or a subject's partner becomes pregnant during the study. A "Pregnancy Report Form" will be generated and the pregnancy will be captured in the safety database and will be followed through to the outcome.
- Evaluating subject safety including assessment of AEs for seriousness, severity, and causality.

Informing the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of AEs as required and SAEs as per IRB/IEC guidelines.

6.2.2.1 Safety Halting Rules

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

Individual halting rules include:

- UC flare, defined by: 1) an increase by 2 points from screening of partial Mayo score at two contiguous visits after SER-287/placebo initiation (if the partial Mayo score changes from Visit 1 to Visit 2, the Visit 2 score should be used in computing the

partial Mayo score at Baseline for the individual halting rules), AND 2) worsening clinical status warranting change in UC treatment as determined by principal investigator.

- Any SAE that is serious, related to study drug, and unexpected, which when referred to the DSMC the recommendation is to withdraw the subject from the study.

If a subject meets the criteria above for at least one of the individual halting rules, he/ she will be discontinued from the study.

6.2.2.2 Reporting Serious Adverse Events

The Investigator must report any SAEs and AESIs to the PAREXEL Medical Services Safety Contact within 24 hours of becoming aware of the event by completing and transmitting the Serious Adverse Event report form by fax or email to the PAREXEL Safety Contact noted below. If questions arise regarding the reporting procedures or the specifics of the reporting event or the site needs to report the event by phone, the investigator may call the Safety Contact listed below. A phone report will need to be followed by faxing or emailing the written SAE report form within the next 24 hours.

The Sponsor (or Sponsor's designated agent) will review each SAE report in detail and will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for expedited reporting to regulatory authorities.

SERIOUS ADVERSE EVENT/ADVERSE EVENTS OF SPECIAL INTEREST REPORTING INSTRUCTIONS

PAREXEL International Corporation

North America Medical Services

Telephone Number: +1-781-434-5010

Fax Number: +1-781-434-5957

Email: NorthAmerica_Medical@PAREXEL.com

Fax the SAE/AESI report form and any supporting documentation to the PAREXEL Medical Services Safety Team within 24 hours of becoming aware of the event.

The SAE/AESI report form should be completed in its entirety as much as possible. If only a partial SAE report is available, preliminary information will be documented on the SAE/AESI Report Form and transmitted to the PAREXEL Safety contact within 24 hours of site awareness. The minimum information required for an initial report is:

- Name of person sending the report (i.e., name, address of Investigator);
- Subject identification (screening/randomization number, initials, NOT subject name);
- Protocol number;
- Description of SAE/AESI;
- Causality assessment, if possible.

When additional relevant information is available, the SAE/AESI report form will be updated with the new information and submitted within 24 hours of site awareness of this new information. The event must be documented in the eCRF.

6.2.2.3 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, until it is unlikely that any additional information can be obtained, or until the subject has died.

6.2.2.4 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the Investigator to PAREXEL/Sponsor on the initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to PAREXEL/Sponsor on the pregnancy outcome report form within 24 hours after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs

If a female partner of a male study subject who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

In the event of pregnancy, the pregnancy should be followed until the outcome of the pregnancy is determined.

6.2.3 Laboratory Variables

Laboratory assessments will be performed by a central laboratory, as identified in the List of Study Personnel.

Blood samples will be taken using standard venipuncture techniques. A laboratory manual will be provided by the central laboratory. This laboratory manual will contain detailed instructions for collection, storage, and shipment of samples (e.g., what kind of tubes, what kind of sample preparation, mailing addresses, etc.).

The following laboratory variables (Table 2) will be determined in accordance with the Schedule of Events (Table 3).

Table 2: Laboratory Assessments

Hematology:	erythrocytes mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) neutrophils eosinophils basophils lymphocytes monocytes platelets leukocytes hemoglobin hematocrit	Urinalysis[1]:	pH protein glucose ketone bilirubin blood nitrite leukocyte esterase
Clinical chemistry:	creatinine glucose triglycerides urea uric acid cholesterol albumin	Liver enzymes:	ALP AST ALT GGT direct and indirect bilirubin total bilirubin
Electrolytes:	sodium potassium		
Pregnancy test[2]:	In women with childbearing potential only		

ALP = alkaline phosphatase; ALT = alanine aminotransaminase; AST = aspartate aminotransferase; CBC = complete blood count; GGT = γ-glutamyl transferase; RBC = red blood cells; WBC = white blood cells.

[1] Urinalysis will be performed by dipstick. If nitrates or leukocytes are positive, a microscopic examination will be performed by the central laboratory.

[2] A serum pregnancy test will be done at Screening. Urine pregnancy tests will be done at Visit 3 (Day 1), Visit 12 (Day 64 ± 3) and at Visit 13 (Day 92 ± 1).

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance and should be recorded as an AE. Actual laboratory results will not be captured on the EDC system. However, if any laboratory results meeting the reporting requirements for an AE, the event term (e.g., elevated transaminase) will be recorded on the EDC system as an AE or SAE, as applicable.

6.2.4 Stool Samples

Stool samples will be collected by the subjects and brought to the clinic at Visit 1, Visit 4, Day 11, Visit 5, Day 18, Visit 6, Visit 12 and Visit 13 or the Early Termination Visit (if applicable), and any Unscheduled Visit.

6.2.5 Biopsy Samples

A total of 4 biopsies will be obtained between 15 and 30 cm of the colon both at Visit 2 and at Visit 12. One biopsy sample will be placed in formalin and 3 biopsies will be placed in RNALater. At the clinical site, samples will be processed and then shipped to the central laboratory according to procedures defined in the Laboratory Manual.

6.2.6 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Events (Table 2):

- Blood pressure (BP; systolic and diastolic; mmHg);
- Heart rate (HR; beats per minute);
- Oral body temperature (°C);
- Respiration rate (breaths per minute).
- Height (taken at Screening only)
- Weight

The Investigator or designee will indicate whether or not a value is of clinical significance and should be recorded as an AE.

6.2.7 Electrocardiograms

Standard 12-lead ECGs will be performed in accordance with the Schedule of Events (Table 2).

Standard safety 12-lead ECGs (single reading) will be performed at Day 8 (before dosing), and at Follow-Up on Day 92 as shown in Table 2, the Schedule of Events.

All ECGs will be evaluated by a qualified physician or delegate for the presence of abnormalities. The Investigator or designee will indicate whether or not a value is of clinical significance and should be recorded as an AE. The ECG data will be collected as: Normal; Abnormal, Not Clinically Significant; and Abnormal, Clinically Significant.

6.2.8 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Events (Table 2).

The physical examination includes an assessment of general appearance and evaluation of the following: Head/Eyes/Ears/Nose/Throat; Neck; Lungs and Heart; Abdomen; Extremities; Neurological; Other.

Abnormal clinically significant findings will be reported as medical history or AEs as determined by Investigator.

6.3 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics consist of those variables that are assessed only at screening/baseline.

6.3.1 Subject Demography

- Age at screening;
- Sex;
- Height;
- Weight;
- 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).

6.3.2 Disease History

For disease history the following will be documented:

- Date of first diagnosis;
- Montreal classification

6.3.3 Baseline Characteristics

- General medical history
- General surgical history
- Smoking history

6.3.4 Medical History

For the documentation of the medical history, any previous and concomitant diseases before screening will be documented. The medical history will be obtained by interviewing the subject or by inspecting his/her medical records.

6.3.5 Prior and Concomitant Medications

Prior and concomitant medication will be documented as described in Section 5.7. Prior and concomitant medications will be coded using the WHO Drug Dictionary.

7 STUDY CONDUCT

7.1 Schedule of Events

The study consists of a Screening Visit (Days -17 to -1), a Screening Visit for lower endoscopy (flexible sigmoidoscopy or colonoscopy) (at least 3 days before Day 1), a pretreatment period (Days 1 to 7), a treatment period (Days 8 to 63), and Short Term Safety Follow-up (Day 64 to 92) and a Long Term Safety Follow-up (Day 93-246). The maximal study duration for an individual subject will be 260 days.

The Schedule of Events is presented in Table 3.

Table 3: Schedule of Events

	Screening with lower endoscopy (flexible sigmoidoscopy or colonoscopy) (Day -17 to Day -1)		Pre-Treatment Period (Day 1-7)	Treatment Period (Day 8-Day 63)										Safety Follow Up Period (Day 64-246)			
VISIT NAME	Visit 1	Visit 2	Visit 3	Visit 4		Visit 5		Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ET (j)	Phone calls	Visit 13	Phone call
VISIT DAY			Day 1	Day 8 +/- 1d		Day 15 +/-1d		Day 22+/-1d	Day 29 +/-1d	Day 36 +/-1d	Day 43 +/-1d	Day 50 +/-1d	Day 57+/-1d	Day 64+/-3d	Weekly on Days 71, 78, 85+/-2d	Day 92+/-2d	Day 246 +/-3d
					Day 11(d)		Day 18(d)										
Visit/Phone Call	Visit	Visit for sigmoidoscopy(f)	Visit	Visit	Stool sample	Visit	Stool sample	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Phone call	Visit	Phone call
Pre-Treatment Drug Dosing			X (c)														
Study Drug Dosing				X(c)	←								→				
Informed consent	X																
Inclusion/ Exclusion Criteria	X	X															
Central Reading Results			X (o)											X			
Medical history	X																
Randomization			X														
Demographic data	X																
Physical Ex	X		X					X		X				X		X	
Vital signs (a)	X		X					X		X				X		X	
ECG				X (b)												X	
Bowel Prep (i)		X												X			
Lower Endoscopy		X												X			
Overnight Fast (required for endoscopy; when possible for other visits)		X (k)	X	X				X		X				X (k)		X	
Blood Testing																	
Hematology	X (g)		X (b)	X(b)						X				X			
Clinical chemistry	X (g)		X(b)	X(b)						X				X			
CMV PCR (l)	X (g)																
Pregnancy test (WOCBP)	X (g)																
Blood for biomedical research			X (b)											X			
Blood for metabolomics	X (h)			X (b)				X		X				X		X	
Blood for CRP	X			X (b)				X		X				X		X	
Serum Cytokine	X (h)													X			

Table 3: Schedule of Events (continued)

	Screening with lower endoscopy (flexible sigmoidoscopy or colonoscopy) (Day -17 to Day -1)		Pre-Treatment Period (Day 1-7)	Treatment Period (Day 8-Day 63)										Safety Follow Up Period (Day 64-246) Short Term Safety Follow-up (Day 64 to 92) and a Long Term Safety Follow-up (Day 93-246).			
VISIT NAME	Visit 1	Visit 2	Visit 3	Visit 4		Visit 5		Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ET (j)	Phone calls	Visit 13	Phone call
VISIT DAY			Day 1	Day 8 +/- 1d		Day 15 +/-1d		Day 22+/-1d	Day 29 +/-1d	Day 36 +/-1d	Day 43 +/-1d	Day 50 +/-1d	Day 57+/-1d	Day 64+/-3d	Weekly on Days 71, 78, 85+/-2d	Day 92+/-2d	Day 246 +/-3d
					Day 11(d)		Day 18(d)										
Visit/Phone Call	Visit	Visit for lower endoscopy (flexible sigmoidoscopy or	Visit	Visit	Stool sample	Visit	Stool sample	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Phone call	Visit	Phone call
Urine Testing																	
Urine Pregnancy			X											X		X	
Urinalysis (e)	X			X (b)						X				X			
Stool Testing																	
Stool for Microbiome	X (h)			X (b)	X	X	X	X						X		X	
Stool for Microbial Culture	X (h)			X (b)	X	X	X	X						X		X	
Stool for Metabolomics	X (h)			X(b)	X			X						X		X	
Stool for cdiff	X (g)																
Stool for Fecal calprotectin	X (h)			X (b)				X						X		X	
Biopsies																	
Mucosal Transcriptomics (2 samples)		X												X			
Mucosal Microbiome (1sample)		X												X			
Histopathology with CMV Stain (1 sample)		X												X			

Table 3: Schedule of Events (continued)

	Screening with lower endoscopy (flexible sigmoidoscopy or colonoscopy) (Day -17 to Day -1)		Pre-Treatment Period (Day 1-7)	Treatment Period (Day 8-Day 63)										Safety Follow Up Period (Day 64-246) Short Term Safety Follow-up (Day 64 to 92) and a Long Term Safety Follow-up (Day 93-246).			
VISIT NAME	Visit 1	Visit 2	Visit 3	Visit 4		Visit 5		Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ET (j)	Phone calls	Visit 13	Phone call
VISIT DAY			Day 1	Day 8 +/- 1d		Day 15 +/-1d		Day 22+/-1d	Day 29 +/-1d	Day 36 +/-1d	Day 43 +/-1d	Day 50 +/-1d	Day 57+/-1d	Day 64+/-3d	Weekly on Days 71, 78, 85+/-2d	Day 92+/-2d	Day 246 +/-3d
					Day 11(d)		Day 18(d)										
Visit/Phone Call	Visit	Visit for sigmoidoscopy(f)	Visit	Visit	Stool sample	Visit	Stool sample	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Phone call	Visit	Phone call
Study Drug Dispensation																	
Dispense pre-trtmt drug			X														
Return pre-trmt drug				X													
Dispense study drug (q)				X		X		X	X	X	X	X	X				
Return study drug						X		X	X	X	X	X	X	X			
Other																	
Diet Inventory	X			X				X						X			
Partial Mayo score	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Total modified Mayo score		X												X			
Adverse event reporting (p)	←																→
Concomitant medications (n)	←																→

BP = blood pressure; cdiff = *Clostridium difficile* ; CMV = cytomegalovirus; Cx = Culture; d = day; CRP = C-reactive protein; ECG = electrocardiogram; ET = early termination; EX = exam; Flex = flexible; HR = heart rate; PCR = polymerase chain reaction; prep = preparation; RR = respiration rate; Sig = sigmoidoscopy; Wk = week; WOCBP = women of childbearing potential.

Notes: (a) Height on screening only; BP, RR, HR, Temp and weight at all vital signs assessments; (b) Prior to dosing; (c) 1st dose observe 1 hr post-dosing; (d) As close to scheduled day as possible ; (e) Urinalysis will be performed by dipstick; If nitrates or leukocytes are positive, a microscopic examination will be performed by the central laboratory (f) Must be performed at least 3 days before Day 1; (g) Sample needs to be obtained and results reviewed prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy) ; (h) Obtain sample and hold. Only samples from subjects that are randomized will be analyzed; (i) Clear liquid diet day before procedure with bowel prep at PI discretion (e.g. two Fleets enemas 1.5 hours before procedure); (j) Subjects who terminate prior to Visit 12 will have a lower endoscopy (flexible sigmoidoscopy or colonoscopy) at the Early Termination visit; (k) Beginning the night before the lower endoscopy (flexible sigmoidoscopy or colonoscopy); (l) Quantitative CMV testing on plasma; (n) Concomitant medications will be recorded from Week 12 through Day 246 only if they are associated with an AE; (o) Prior to randomization; (p) Following Visit 13 throughDay 246/ET only SAEs, and concomitant medications associated with SAEs will be collected; (q) Instruct subject to take study drug at the same time each day when possible

7.2 Procedures by Visit

Visits should occur within ± 1 day of the scheduled visit. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

7.2.1 Screening Day -17 to Day -1 (Visit 1)

- Obtain written informed consent for study;
- Verify conformance with inclusion/exclusion entry criteria;
- Record medical history;
- Record Demographics;
- Begin Adverse event monitoring;
- Record prior/concomitant medication history;
- Perform physical exam;
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature);
- Obtain weight and height
- Blood sampling for hematology, clinical chemistry, C-reactive protein (CRP);
- Urinalysis;
- Blood sampling for quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) testing on plasma;
- Blood sampling for metabolomics, serum cytokines
- Blood sampling for pregnancy test for women of childbearing potential (WOCBP);
- Stool sampling for *Clostridium difficile*, microbiome, microbial culture, metabolomics, fecal calprotectin;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Obtain diet inventory;

7.2.2 Screening Visit 2 Day -17 to Day -1 (Visit 2)

- Verify conformance with inclusion/exclusion entry criteria;
- Confirm subject has had no liquids 6 hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy);
- Confirm subject performed bowel preparation at PI discretion (e.g., two Fleets enemas 1.5 hours before procedure);
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy);
- Obtain biopsy for mucosal transcriptomics (2 samples);
- Obtain biopsy for histopathology with CMV stain (1 sample);
- Obtain biopsy for mucosal microbiome (1 sample);
- Obtain Partial Mayo score; scores should reflect the 24-hour period before initiation of bowel preparation.

  - Partial Mayo score at Screening Visit 2 should be used when calculating the Total modified Mayo score to determine subject eligibility.
- Obtain Total modified Mayo score;
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.3 Pretreatment Period Day 1 (Visit 3)

- Perform central review of results prior to randomization;
- Confirm eligibility with Medical Monitor pre-randomization
- Perform randomization;
- Begin pre-treatment drug dosing (observe subject 1 hour post-dosing)
- Perform physical exam;
- Assess vital signs (systolic and diastolic blood pressure, respiratory rate, temperature);
- Obtain weight;
- Blood sampling pre-dose for hematology, clinical chemistry;
- Blood sampling pre-dose for biomedical research;
- Obtain urine sample for pregnancy testing;
- Dispense pre-treatment drug;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.4 Treatment Period Day 8 ± 1 (Visit 4)

- Pre-dosing
  - Return any remaining pre-treatment drug and all bottles dispensed;
  - Begin treatment period drug dosing (observe subject 1 hour post-dosing);
  - Blood sampling pre-dose for hematology, clinical chemistry, C-reactive protein (CRP);
  - Perform 12-lead ECG;
  - Blood sampling pre-dose for metabolomics;
  - Urinalysis;
  - Stool sampling pre-dose for microbiome, microbial culture, metabolomics, fecal calprotectin;
- Dosing
  - Dispense study drug;
  - Obtain diet inventory;
  - Obtain Partial Mayo score;
  - Continue adverse event monitoring;

- Record concomitant medications.

7.2.5 Treatment Period Day 11 (as close to scheduled day as possible)

- Study drug dosing;
- Stool sampling for microbiome, microbial culture;
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.6 Treatment Period Day 15 ± 1 (Visit 5)

- Return study drug;
- Dispense study drug
- Study drug dosing;
- Stool sampling for microbiome, microbial culture;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications;
- Remind subject to begin overnight fast where possible the night prior to Visit 6.

7.2.7 Treatment Period Day 18 (as close to scheduled day as possible)

- Study drug dosing;
- Stool sampling for microbiome, microbial culture;
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.8 Treatment Period Day 22 ± 1 (Visit 6)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Perform physical exam;
- Blood sampling for C-reactive protein (CRP);
- Blood sampling for metabolomics;
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature);
- Obtain weight;
- Stool sampling for microbiome, microbial culture, metabolomics, fecal calprotectin;
- Obtain diet inventory;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.9 Treatment Period Day 29 ± 1 (Visit 7)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications.
- Remind subject to begin overnight fast where possible the night prior to Visit 8;

7.2.10 Treatment Period Day 36 ± 1 (Visit 8)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Perform physical exam;
- Blood sampling for hematology, clinical chemistry, C-reactive protein (CRP);
- Blood sampling for metabolomics;
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature);
- Obtain weight;
- Urinalysis;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.11 Treatment Period Day 43 ± 1 (Visit 9)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Obtain Partial Mayo score;
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.12 Treatment Period Day 50 ± 1 (Visit 10)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;

- Record concomitant medications.

7.2.13 Treatment Period Day 57 ± 1 (Visit 11)

- Return all unused study drug and any bottles dispensed;
- Dispense study drug;
- Study drug dosing;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications;
- Remind subject to begin overnight fast the night prior to the lower endoscopy (flexible sigmoidoscopy or colonoscopy).

7.2.14 Follow-up Period Day 64 ± 3 (Visit 12)/Early Termination

- Return all unused study drug and any bottles dispensed;
- Perform physical exam;
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature);
- Obtain weight;
- Confirm subject has had no liquids 6 hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy);
- Confirm subject has performed bowel preparation at PI discretion (e.g. two Fleets enemas 1.5 hours before procedure);
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy);
- Blood sampling for hematology, clinical chemistry, C-reactive protein (CRP);
- Urinalysis;
- Blood sampling for metabolomics, serum cytokines;
- Blood sampling for biomedical research;
- Obtain urine sample for pregnancy testing;
- Obtain biopsy for mucosal transcriptomics (2 samples);
- Obtain biopsy for histopathology with CMV stain (1 sample);
- Obtain biopsy for mucosal microbiome (1 sample);
- Stool sampling for microbiome, microbial culture, metabolomics, fecal calprotectin;
- Obtain diet inventory;
- Obtain Partial Mayo score; scores should reflect the 24-hour period before initiation of bowel preparation.
- Obtain Total modified Mayo score;
- Continue adverse event monitoring;
- Record concomitant medications;
- Remind subject to begin overnight fast where possible the night prior to Visit 13.

7.2.15 Follow-up Period Day 71 ± 2 (Phone Call)

- Obtain Partial Mayo score; Physician Rating of Disease Activity not collected
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.16 Follow-up Period Day 78 ± 2 (Phone Call)

- Obtain Partial Mayo score; Physician Rating of Disease Activity not collected
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.17 Follow-up Period Day 85 ± 2 (Phone Call)

- Obtain Partial Mayo score; Physician Rating of Disease Activity not collected
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.18 Follow-up Period Day 92 ± 1 (Visit 13)

- Perform physical exam;
- Assess vital signs (systolic and diastolic blood pressure, respiratory rate, temperature);
- Obtain weight;
- Perform 12-lead ECG;
- Blood sampling for C-reactive protein (CRP);
- Blood sampling for metabolomics;
- Obtain urine sample for pregnancy testing;
- Stool sampling for microbiome, microbial culture, metabolomics, fecal calprotectin;
- Obtain Partial Mayo score; scores should reflect the prior 24 hours
- Continue adverse event monitoring;
- Record concomitant medications.

7.2.19 Early Termination Visit

Subjects who discontinue early from the study before Visit 12 should, where possible, have an Early Termination visit. This visit should take place as soon as possible after the subject stops taking study drug. The observations and procedures scheduled for the Follow-Up Visit 12, including a urine pregnancy test, should be performed at the Early Termination visit.

For subjects who terminate between Visit 12 and 13, the observations and procedures scheduled for the Follow-Up Visit 13 should be performed.

7.2.20 Follow-up Period Day 246 ± 3 (Phone Call)

- Obtain Partial Mayo score; Physician Rating of Disease Activity not collected

- Continue adverse event monitoring;
- Record concomitant medications.

8 STATISTICAL METHODS

This study has a primary study period (from Visit 1 through Visit 13) followed by a long term safety follow-up period to Day 246. The primary study period will be conducted as a double-blind study. The final database for the primary study period will remain blinded until all data collected through Visit 13 has been entered, cleaned and declared complete and final. The CSR will be finalized after results from the primary study period are complete; all available data post-Visit 13 pertaining to mortality will be provided. Results of the long term safety period (through Day 246) will be presented in a separate report.

Before the primary study period data is declared complete and final, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

8.1 Study Subjects

8.1.1 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented, by treatment group.

8.1.2 Protocol Deviations

Protocol deviations will be listed by subject.

8.1.3 Analysis Sets

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 will be conducted based on the Safety Population.
Intent-to-Treat Analysis 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 randomly assigned.
Modified Intent-to-Treat Population:	The modified Intent-to-Treat (mITT) Population will consist of all randomized patients with baseline and at least one post-baseline stool sample, 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 response analyses will be conducted in the ITT population and in the mITT population as sensitivity analyses.

All microbiome alterations analyses will be conducted in the mITT population.

8.2 Endpoints for Analysis

8.2.1 Endpoints and Analysis for Primary Objectives

The primary endpoint for assessment of safety and tolerability will be AEs, classified to body system and preferred term as well as severity and causality. Other safety and tolerability endpoints are AESIs, laboratory evaluation results, vital sign measurements and physical examination findings. 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.

Composition of the microbiome at Visit 1, Visit 4, Visit 5, Visit 6, Visit 12, Visit 13, or at early termination will be measured in terms of both the total number of unique types of bacteria (i.e., α-diversity) and the microbial composition (i.e., β-diversity). Engraftment is defined as the germination and outgrowth of bacteria that comprise the SER-287 spore ecology in a subject's gastrointestinal tract post-treatment. Engraftment will be assessed at time points between Visit 4 and Visit 13.

Differences between changes in the microbiome across the various treatment arms will be evaluated using both non-parametric tests for α-diversity and multivariate analysis of variances of dissimilarity matrices for β-diversity. Dissimilarity will be defined by using the unweighted Unifrac dissimilarity metric, which evaluates changes in the overall phylogenetic composition between two samples; this method is widely used in the study of microbial communities and represents a balanced approach with minimal bias to the presence of low- and high-abundance bacteria.

Additional measures of dissimilarity that are routinely used in the analysis of microbiome data sets will be further evaluated.

8.2.2 Endpoints and Analysis for Secondary Objectives

Efficacy response endpoints comprise clinical response, complete remission and endoscopic improvement. The primary time point for analysis is Visit 12. Estimates of the risk difference and confidence interval will be reported for treatment groups A, C and D separately compared to placebo.

Serum biomarkers (CRP) and fecal biomarkers (fecal calprotectin) at Visit 1, Visit 4, Visit 6, Visit 12 and Visit 13 will be assessed using descriptive summary tables and treatment mean [+/- standard deviation (SD)] profile plots (response versus timepoint).

8.2.3 Exploratory Endpoints

All time points of exploratory endpoint will be listed and presented in descriptive summary tables.

- Stool and blood metabolic pathways

- Serum cytokine profile
- Mucosal transcriptomic profile
- Mucosal microbiome
- Mucosal Histopathology, including cytomegalovirus (CMV) Immunohistology stains
- Microbial Culture Endpoints:
    - Candida titer and diversity

8.3 General Considerations

8.3.1 Statistical Methods

All safety and tolerability, intestinal microbiome, clinical efficacy, and biomarker data will be listed and presented in descriptive summaries by study arm, visit and time point. At a minimum, continuous data will be summarized by study arm using descriptive statistics (number, mean, SD minimum, median and maximum). Categorical data will be summarized by study arm using frequency tables (number and percentage).

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

8.3.2 Statistical Significance

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 will be 95%, two-sided. P-values and/or confidence intervals 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 also the comparisons A versus D and C versus D. For continuous data these comparisons will be assessed using confidence intervals estimated using one-way analysis of variance (ANOVA) models fit to the separate results of each visit. For binary data these comparisons will be assessed by analysis of two-by-two tables and calculation the risk difference and confidence interval. Additional details of the statistical analysis will be addressed in a statistical analysis plan, finalized prior to the time the primary study period (Visit 1 to Visit 13) data is declared complete and final and study unblinding.

8.3.3 Missing or Spurious Data

Any AE with incomplete date or time will be evaluated conservatively in the classification of treatment emergent AE. Any apparently spurious data will be verified. No verified data will be excluded from summaries or analysis.

Several missing imputation methods, such as worst case analyses, observed case analyses and last observation carried forward, will be applied to analyze the clinical efficacy endpoints.

8.4 Safety Analyses

8.4.1 Adverse Events

Adverse events will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of treatment-emergent adverse events (TEAEs) by treatment group will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity after initiation of study drug. A listing of all AEs, including those occurring before the start of study drug, will be provided. The percentage of subjects with 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 by severity, and by relationship to treatment. Tables of any TEAEs leading to study drug discontinuation, AESIs and SAEs will also be provided.

8.4.2 Clinical Laboratory Tests

All scheduled and unscheduled laboratory results will be presented for each subject, sorted by category, subject, test and sample time. Flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment. A separate listing of abnormal results will be presented, ordered by test, subject and sample time.

Quantitative chemistry and hematology tests (observed values and change from baseline) will be summarized descriptively in tabular format. A shift table will be presented for chemistry, hematology and urinalysis tests shift from baseline to each post-baseline visit and also the shift from baseline to highest and to lowest post-baseline assessment.

8.4.3 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Descriptive statistics of the vital signs will be presented by treatment group for all study visits at which they were collected. The change from baseline to each post-baseline visit will also be summarized by treatment group.

8.4.4 Physical Examination Findings

Abnormal clinically significant physical examination (PE) finding will be reported as medical history (MH) or as an AE.

8.4.5 Pharmacokinetic Analyses

Not applicable

8.5 Gastrointestinal Tract Microbiome

The gastrointestinal (GI) microbiome of subjects will be characterized by using at minimum recombinant deoxyribonucleic acid (rDNA) 16S V4 genomic data sets generated from stool collected at the time points defined above for the various endpoints. Genomic data sets will define the microbial composition of the microbiome of a subject at a given time point. Genomic sequence read data sets will be analyzed to assign a taxonomic identity at the resolution of an operational taxonomic unit (OTU) and

phylogenetic clade (clade) and, further, to define the relative proportion of each OTU and clade to all other OTUs and clades in a given sample.

Changes in the composition of the microbiome will be measured and analyzed as described in Section 8.2.1.

8.6 Interim Analyses

No interim analysis is planned for this study.

8.7 Determination of 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. All comparisons performed in this study will be descriptive in nature. P-values and/or confidence intervals generated for this study are not intended to be conclusive, but are provided for guidance only.

9 ADMINISTRATIVE REQUIREMENTS

9.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the Investigational product. Essential clinical documents will be maintained to demonstrate the validity of the study and integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

- The Principal Investigator has the overall responsibility for the conduct and administration of the study at the clinical site and for contacts with the sponsor, the IRB/IEC, and local authorities.
- The Principal Investigator is responsible for ensuring the privacy, health, and welfare of the subjects during and after the clinical study.
- All Investigators are responsible for performing the study in accordance with the protocol and the above guidelines and regulations, and for collecting, documenting, and reporting the data accurately.
- All Investigators must be familiar with the background and requirements of the study and with the properties of the investigational product as described in the current version of the Investigator's Brochure
- The Principal Investigator is responsible for distributing study information and documentation to all appropriate staff members before and during the course of the study as updated information becomes available.

9.2 Ethical Considerations

The study will be conducted in accordance with ethical principles in the Belmont Report, and in compliance with local IRB/IEC requirements and institutional guidelines.

The Investigator must obtain IRB/IEC approval of the protocol, ICF, and other required study documentation before starting the study. It is the responsibility of the Investigator to ensure that all aspects of IRB/IEC review are conducted in accordance with current governmental regulations.

A progress report must be submitted to the IRB/IEC at the required intervals and not less than annually. At the completion or termination of the study, the Investigator must submit a closeout letter to the IRB/IEC.

9.3 Subject Information and Informed Consent

Before any testing under this protocol, including screening tests and assessments, written informed consent with the IRB/IEC-approved ICF must be obtained from the subject in accordance with local practice and regulations.

The background of the proposed study, procedures, and benefits and risks of the study must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Each ICF should contain an authorization allowing the Investigator to use and disclose subject health information (i.e., subject-identifiable health information) in compliance with local law.

9.4 Subject Confidentiality

Subject confidentiality is held strictly in trust by the Investigator and medical and laboratory staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. The Investigator will grant regulatory authority(ies) access to the subject's original medical records for verification of data gathered and to audit the data collection process. The subjects' and donors' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will not be identified by name in any study reports, and these reports will be used for research purposes only.

9.5 Protocol Compliance

The Investigator will conduct the study in compliance with the IRB/IEC-approved protocol without any changes or deviations. Modifications to the protocol will require approval from the sponsor and written IRB/IEC approval before implementation, except when the modification is needed to eliminate an immediate hazard to the subject. Any change, intentional or otherwise, must be reported immediately to the sponsor and to the relevant IRB/IEC and/or regulatory authority as required by guidelines or regulation. Sites that fail to comply may be terminated.

9.6 Future Use of Stored Specimens

The sponsor may conduct future biomedical research on specimens (including blood and feces) routinely and specifically collected during this clinical study that may be used for potential commercial use by Seres Therapeutics and may be stored for up to 10 years. This research may include genetic analyses [deoxyribonucleic acid (DNA)] and/or the measurement of other analytes.

9.7 Study Monitoring

Regular monitoring is defined in ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 1.38, as "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, Good Clinical Practice (GCP), and the applicable regulatory requirement(s)." The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected.

- The reported study data are accurate, complete, and verifiable from source documents.
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.

It will be the responsibility of the Investigator to ensure that the essential documents are available at the Investigator or institutional site. Any or all of these documents may be pertinent to, and should be available for, monitoring by the sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

The sponsor or an authorized sponsor representative will conduct regular site monitoring visits to review and validate study data as defined in the monitoring plan by reviewing subjects' medical records and eCRFs in accordance with written standard operating procedures, ICH guidelines, GCP, and applicable regulations and guidelines. The Investigator will allow representatives of the sponsor or regulatory authorities to inspect facilities and records relevant to this study.

9.8 Data and Safety Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DSMC will monitor the safety data from this study. The members of the DSMC will not be involved with the study (i.e., they are not study investigators) and must have no competing interests that could affect their roles with respect to the study. The DSMC will include 2 clinicians experienced in Gastroenterology and a statistician. 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 will be described in a separate charter that is reviewed and approved by the DSMC.

9.9 Case Report Forms and Study Records

Data will be collected for this study by using an eCRF. The Investigator and study site staff will receive training and support on the use of the eCRF. All eCRF data are to be completed by the study coordinator or other designated site personnel. All data entry, modification, or deletion will be recorded automatically in the electronic audit trail. All data changes will be clearly indicated with a means to locate prior values. A unique user identification and password will be assigned to all personnel approved to enter or change data to prevent unauthorized access to the data.

All electronic data entered by the site (including the electronic audit trail) will be maintained or made available at the site in compliance with Title 21 Part 11 of the Code of Federal Regulations (CFR) and other applicable retention regulations. The computerized system is able to generate accurate and complete copies of records in paper or electronic form for inspection and review by applicable regulatory authorities, the IRB/IEC/Research Ethics Board, and auditors or other designees authorized by the sponsor.

In addition to capturing the user identification as part of the audit trail for all data entry, the eCRF allows for application of electronic signatures. The Investigator or designated subInvestigator, after review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature. This electronic signature will be certified as outlined in 21 CFR Part 11.

The sponsor will retain the original eCRF data and audit trail. An electronic or certified paper copy of all completed eCRF data, including query resolution correspondence, will be provided to the Investigator at the end of the study.

9.10 Study Completion

The sponsor requires the following data and materials to be submitted before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from informed consent through the End-of-Study Visit at Week 13 and the final phone call on Day 246
- Electronic CRFs properly completed by appropriate study personnel and signed and dated by the Investigator
- Complete study drug accountability records
- Copies of IRB/IEC approval and notification of the original protocol and of any protocol amendments, if appropriate
- A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable)

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APPENDICES

Appendix 1: Total Modified Mayo Score

Stool Frequency

0= Normal

1= 1-2 stools/day more than normal

2= 3-4 stools/day more than normal

3= >4 stools/day more than normal

Rectal Bleeding

0= None

1= Visible blood with stool less than half the time

2= Visible blood with stool half of the time or more

3= Passing blood alone

Mucosal Appearance at Endoscopy[a]

0= Normal

1= Mild disease (erythema, decreased vascular pattern)

2= Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3= Severe disease (spontaneous bleeding, ulcerations)

Physician Rating of Disease Activity

0= Normal

1= Mild

2= Moderate

3= Severe

a: The mucosal appearance at endoscopy is not included in the partial Mayo score

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Appendix 2: Diet Inventory

	Did you eat or drink the following products in the last 7 days?	**If yes, how recently?** *please choose only one response per category, from this column
Example: **Vegetables** (salad, tomatoes, onions, greens, carrots, peppers, green beans, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ● **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Tea or coffee no sugar and no sugar replacement	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Soft drinks, tea or coffee with sugar (corn syrup, maple syrup, cane sugar, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Diet soft drinks, tea or coffee with sugar substitute (Stevia, Equal, Splenda, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Fruit juice (orange, apple, cranberry, prune, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Water	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Alcohol (beer, brandy, spirits, hard liquor, wine, aperitif, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Yogurt or other foods containing active bacterial cultures (kefir, sauerkraut, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Dairy (milk, cream, ice cream, cheese, cream cheese)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Probiotic (other than yogurt)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times

Fruits (no juice) (Apples, raisins, bananas, oranges, strawberries, blueberries, etc. (frozen or fresh)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Vegetables (salad, tomatoes, onions, greens, carrots, peppers, green beans, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Beans (tofu, soy, soy burgers, lentils, Mexican beans, lima beans, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Whole grains (wheat, oats, brown rice, rye, quinoa, wheat bread, wheat pasta, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Starch (white rice, bread, pizza, potatoes, yam, cereals, pancakes, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Eggs	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Processed meat (other red meat and other white meat such as lunch meat, ham, salami, bologna, sausage, kielbasa, hotdog, bacon, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Red meat (beef, hamburger, pork, lamb)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
White meat (chicken, turkey, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Shellfish (shrimp, lobster scallops, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Fish (fish nuggets, breaded fish, fish cakes, salmon, tuna, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times
Sweets (pies, jam, chocolate, cake, cookies, etc.)	○ No, I did not consume these products in the last 7 days	○ Within the past **4 to 7 days** ○ Within the past **2 to 3 days** ○ **Within 24 hrs**, **1 to 2** times ○ **Within 24 hrs**, **3 or more** times

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Appendix 3: Montreal Classification of Extent of Ulcerative Colitis

E1: Ulcerative Proctitis – Involvement limited to the rectum (proximal extent of inflammation is distal to the rectosimgoid junction

E2: Left-sided UC (distal UC)—Involvement limited to a portion of the colorectum distal to the splenic flexure

E3: Extensive UC (pancolitis)—Involvement extends proximal to the splenic flexure

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