SERES THERAPEUTICS®

Leading the Microbiome Revolution®

# CLINICAL STUDY PROTOCOL

## SER-287

(Eubacterial Spores, Purified Suspension, Encapsulated)

## ECO-RESET: A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Study to Assess Efficacy and Safety of SER-287 in Adults with Active Mild-to-Moderate Ulcerative Colitis

**SPONSOR:**

Seres Therapeutics, Inc.
200 Sidney Street, Suite 410
Cambridge, MA 02139
USA
Telephone: +1-617-945-9626

**TITLE:**

ECO-RESET: A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Study to Assess Efficacy and Safety of SER-287 in Adults with Active Mild-to-Moderate Ulcerative Colitis

**CLINICAL PHASE:** 2B

[redacted]

Original Protocol Date: 12-March-2018

Amendment 1 Date: 09-July-2018

Amendment 2 Date: 17-October-2018

Amendment 3 Date: 08-October-2019

[redacted]

**THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF SERES THERAPEUTICS, INC.**

## SIGNATURE PAGE

**Declaration of Sponsor or Responsible Medical Officer**

**Title: ECO-RESET: A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Study to Assess Efficacy and Safety of SER-287 in Adults with Active 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.

**Declaration of the Investigator**

**Title: ECO-RESET: A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Study to Assess Efficacy and Safety of SER-287 in Adults with Active Mild-to-Moderate Ulcerative Colitis**

I have received and read the SERES-201 Protocol dated 08-October-2019 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____

Printed Name of Investigator Date

_____

Signature of Investigator

## PROTOCOL SYNOPSIS

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|---|---|
| **Title** | ECO-RESET: A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Study to Assess Efficacy and Safety of SER-287 in Adults with Active Mild-to-Moderate Ulcerative Colitis |
| **Sponsor** | Seres Therapeutics, Inc. |
| **Active Ingredient** | SER-287 (Eubacterial Spores, Purified Suspension, Encapsulated) |
| **Phase** | 2B |
| **Sponsor Study No.** | SERES-201 |
| **Population** | Male or female adult subjects 18-80 years of age, inclusive, with active mild-to-moderate Ulcerative Colitis |
| **Number of Subjects** | Approximately 201 subjects will be enrolled, approximately 67 subjects in each of three (3) treatment arms |
| **Study Centers** | Approximately 104 study centers in North America |
| **Planned Enrollment Duration:** | Approximately 17 months |
| **Objectives** | Primary Objective:<br>• To demonstrate the efficacy of SER-287, after 10 weeks of induction dosing (following vancomycin pre-treatment), in achieving clinical remission<br><br>Key Secondary Objectives:<br>• To demonstrate the efficacy of SER-287, after 10 weeks of step-down induction dosing (following vancomycin pre-treatment), in achieving clinical remission<br>• To demonstrate the efficacy of SER-287, after 10 weeks of induction dosing (following vancomycin pre-treatment), in achieving endoscopic improvement<br>• To demonstrate the efficacy of SER-287, after 10 weeks of step-down induction dosing (following vancomycin pre-treatment), in achieving endoscopic improvement<br><br>Other Secondary Objectives:<br>• To demonstrate the efficacy of each SER-287 treatment arm in achieving endoscopic remission after 10 weeks of induction treatment<br>• To demonstrate the efficacy of each SER-287 treatment arm in achieving histological mucosal healing after 10 weeks of induction treatment<br>• To demonstrate the efficacy of each SER-287 treatment arm in achieving clinical remission with normalization of stool frequency after 10 weeks of induction treatment<br>• To evaluate the efficacy of each SER-287 treatment arm on symptomatic remission (rectal bleeding and stool frequency) after 10 weeks of induction treatment<br>• To evaluate the engraftment of SER-287 bacteria from each SER-287 treatment arm into the intestinal microbial community over time<br>• For EMA consideration only (see Section 3, Definitions):<br>  ○ To demonstrate the efficacy of SER-287 to induce clinical remission, using less stringent definition<br>  ○ To demonstrate the efficacy of SER-287 to induce clinical remission, using more stringent definition<br>  ○ To demonstrate the efficacy of SER-287 to induce symptomatic remission and endoscopic remission as co-endpoints<br><br>Safety Objective:<br>To evaluate safety and tolerability of SER-287 |

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| | Exploratory Objectives:<br>• To evaluate clinical remission at the end of maintenance treatment<br>• To evaluate endoscopic remission at the end of maintenance treatment<br>• To evaluate histological mucosal healing at the end of maintenance treatment<br>• To evaluate clinical remission at the end of open-label treatment<br>• To evaluate endoscopic improvement at the end of open-label treatment<br>• To evaluate endoscopic remission at the end of open-label treatment<br>• To evaluate histological mucosal healing at the end of open-label treatment<br>• To evaluate the effect of SER-287 treatment on symptomatic remission (rectal bleeding and stool frequency) over time<br>• To evaluate the clinical remission rate of SER-287, by donor, after 10 weeks of induction treatment<br>• To assess improvement in quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ)<br>• To assess changes in serum biomarkers (C-reactive protein [CRP]) and fecal biomarkers (fecal calprotectin)<br>• To evaluate changes in the composition of the intestinal microbiome over time<br>• To evaluate changes in signatures of host and microbial functional responses over time |
| **Efficacy Endpoints** | Primary Endpoint (See Section 3, Definitions):<br>• Clinical remission with SER-287, after 10 weeks of induction dosing, following vancomycin pre-treatment (Treatment Arm B), compared to placebo, following placebo pre-treatment (Treatment Arm A)<br><br>Key Secondary Endpoints (See Section 3, Definitions):<br>• Clinical remission with SER-287, after 10 weeks of step-down induction dosing, following vancomycin pre-treatment (Treatment Arm C), compared to placebo, following placebo pre-treatment (Treatment Arm A)<br>• Endoscopic improvement with SER-287, after 10 weeks of induction dosing, following vancomycin pre-treatment (Treatment Arm B), compared to placebo, following placebo pre-treatment (Treatment Arm A)<br>• Endoscopic improvement with SER-287, after 10 weeks of step-down induction dosing, following vancomycin pre-treatment (Treatment Arm C), compared to placebo, following placebo pre-treatment (Treatment Arm A)<br><br>Other Secondary Endpoints (See Section 3, Definitions):<br>• Endoscopic remission after 10 weeks of induction treatment<br>• Histological mucosal healing after 10 weeks of induction treatment<br>• Clinical remission with normalization of stool frequency after 10 weeks of induction treatment<br>• Symptomatic remission (rectal bleeding and stool frequency) after 10 weeks of induction treatment<br>• Engraftment of SER-287 bacteria over time<br>• For EMA consideration only (See Section 3, Definitions):<br>  ○ Clinical remission (less stringent criteria) after 10 weeks of induction treatment<br>  ○ Clinical remission (more stringent criteria) after 10 weeks of induction treatment<br>  ○ Clinical remission co-endpoints: symptomatic remission and endoscopic remission after 10 weeks of induction treatment<br><br>Exploratory Endpoints (See Section 3, Definitions):<br>• Clinical remission at the end of maintenance treatment and at the end of open-label treatment<br>• Endoscopic improvement at the end of open-label treatment |

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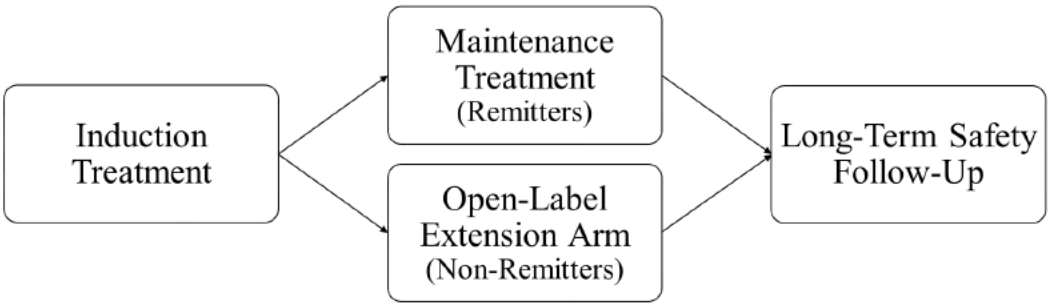
| | • Endoscopic remission at the end of maintenance treatment and at the end of open-label treatment<br>• Histological mucosal healing at the end of maintenance treatment and at the end of open-label treatment<br>• Symptomatic remission (rectal bleeding and stool frequency) over time<br>• Clinical remission after 10 weeks of induction treatment for each SER-287 donor used in the induction treatment period<br>• IBDQ scores after 10 weeks of induction, at the end of maintenance treatment, and at the end of open-label treatment<br>• Serum biomarkers: CRP after 10 weeks of induction treatment (Week 11), at the end of maintenance treatment and at the end of open-label treatment<br>• Fecal biomarkers: fecal calprotectin levels after 10 weeks of induction treatment (Week 11), at the end of maintenance treatment and at the end of open-label treatment<br>• Composition of the intestinal microbiome through the end of the maintenance treatment and open-label treatment periods<br>• Signatures of host and microbial functional responses through the end of the maintenance treatment and open-label treatment periods |
| **Evaluation of Safety** | The evaluation of safety data will be performed by comparing various safety parameters across treatment arms. The following safety endpoints will be measured:<br>• Incidence of AEs, SAEs and AESIs<br>• Laboratory evaluation results<br>• Vital sign measurements<br>• Physical examination findings<br><br>Incidence of AEs, SAEs and AESIs will be summarized for each SER-287 donor overall and within each treatment arm.<br><br>Safety endpoints will be summarized at the end of the pre-treatment period (Week 1), Week 3, Week 7, after 10 weeks of induction treatment (Week 11), at the end of maintenance treatment or open-label treatment and at end-of-study. |
| **Study Design** | This is a Phase 2B, randomized, double-blind, placebo-controlled, multiple dose, multicenter study designed to evaluate the efficacy and safety of SER-287 in adult subjects, 18-80 years of age, inclusive, with active mild-to-moderate ulcerative colitis (UC).<br><br>Approximately 201 subjects will be enrolled. Enrollment in this trial, as well as the clinical endpoints, will be based upon a composite Three-Component Modified Mayo Score of 3 to 7, inclusive, which sums patient-reported rectal bleeding and stool frequency subscores with endoscopic subscore. Endoscopic subscores will be determined by local and independent, blinded central readers. The endoscopy central readers will remain blinded to subjects' treatment assignments throughout the entire study.<br><br>The key study phases after Screening and randomization are: Induction Treatment (three [3] treatment arms), Maintenance Treatment (for Remitters) or an Open-Label Extension Arm (for Non-Remitters), and Long-Term Safety Follow-Up: |




"Remitters" are defined as subjects who have a stool frequency (SF) subscore of 0 or 1, with at least one-point decrease from baseline, a rectal bleeding (RB) subscore of 0 and ES of 0 or 1, with at least one-point decrease from baseline, and had no occurrence of a UC flare during the treatment period.

Study Duration: Up to a total of 67 weeks (includes Screening), as detailed below:

| Study Period | Duration | Study Weeks |
|---|---|---|
| Screening | Up to 4 weeks | -4 to -1 |
| Pre-Treatment | 6 days | 0 |
| Induction Treatment | 10 weeks | 1-11 |

| Maintenance Treatment (Remitters) | | |
|---|---|---|
| Study Period | Duration | Study Week(s) |
| Maintenance Treatment | 26 weeks | M-11-37 |
| Long-Term Safety Follow-Up | 26 weeks | M-37-63 |

| Open-Label Extension (Non-Remitters) | | |
|---|---|---|
| Study Period | Duration | Study Week(s) |
| Pre-Treatment | 6 days | OL-0 |
| Induction Treatment | 10 weeks | OL-1-11 |
| Long-Term Safety Follow-Up | 26 weeks | OL-11-37 |

1. Screening:
   a. Visit 1: Assess inclusion/exclusion criteria; collect medical history & demographics; instruct subject to complete electronic diary (eDiary) for documenting SF and RB subscores, daily, during the Screening period. A minimum of seven (7) days between Visit 1 and Visit 2 are required to ensure there are a sufficient quantity of eDiary entries to calculate the SF subscore. Subjects who meet all screening criteria and have a SF subscore $\geq 1$ will be eligible for endoscopic assessment at Visit 2. Sites will receive a preliminary notification from the interactive web/voice response system (IXRS) two days prior to the scheduled endoscopy that the subject meets, or does not meet, this requirement thus far. Sites must then check the IXRS Stool Frequency Report one day prior to the scheduled endoscopy to confirm the subject has a SF $\geq 1$.
   b. Visit 2: Lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies. Subjects with ES $\geq 1$ will be eligible for randomization. Sites will receive a notification from the IXRS that the subject meets, or does not meet, this requirement, as well as if their Three-Component Modified Mayo Score meets the study inclusion requirement (score of 3 to 7, inclusive). There will be a maximum time of seven (7) business days between the Screening endoscopy and randomization.

2. Pre-Treatment: Eligible subjects will be randomized into one (1) of three (3) treatment arms and receive six (6) days of pre-treatment with oral vancomycin or matching placebo. Subjects will visit the clinic one (1) time during this period. Subjects will begin pre-treatment drug dosing on-site at the clinic and thereafter continue dosing independently. Subjects will document SF and RB subscores, daily, via eDiary.

   Subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening) during Pre-Treatment or beyond (Induction, Maintenance or Open-Label Treatment Periods) will have an assessment by the principal investigator (PI) to determine if the subject is experiencing a UC flare. If the subject is experiencing a UC flare, they will discontinue study drug, and will be followed for safety for 26 weeks. Subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies prior to a change in UC treatment medication, and discontinuation from study drug, if possible.

3. Induction Treatment: Subjects who complete the Pre-Treatment will receive 10 weeks of once-daily treatment with SER-287 (following vancomycin pre-treatment) or matching placebo (following placebo pre-treatment, Figure 1). Subjects will begin Induction Treatment drug dosing on-site at the clinic and thereafter continue daily dosing independently. Subjects will visit the clinic four (4) times during this period and will be asked to provide blood and stool samples. They will continue to document SF and RB subscores, daily, via eDiary, and will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies after 10 weeks of induction treatment, or early termination.

| Arm | Pre-Treatment (QID for 6 days) | Induction Treatment (QD for 10 weeks) |
|---|---|---|
| A | Placebo | Placebo |
| B | Vancomycin | SER-287 Induction Dose |
| C | Vancomycin | SER-287 Step-Down Induction Dose |

[redacted]

4. Subjects who complete the Induction Treatment period will be assessed for clinical remission status, and will enter one of the following treatment regimens:

   a. Maintenance Treatment
   Remitters (subjects who meet the remitter criteria, as defined in Section 3, Definitions) will be re-randomized to receive a SER-287 Maintenance Dose, once-weekly, or matching placebo, for 26 weeks (Figure 2A). Subjects will visit the clinic seven (7) times during this period. Subjects will continue to document SF and RB subscores, daily, via eDiary. After the end of the 26-week Maintenance Treatment period, subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies at Week 37, or early termination. Subjects who experience a UC flare during the first 13 weeks of Maintenance Treatment (prior to M-Week 24) will have the option to enter the Open-Label Extension arm; those who do not enter Open-Label will be followed for safety for 26 weeks.

   b. Open-Label Extension
   Non-Remitters (subjects who do not meet the remitter criteria) will enter the Open-Label Extension arm, where they will receive six (6) days of vancomycin pre-treatment and 10 weeks of SER-287 (Induction Dose), once-daily (Figure 2B). Subjects will visit the clinic four (4) times during this period. Subjects will continue to document SF and RB subscores, daily, via eDiary. After 10 weeks of daily treatment, subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies at Open-Label-Week 11. The endoscopy central

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| | reader will remain blinded to treatment assignment. Subjects who experience a UC flare during the Open-Label treatment period will discontinue study drug and will be followed for safety for 26 weeks.<br><br>5. Long-Term Safety Follow-Up: All subjects will be followed for long-term safety for 26 weeks following their last treatment dose. No office visits are required during this period. Site personnel will conduct follow-up phone calls every four (4) weeks. During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected. During subsequent follow-up phone calls, subjects will be asked about any SAEs/AESIs and any concomitant medications associated with an SAE/AESI. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period. |
| **Inclusion Criteria** | 1. Signed informed consent prior to initiation of any study-specific procedure or treatment. The subject must be willing to provide written informed consent and understand the potential risks and benefits from study enrollment and treatment. The subject must also be willing and able to comply with the scheduled visits, treatment plan, laboratory tests, daily eDiary and other study procedures.<br>2. Male or female (non-lactating), 18-80 years of age, inclusive<br>3. Documented diagnosis of ulcerative colitis at least three (3) months prior to Screening. Documentation should include lower endoscopic (flexible sigmoidoscopy or colonoscopy) evidence or histological evidence (biopsy report) of UC; however, UC medical treatment records may be sufficient, as determined by the PI. Subjects must also have a minimum disease extent of 15 cm from the anal verge, as determined at the Screening endoscopy.<br>4. Active mild-to-moderate UC as determined by a Three-Component Modified Mayo Score of 3 to 7, inclusive, composed of endoscopic subscore (≥ 1, as determined by local and central reader scores, with adjudication by a second central reader, if necessary), stool frequency subscore (≥ 1) and rectal bleeding subscore (no eligibility requirement). There will be a maximum time of seven (7) business days between the Screening endoscopy and randomization.<br>5. Subjects must be willing to undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy), including biopsy sample collection, at all specified timepoints.<br>6. Subjects with an inadequate response to, loss of response to, or intolerance of, at least one (1) of the following conventional therapies: 5-ASA compounds, corticosteroids, 6-mercaptopurine (6-MP) or azathioprine (AZA), anti-TNFα, anti-integrin or tofacitinib (note full definition within Section 5.1, Inclusion Criteria)<br>7. If female, is either:<br>a. Not of childbearing potential, defined as postmenopausal (≥ 12 continuous months of amenorrhea with no other cause than menopause) or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy<br>b. Of childbearing potential and participates in any activity associated with risk of pregnancy: is practicing at least one (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 one (1) of the above methods for the duration of the study.<br>8. If male and partner is of childbearing potential, subject agrees to practice at least one (1) highly effective method of birth control for the duration of the study. |
| **Exclusion Criteria** | 1. Known history of Crohn's disease<br>2. No previous history of treatment for UC (treatment-naïve subjects should not be enrolled)<br>3. Subjects on steroid medication (e.g. prednisone, budesonide, budesonide MMX®) who are unable to have steroids tapered, and be completely off steroids at least two (2) weeks prior to Screening |

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| | 4. Subjects who have received any investigational or approved biologic therapy (e.g. infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, natalizumab) within eight (8) weeks prior to Screening or five (5) half-lives prior to Screening (whichever is longer)<br>5. Subjects who have received any investigational or approved non-biologic therapy (e.g. cyclosporine, tacrolimus, thalidomide, methotrexate, tofacitinib), except for those specifically listed in the Permitted Concomitant Medications (e.g. stable dose of 6-mercaptopurine, azathioprine, methotrexate for ≥ 12 weeks prior to Screening), for the treatment of underlying disease, within 30 days or five (5) half-lives prior to Screening (whichever is longer)<br>6. Major gastrointestinal surgery (not including appendectomy or cholecystectomy) within two (2) months before Screening, or any history of total colectomy<br>7. Subjects with active celiac disease (i.e., active diarrhea due to documented celiac disease)<br>8. Subjects with evidence of, or treatment for, *Clostridium difficile* infection, or other intestinal pathogen, within 30 days prior to Screening<br>9. Subjects with *Clostridium difficile* positive stool, performed with a toxin enzyme immunoassay (EIA) by the Central Laboratory. Subjects who test positive for *C. difficile* can be treated with standard of care antibiotics and rescreened for the study after 30 days, as per Exclusion Criterion #8.<br>10. Oral antibiotic use within 30 days before Screening<br>11. Expected to receive antibiotics (i.e., for planned/anticipated procedure) within the Induction Treatment period<br>12. Received an investigational drug or live vaccine within two (2) months before Screening<br>13. Previously enrolled in a Seres Therapeutics SER-109 or SER-287 study<br>14. Received a fecal microbiota transplant (FMT; includes human microbiota-based therapeutics) within three (3) months prior to Screening<br>15. 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:<br>a. Known hypogammaglobulinemia<br>b. Known severe immunodeficiency<br>c. Underlying liver function test (LFT) [Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] abnormalities greater than 3x upper limit of normal (ULN)<br>d. Absolute neutrophil count (ANC) < 500 cells/$mm^3$<br>e. Hemoglobin levels < 9 g/dL<br>16. Subjects with anatomic or medical contraindications to lower endoscopy (flexible sigmoidoscopy or colonoscopy), including but not necessarily limited to toxic megacolon, gastrointestinal 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)<br>17. Unable to stop steroid enemas or suppositories, or 5-ASA enemas or suppositories, at least two (2) weeks prior to Screening<br>18. Unable to stop probiotic treatment at least one (1) week prior to Screening. Note: food containing probiotics are permitted.<br>19. Known active malignancy, except for basal cell skin cancer or squamous cell skin cancer, or concurrent intensive induction chemotherapy, radiotherapy, or biologic treatment for active malignancy (subjects on maintenance chemotherapy may only be enrolled after consultation with medical monitor)<br>20. Unable to comply with the protocol requirements, including the ability to take oral drugs; or any condition that, in the opinion of the investigator, might interfere with study objectives or compromise patient safety, including if the subject is likely to require surgery for UC during the study period<br>21. Known allergy or intolerance to oral vancomycin<br>22. Current or recent history (six [6] months prior to Screening) of drug or alcohol abuse |

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| **Concomitant Medications** | Permitted Concomitant Medications:<br>The below medications are allowed at study entry. Doses must remain stable during the study treatment period.<br>1. Oral aminosalicylates (if taken for at least six [6] weeks prior to Screening, with a stable dose for ≥ 2 weeks prior to Screening)<br>2. Immunomodulator: 6-Mercaptopurine, Azathioprine, Methotrexate (Stable dose for ≥ 12 weeks prior to Screening)<br>3. Pain medication (stable dose), including low-dose aspirin (81 mg); Note: temporary use of pain medication is permitted during the treatment period (e.g. for minor surgery), and is defined as no more than 48 hours. Temporary use of opiates should be discussed with the medical monitor.<br>4. Inhaled steroids for non-UC-related treatment (taper-down is also acceptable)<br>5. Inactivated influenza vaccine<br><br>Prohibited Concomitant Medications and Nutritional Supplements:<br>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 drug administration.<br>1. Oral, intravenous (IV) and rectal steroids (e.g. prednisone, budesonide, budesonide MMX®)<br>2. 5-ASA enemas or suppositories<br>3. Any investigational or approved biologic therapy (e.g. infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, natalizumab)<br>4. Any investigational or approved non-biologic therapy (e.g. cyclosporine, tacrolimus, thalidomide, methotrexate, tofacitinib)<br>5. Anti-diarrheals (e.g. loperamide, diphenoxylate/atropine, or bile-salt sequestrant [cholestyramine, colesevelam])<br>6. Probiotics (food containing probiotics are permitted)<br>7. Use of any nutritional supplement which claims to support or promote gut health should be determined by medical monitor. |
| **Statistical Methods** | **Analysis Populations**<br>The Intent-to-Treat (ITT) Population will consist of all subjects who are randomly assigned, including those who are not exposed to any study drug, and will be analyzed based on the treatment to which they were randomized. The ITT population will be the primary analysis population for all efficacy endpoints.<br><br>The Modified Intent-to-Treat 1 (mITT-1) Population will consist of all randomized subjects with a baseline evaluation, who have active mild-to-moderate UC and receive any amount of study drug, and will be analyzed based on the treatment to which they were randomized.<br><br>The Modified Intent-to-Treat 2 (mITT-2) Population will consist of all randomized subjects with a baseline evaluation, who have active mild-to-moderate UC and receive any amount of study drug, and will be analyzed based on the treatment to which they are randomized. Subjects who are confirmed to have normal histology at baseline will be excluded from this analysis population.<br><br>The Per Protocol (PP) Population will consist of subjects from the mITT-2 Population who do not have any major protocol deviations. The details of the PP Population will be provided in the Statistical Analysis Plan (SAP) and defined before unblinding of the data.<br><br>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 are randomly assigned. All safety analyses will be conducted based on the Safety Population. |

The Microbiome Modified Intent-to-Treat (mcITT) Population will be used for analysis of microbiome data. It will consist of all randomized subjects with an evaluable stool sample collected at baseline, and at least one (1) evaluable stool sample collected after the start of dosing, who are exposed to any amount of study drug, and will be analyzed based on the treatment to which they are randomized.

**Analysis of the Primary Efficacy Endpoint**

The primary efficacy outcome measure for this study will be the difference in clinical remission rates after 10 weeks of induction treatment between SER-287 (Induction Dose after pre-treatment with vancomycin – Arm B) and placebo (Arm A). The primary efficacy endpoint analysis will be based on the Cochran-Mantel-Haenszel (CMH) test, stratified by endoscopic score at baseline (1-2 vs. 3), and UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none) in the ITT population.

**Analysis of the Key Secondary Efficacy Endpoints**

The key secondary efficacy endpoints will be analyzed using the same method used for the primary efficacy endpoint.

Sensitivity Analyses for the primary and key secondary endpoint will be performed in the mITT-1, mITT-2, PP and Safety populations.

**Multiplicity Adjustment**

Adjustments for multiple testing will be made to test the primary efficacy and key secondary efficacy endpoints. A fixed-sequence method will be used to maintain a study-wide 2-sided Type I error rate of 0.05. Testing of the key hypotheses will be conducted in the following order, all at the same significance level (2-sided $\alpha = 0.05$):

1. $H_{01}$: No difference in clinical remission rates after 10 weeks of induction treatment between Arm B (SER-287 at Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
2. $H_{02}$: No difference in clinical remission rates after 10 weeks of induction treatment between Arm C (SER-287 at Step-Down Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
3. $H_{03}$: No difference in endoscopic improvement rates after 10 weeks of induction treatment between Arm B (SER-287 at Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
4. $H_{04}$: No difference in endoscopic improvement rates after 10 weeks of induction treatment between Arm C (SER-287 at Step-Down Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population

Testing of later hypotheses in the sequence stops as soon as failure to show statistical significance at the 2-sided 0.05 level is observed in a hypothesis earlier in the sequence.

**Determination of Sample Size**

The planned sample size for this study is 67 subjects per treatment arm for a total sample size of 201 subjects. Assuming a clinical remission rate of 29% in the SER-287 arms and a clinical remission rate of 9% in the placebo arm, this sample size will provide 86% power to detect a difference of 20% in clinical remission rates between SER-287 to placebo, using a 2-sided significance level of 0.05.

**Figure 1: Subject Treatment Overview: Screening Through Week 11**

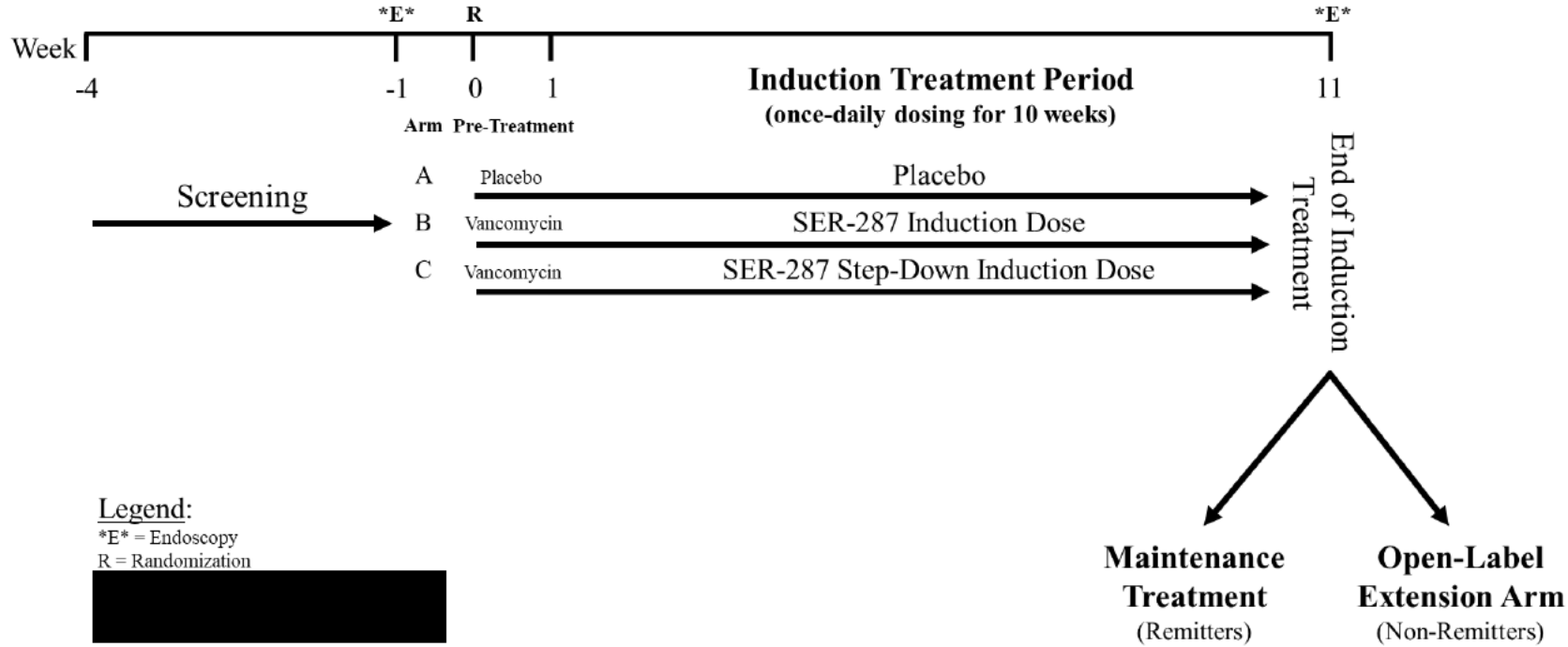
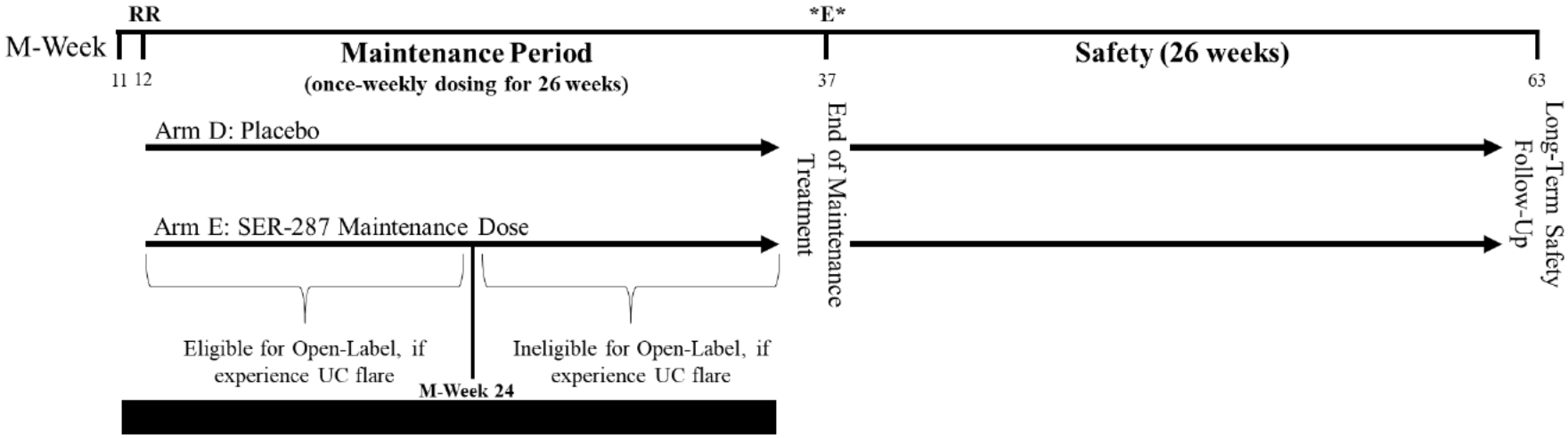
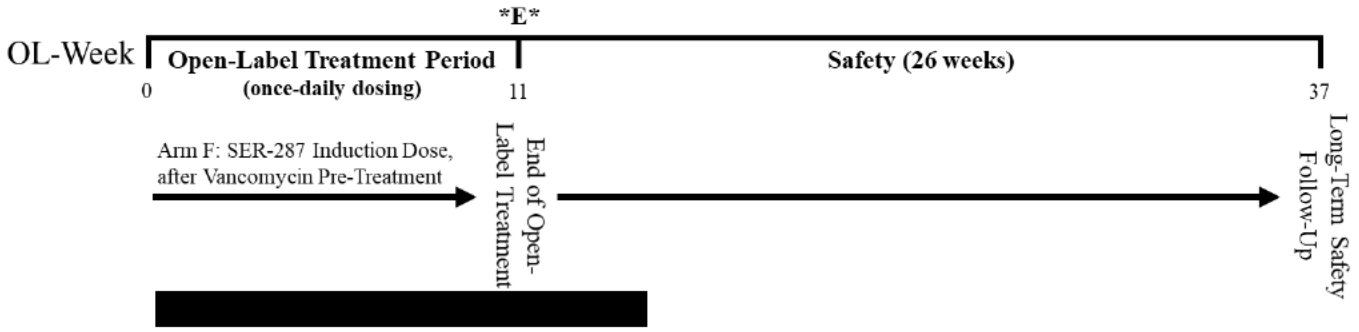


**Figure 2: Subject Treatment Overview: Week 11 Through End-of-Study**

A. Maintenance Treatment: Remitters




B. Open-Label Extension Arm: Non-Remitters



## Table 1: Schedule of Events: Induction Treatment

| | Screening | | Pre-Treatment | Induction Treatment Period - 10 Weeks | | | | | Long-Term Safety Follow-Up[o] | Unscheduled Visit/EoT[n] |
|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **Week -4 to -1** | | **Week 0** | **Week 1 +/-1d** | **Week 3 +3d** | **Week 7 +3d** | **Week 11 +3d** | | **Every 4 Weeks to Week 37/EoS[m] +/-3d** | |
| **VISIT NUMBER** | **1** | **2*** | **3** | **4** | **5** | **6** | **7** | | **8-14** | |
| **Visit Type** | **Clinic** | **Clinic/Endoscopy** (max. 7 days between endoscopy and randomization) | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | | **Phone Calls** | **Clinic** (may include endoscopy) |
| **Procedure/Assessments** | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X | X | | | | | | | | |
| Medical History | X | | | | | | | | | |
| UC History | X | | | | | | | | | |
| Prior Medications & UC Therapies | X | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | | X | X |
| Concomitant Procedures for UC [a] | | X | X | X | X | X | X | | X | X |
| Demographic Data | X | | | | | | | | | |
| Full Physical Exam | X | | | | | | | | | |
| Focused Physical Exam | | | X[i] | | | | X | | | X |
| Vital signs | X | | X[i] | | | | X | | | X |
| Height (at Screening only), Weight | X | | X | | | | X | | | X |
| Review lower endoscopy preparation instructions with subject prior to lower endoscopy[b] | | X | | | | | X | | | X |
| Lower Endoscopy (Local and Central Reads) | | X | | | | | X | | | X |
| Biopsies (4 samples) | | X | | | | | X | | | X |
| Three-Component Modified Mayo Score [c] | | X | | | | | X | | | X |
| IXRS Randomization | | | X | | | | | | | |
| Dispense pre-treatment study drug | | | X[g] | | | | | | | |
| Administer study drug at clinic | | | X[g] | X[g] | | | | | | |
| Return unused study drug | | | | X | X | X | X | | | X |
| Review study drug compliance | | | | X | X | X | X | | | X |
| Dispense study drug [d] | | | | X[j] | X[j] | X[j] | | | | |
| Adverse Event monitoring | | | X[h] | X | X | X | X | | X[l] | X |
| **Clinical Laboratory Tests** | | | | | | | | | | |
| Hematology | X | | X[i] | X[i] | | | X | | | X |
| Blood chemistry | X | | X[i] | X[i] | | | X | | | X |
| Blood for CRP | | | X[i] | | | | X | | | X |
| Blood & Serum for Future Biomedical Research | X | | | X | | | X | | | X |
| Urine Pregnancy test (WOCBP only) Note: Serum at Screening visit only | X | | X[i] | X[i] | X | X | X | | | X |
| Routine Urine Dipstick[c] | X | | | | | | | | | |

## Table 1: Schedule of Events: Induction Treatment (continued)

| | Screening | | Pre-Treatment | Induction Treatment Period - 10 Weeks | | | | | Long-Term Safety Follow-Up[o] | Unscheduled Visit/EoT[n] |
|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **Week -4 to -1** | | **Week 0** | **Week 1 +/-1d** | **Week 3 +3d** | **Week 7 +3d** | **Week 11 +3d** | | **Every 4 Weeks to Week 37/EoS[m] +/-3d** | |
| **VISIT NUMBER** | **1** | **2*** | **3** | **4** | **5** | **6** | **7** | | **8-14** | |
| **Visit Type** | **Clinic** | **Clinic/Endoscopy (max. 7 days between endoscopy and randomization)** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | | **Phone Calls** | **Clinic (may include endoscopy)** |
| **Procedure/Assessments** | | | | | | | | | | |
| Provide Stool Collection Kit | X | | X | X | X | X | X | | | |
| Stool Sample for *C. diff.* testing by toxin assay (EIA) | X[f] | | | | | | | | | |
| Review Stool Collection, Handling & Storage Instructions with Subject | X | | X | X | | | | | | |
| Stool Sample for Microbiome, Metabolomics, Future Biomedical Research | X[f] | | | X | X | X | X[k] | | | X[k] |
| Fecal Calprotectin | X[f] | | | | | | X | | | X |
| IBDQ | | | X[i] | | | | X | | | X |
| Review Subject eDiary Instructions with Subject | X | | | | | | | | | |
| Subject eDiary (daily rectal bleeding and stool frequency) | X | X | X | X | X | X | X | | | X |
| Review Subject eDiary for compliance | | X | X | X | X | X | X | | | X |

(*) A minimum of seven (7) days between Visit 1 and Visit 2 are required to ensure there are a sufficient quantity of eDiary entries to calculate the Stool Frequency subscore; (a) Lower endoscopies performed during study are not to be recorded as a concomitant procedure; (b) Remind subjects when to start clear liquid diet, overnight fast, and bowel prep prior to scheduled lower endoscopy; (c) Three-Component Modified Mayo Score will be calculated electronically from subject diary and central endoscopy read; (d) Instruct subject to take study medication at the same time every morning; At Screening Visit 1, subjects should be asked about their stool frequency and rectal bleeding over the past seven (7) days. Subjects will be provided an electronic diary at Screening Visit 1 to begin daily collection of rectal bleeding & stool frequency; (e) Urine dipstick performed at the study site; if positive for nitrates and/or leukocytes, send sample to central laboratory for analysis; (f) If possible, subjects should provide stool sample on site. If not possible, subject should collect stool sample at home and return to the site as soon as possible. *C. diff* test results must be received before performing lower endoscopy at Screening Visit 2; Remind subjects when to start clear liquid diet, overnight fast, and bowel prep prior to scheduled lower endoscopy; (g) first dose observe for one (1) hour post-dosing (h) Recording of AEs for study will begin after first dose of pre-treatment IP; (i) Perform prior to dosing; (j) IP to be dispensed at this clinic visit; (k) Stool sample to be collected prior to subject starting clear liquid diet for lower endoscopy; (l) During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected. Only SAEs/AESIs and concomitant medications associated with the treatment of SAEs/AESIs will be collected starting from the four (4) week follow-up call through the End of Study. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period; (m) The last safety follow-up call will occur after six (6) weeks, rather than four (4); (n) To accommodate scheduling of clinic visit and/or endoscopy, assessments & procedures for an Unscheduled Visit do not need to take place during one (1) clinic visit; The Unscheduled Visit may also be used for dispensation of study drug as needed; For subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening), an Unscheduled Visit may be used by the PI to determine if the subject is experiencing a UC flare; The Unscheduled Visit can serve as an 'End of Treatment' visit for a subject who ends treatment early in the study but will continue to be followed for safety, or for subjects who decide to leave the study early and not be followed for safety. If subjects decide to end treatment early or early terminate from the study, all study IP should be returned by the subject; (o) Subjects who discontinue early and do not go into either the Maintenance arm or Open Label arm, will be followed for long term safety for 26 weeks post last study drug dose.

## Table 2: Schedule of Events: Maintenance Treatment for Remitters

| | Maintenance Treatment Period - 26 Weeks | | | | | | | Long Term Safety Follow-Up | | Unscheduled Visit/EoT [j] |
|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **M-Week 12 +/-2d** | **M-Week 16 +3d** | **M-Week 20 +3d** | **M-Week 24 +3d** | **M-Week 28 +3d** | **M-Week 32 +3d** | **M-Week 37 +3d/EoT** | **Every 4 Weeks to M-Week 63/EoS[h] +/-3d** | | |
| **VISIT NUMBER** | **M-1** | **M-2** | **M-3** | **M-4** | **M-5** | **M-6** | **M-7** | **M-8 - M-13** | | |
| **Visit Type** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | **Phone Calls** | | **Clinic (may include endoscopy)** |
| **Procedure/Assessments** | | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | | X |
| Concomitant Procedures for UC[a] | X | X | X | X | X | X | X | X | | X |
| **IXRS Re-Randomization** | X | | | | | | | | | |
| Focused Physical Exam | | | | X | | | X | | | X |
| Vital signs | | | | | | | X | | | X |
| Weight | | | | | | | X | | | |
| Review lower endoscopy preparation instructions with subject prior to endoscopy [b] | | | | | | | X | | | X |
| Lower Endoscopy (Local and Central Reads) | | | | | | | X | | | X |
| Biopsies (4 samples) | | | | | | | X | | | X |
| Three-Component Modified Mayo Score[c] | | | | | | | X | | | X |
| Return unused study drug | | X | X | X | X | X | X | | | X |
| Review study drug compliance | | X | X | X | X | X | X | | | X |
| Dispense study drug[d] | X | X | X | X | X | X | | | | |
| Adverse Event monitoring | X | X | X | X | X | X | X | X[i] | | X |
| **Clinical Laboratory Tests** | | | | | | | | | | |
| Hematology | | | | | | | X | | | X |
| Blood chemistry | | | | | | | X | | | X |
| Urine Pregnancy test (WOCBP only) | | X | X | X | X | X | X | | | X |
| Blood & Serum for Future Biomedical Research | | | | | | | X | | | X |
| Blood for CRP | | | | | | | X | | | X |

## Table 2: Schedule of Events: Maintenance Treatment for Remitters (continued)

| | Maintenance Treatment Period - 26 Weeks | | | | | | | Long Term Safety Follow-Up | | Unscheduled Visit/EoT [j] |
|---|---|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **M-Week 12 +/-2d** | **M-Week 16 +3d** | **M-Week 20 +3d** | **M-Week 24 +3d** | **M-Week 28 +3d** | **M-Week 32 +3d** | **M-Week 37 +3d/EoT** | **Every 4 Weeks to M-Week 63/EoS[h] +/-3d** | | |
| **VISIT NUMBER** | **M-1** | **M-2** | **M-3** | **M-4** | **M-5** | **M-6** | **M-7** | **M-8 - M-13** | | |
| **Visit Type** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | **Phone Calls** | | **Clinic (may include endoscopy)** |
| **Procedure/Assessments** | | | | | | | | | | |
| Provide Stool Collection Kit | X | X | X | X | X | X | | | | |
| Stool sample for Microbiome, Metabolomics, Future Biomedical Research | | X | X | X | X | X | X[g] | | | X |
| Fecal Calprotectin | | | | | | | X[g] | | | X |
| IBDQ | | | | | | | X | | | X |
| Subject eDiary (daily rectal bleeding and stool frequency) [e] | X | X | X | X | X | X | X | | | X |
| Review subject eDiary for compliance | X | X | X | X | X | X | X[f] | | | X |

(a) Lower endoscopies performed during study are not to be recorded as concomitant procedure; (b) Remind subjects when to start clear liquid diet, overnight fast, and bowel prep prior to scheduled lower endoscopy; (c) Three-Component Modified Mayo Score will be calculated electronically from subject diary and central endoscopy read; (d) IP for weekly dosing will be dispensed at this clinic visit; Instruct subject to take study drug at the same time every morning; (e) Subjects will continue using same electronic diary; (f) Subjects use of eDiary complete at this visit; subject to leave device on site; (g) Stool sample to be collected prior to subject starting clear liquid diet for lower endoscopy. An aliquot for Fecal Calprotectin is taken from this one stool sample collected at M-Week 37 visit; (h) The last safety follow-up call will occur after six (6) weeks, rather than four (4); (i) During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected. Only SAEs/AESIs and concomitant medications associated with the treatment of the SAEs/AESIs, will be collected starting from the four (4) week follow-up call through the End of Study. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period; (j) To accommodate scheduling of clinic visit and/or endoscopy, assessments & procedures for an Unscheduled Visit do not need to take place during one (1) clinic visit; The Unscheduled Visit may also be used for dispensation of study drug as needed; For subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening), an Unscheduled Visit may be used by the PI to determine if the subject is experiencing a UC flare; The Unscheduled Visit can serve as an 'End of Treatment' visit for a subject who ends treatment early in the study but will continue to be followed for safety, or for subjects who decide to leave the study early and not be followed for safety. If subjects decide to end treatment early or early terminate from the study, all study IP should be returned by the subject.

## Table 3: Schedule of Events: Open-Label Extension Arm for Non-Remitters

| | Open-Label Treatment Period - 11 Weeks | | | | | Long-Term Safety Follow-Up | | Unscheduled Visit/EoT [k] |
|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **OL-Week 0 +/-2d** | **OL-Week 1 +/-1d** | **OL-Week 3 +3d** | **OL-Week 7 +3d** | **OL-Week 11 +3d** | **Every 4 Weeks for 26 Weeks/EoS[j] +/-3d** | | |
| **VISIT NUMBER** | **OL-1** | **OL-2** | **OL-3** | **OL-4** | **OL-5/EoT** | **OL-6 – OL-11** | | |
| **Visit Type** | **Clinic** | **Stool Sample Home Collection** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | **Phone Calls** | | **Clinic (may include endoscopy)** |
| **Procedure/Assessments** | | | | | | | | |
| Concomitant Medications | X | | X | X | X | X | | X |
| Concomitant Procedures for UC[a] | X | | X | X | X | X | | X |
| Focused Physical Exam | | | | | X | | | X |
| Vital signs | | | | | X | | | X |
| Weight | | | | | X | | | |
| IXRS Registration for Open-Label | X | | | | | | | |
| Dispense vancomycin pre-treatment | X | | | | | | | |
| Administer vancomycin pre-treatment at clinic | X | | | | | | | |
| Return unused study drug | | | X | X | X | | | X |
| Review study drug compliance | | | X | X | X | | | |
| Dispense SER-287 | X[e] | | X[g] | X[g] | | | | |
| Adverse Event monitoring | X | | X | X | X | X[i] | | X |
| **Clinical Laboratory Tests** | | | | | | | | |
| Hematology | | | | | X | | | X |
| Blood chemistry | | | | | X | | | X |
| Blood & Serum for Future Biomedical Research | | | | | X | | | X |
| Blood for CRP | | | | | X | | | X |
| Urine Pregnancy test (WOCBP) | X | | X | X | X | | | X |

## Table 3: Schedule of Events: Open-Label Extension Arm for Non-Remitters (continued)

| | Open-Label Treatment Period - 11 Weeks | | | | | Long-Term Safety Follow-Up | | Unscheduled Visit/EoT [k] |
|---|---|---|---|---|---|---|---|---|
| **WEEK NUMBER** | **OL-Week 0 +/-2d** | **OL-Week 1 +/-1d** | **OL-Week 3 +3d** | **OL-Week 7 +3d** | **OL-Week 11 +3d** | **Every 4 Weeks for 26 Weeks/EoS[j] +/-3d** | | |
| **VISIT NUMBER** | **OL-1** | **OL-2** | **OL-3** | **OL-4** | **OL-5/EoT** | **OL-6 – OL-11** | | |
| **Visit Type** | **Clinic** | **Stool Sample Home Collection** | **Clinic** | **Clinic** | **Clinic/ Endoscopy** | **Phone Calls** | | **Clinic (may include endoscopy)** |
| **Procedure/Assessments** | | | | | | | | |
| Provide Stool Collection Kit | X | X | X | X | | | | |
| Stool sample for Microbiome, Metabolomics, Future Biomedical Research | | X[f] | X | | X[l] | | | X |
| Fecal Calprotectin | | | | | X[f] | | | X |
| IBDQ | | | | | X | | | X |
| Subject eDiary (daily rectal bleeding and stool frequency) [b] | X | X | X | X | X[h] | | | X |
| Review subject eDiary for compliance | X | | X | X | X | | | X |
| Review lower endoscopy preparation instructions with subject prior to endoscopy[c] | | | | | X | | | X |
| Lower Endoscopy (Local and Central Reads) | | | | | X | | | X |
| Biopsies (4 samples) | | | | | X | | | X |
| Three-Component Modified Mayo Score[d] | | | | | X | | | X |

(a) Lower endoscopies performed during study are not to be recorded as concomitant procedure; (b) Subjects will continue using same electronic diary; Review pre-treatment dosing and study drug dosing with subject; (c) Remind subjects when to start clear liquid diet, overnight fast, and bowel prep prior to scheduled lower endoscopy; Subjects will return every four (4) weeks for re-supply of study drug that will be taken once-weekly; (d) Three-Component Modified Mayo Score will be calculated electronically from subject diary and central endoscopy read; (e) Two (2) weeks of IP is dispensed at clinic visit; subject should take Open-Label Week 3 dose on site; (f) Stool sample to be collected at home. Subject can return stool sample to clinic or it can be returned via courier to clinical site. An aliquot for Fecal Calprotectin is taken from this one stool sample collected at OL-Week 11 visit; (g) IP is dispensed at this clinic visit; (h) Subjects use of eDiary complete at this visit; subject to leave device on site; (i) During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected. Only SAEs/AESIs and concomitant medications associated with the treatment of SAEs/AESIs will be collected starting from the four (4) week follow-up call through the End of Study. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period; (j) The last safety follow-up call will occur after six (6) weeks, rather than four (4); (k) To accommodate scheduling of clinic visit and/or endoscopy, assessments & procedures for an Unscheduled Visit do not need to take place during one (1) clinic visit; The Unscheduled Visit may also be used for dispensation of study drug as needed; For subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening), an Unscheduled Visit may be used by the PI to determine if the subject is experiencing a UC flare; The Unscheduled Visit can serve as an 'End of Treatment' visit for a subject who ends treatment early in the study but will continue to be followed for safety, or for subjects who decide to leave the study early and not be followed for safety. If subjects decide to end treatment early or early terminate from the study, all study IP should be returned by the subject; (l) Stool sample to be collected prior to subject starting clear liquid diet for lower endoscopy

## LIST OF STUDY PERSONNEL

| | |
|---|---|
| **Sponsor** | Seres Therapeutics, Inc.<br>200 Sidney Street<br>Cambridge, MA 02139<br>USA |
| **Contract Research Organization** | [redacted] |
| **Central Laboratory** | [redacted] |
| **Central Reader** | [redacted] |

# 1 Table of Contents

**Tables in Text**



**Figures in Text**

## List of Abbreviations

| Abbreviation | Term |
|---|---|
| 5-ASA | 5-aminosalicylate |
| 6-MP | 6-mercaptopurine |
| AE | Adverse event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| AZA | Azathioprine |
| BP | Blood pressure |
| cc | Cubic centimeter |
| CD | Crohn's disease |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CHMP | Committee for Medicinal Products for Human Use |
| Cm | Centimeter |
| CMH | Cochran-Mantel-Haenszel |
| CRO | Contract research organization |
| CRP | C-reactive protein |
| CSR | Clinical Study Report |
| D | Day |
| dL | Deciliter |
| DNA | Deoxyribonucleic acid |
| eCRF | Electronic case report form |
| EIA | Enzyme immunoassay |
| EMA | European Medicines Agency |
| EDC | Electronic data capture |
| eDiary | Electronic diary |
| EOT | End-of-treatment |
| ES | Endoscopic subscore |
| FDA | Food and Drug Administration |
| FMT | Fecal microbiota transplantation |
| g | Grams |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| HCl | Hydrogen chloride |
| HDPE | High-density polyethylene |
| HR | Heart rate |
| IB | Investigator's Brochure |
| IBD | Inflammatory bowel disease |
| IBDQ | Inflammatory Bowel Disease Questionnaire |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug Application |
| IP | Investigational product |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat; Intention-to-Treat |
| IXRS | Interactive web/voice response system |
| JAK | Janus kinase |
| LFT | Liver function test |
| LOCF | Last observation carried forward |
| mcITT | Microbiome Modified Intent-to-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| MH | Medical history |
| mITT | Modified Intent-to-Treat |
| mL | Milliliter |
| $mm^3$ | Cubic millimeter |
| mmHg | Millimeters of mercury |
| MMX | Multi-matrix system |
| Pbo | Placebo |
| PE | Physical examination |
| PGA | Physician Global Assessment |
| PI | Principal Investigator |
| PP | Per Protocol |
| PT | Preferred term |
| QD | Once-daily |

| | |
|---|---|
| QID | Four (4) times per day |
| RB | Rectal bleeding subscore |
| RHI | Robarts Histopathological Index |
| rRNA | Ribosomal ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| [redacted] | [redacted] |
| SD | Standard deviation |
| SF | Stool frequency subscore |
| SID | Subject identification |
| SOC | System organ class |
| [redacted] | [redacted] |
| TEAE | Treatment emergent adverse event |
| TLF | Tables, listings and figures |
| TNF | Tumor necrosis factor |
| UC | Ulcerative colitis |
| ULN | Upper limit of normal |
| U.S. | United States |
| USP | United States Pharmacopeia |
| Vanco. | Vancomycin |
| Wk, wks, wkly | Week, weeks, weekly |
| WHO | World Health Organization |
| WMS | Whole metagenomic sequencing |
| WOCBP | Women of child bearing potential |

# 1 INTRODUCTION

## 1.1 Background

### *1.1.1 Indication and Prevalence*

Ulcerative colitis (UC) is a relapsing-remitting chronic inflammatory disorder affecting the mucosal surface of the colon, leading to episodes of rectal bleeding, increased stool frequency, urgency and mucosal inflammation (Danese and Fiocchi, 2011). The disease mostly affects young and middle-aged individuals, and 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 incidence of ulcerative colitis is rising worldwide, and the prevalence of the disease is highest in the United States, Canada, and Europe. In the United States alone, the prevalence of ulcerative colitis in adults is estimated to be 263 per 100,000, while in the pediatric population (age <20 years), prevalence of the disease is estimated to be 33.9 per 100,000 (Kappelman et al., 2013).

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 five (5) years of disease. There is currently no cure for UC. Therefore, the therapeutic goal is two-fold: first, to alleviate and control symptoms (induction of clinical remission) and to promote endoscopic remission; second, to prevent disease recurrence (maintenance of clinical remission).

### *1.1.2 Existing Practices*

Current medical therapies for UC include sulfasalazine, aminosalicylates (5-ASAs), steroids, immunomodulators (azathioprine, methotrexate and 6-mercaptopurine), anti-TNF agents (infliximab, adalimumab, golimumab), anti-integrin agents (vedolizumab), and calcineurin inhibitors (cyclosporine and tacrolimus) (Grinspan and Kornbluth, 2015). Most of these medications are immunosuppressant agents targeted for moderate-to-severe disease, while there remains an unmet need for safer agents with novel mechanisms of action. This is especially true for patients with mild-to-moderate UC, who experience frequent flares on aminosalicylates or immunomodulators, or as an alternative to aminosalicylate or immunomodulator therapy in those intolerant to these classes of medications. Alterations in the intestinal microbiome has been identified in patients with UC, and preliminary evidence suggests that SER-287, may affect clinical outcomes. This study will assess whether an ecology of bacterial spores in SER-287 can correct the microbial alterations in UC and lead to clinical efficacy in patients with active mild-to-moderate UC.

### *1.1.3 Disease Pathogenesis and Microbiome Involvement*

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).

The microbiomes of adults are comprised of four (4) principal bacterial phyla: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria, of which Bacteroidetes and Firmicutes are the dominant members in healthy subjects (Human Microbiome Project Consortium, 2012). Inflammatory bowel disease (IBD), including UC, is widely thought to be linked to the gut microbiome, and, in turn, to environmental factors which affect microbiome composition (Huttenhower et al., 2014). Multiple cohort studies have characterized changes in fecal and mucosal microbiomes associated with UC using next generation sequencing methods including 16S rRNA and whole metagenomic shotgun sequencing (WMS) (Frank et al., 2007; Morgan et al., 2012; Papa et al., 2012; Walujkar et al., 2014; Willing et al., 2010; Wills et al., 2014, Halfvarson et al., 2017, Schirmer et al., 2018).

The emerging picture from these studies is that the microbiome of UC patients tends to exhibit certain general features of dysbiosis, including: (1) lower microbial diversity, (2) a greater prevalence of facultative anaerobes in the family *Enterobacteriaceae,* and (3) a depletion of commensal spore-forming taxa in 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). Importantly, however, multiple studies have identified substantial variability in UC microbiomes related to disease subtype and disease severity (Morgan et al., 2012; Papa et al., 2012, Halfverson et al., 2017; Schirmer et al., 2018). Studies focusing primarily on UC subjects in clinical remission, or with mild forms of disease, find little differentiation between microbiomes from UC subjects and those from healthy individuals (Willing et al., 2010), and other studies have found a clear connection between increased disease severity and increased dysbiosis (Papa et al., 2012; Walujkar et al., 2014). A meta-analysis of four (4) cohort studies (Morgan et al., 2012; Papa et al., 2012; Willing et al., 2010; Wills et al., 2014), conducted by Seres, supports the above general conclusions from the literature. Comparison of bacterial richness (α-diversity) and composition (β-diversity) of microbiomes from UC subjects to 313 healthy individuals characterized with 16S rRNA sequencing (The Human Microbiome Project Consortium, 2012) showed that UC subjects with active disease tended to have less diverse microbiomes than individuals with inactive disease, and that UC subject microbiomes were significantly enriched in genera from the family *Enterobacteriaceae*, which have been implicated in several studies as related to increased oxidative stress and host inflammatory response (Winter et al., 2013; Caballero and Pamer, 2015; Morgan et al., 2012; Lawley and Walker, 2013).

### *1.1.4 Pharmacological Concept for Microbiome Therapeutic*

Fecal microbiota transplantation is the transfer of stool from a healthy donor to a recipient. The use of fecal microbiota transplantation (FMT) to treat UC provided proof-of-concept that administering a microbiome therapeutic results in restoration of a healthy microbiome and a clinical benefit in UC (Moayyedi et al., 2015; Rossen et al., 2015; Paramsothy et al., 2017). SER-287 is composed of the spore-forming fraction of the intestinal microbiota that is underrepresented in UC patients and is potentially safer and more effective than traditional FMT for UC.

### *1.1.5 Investigational Product*

SER-287 (Eubacterial Spores, Purified Suspension, Encapsulated) is an ecology of bacterial spores enriched from fecal donations obtained from healthy, screened donors, [redacted]. 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 administration to subjects.

## 1.2 SER-287 SERES-101 Data in Active Mild-to-Moderate Subjects

### *1.2.1 Clinical Efficacy*

Clinical experience with SER-287 includes a completed Phase 1B study (SERES-101): a multicenter, randomized, double-blind, placebo-controlled, multiple dose study which evaluated the safety and tolerability of SER-287, in addition to the microbiome alterations and pharmacodynamics, associated with three (3) SER-287 dosing regimens, involving two (2) dose levels, in adult subjects with active mild-to-moderate ulcerative colitis. Subjects with Mayo scores of 4 to 10, at 20 sites across the United States, were eligible for enrollment.

A total of 58 subjects were randomized into one (1) of four (4) treatment arms (Table 4), and endpoints were assessed following a six-day pre-treatment period (vancomycin or placebo) followed by an eight-week induction treatment period (SER-287 or matching placebo).

**Table 4: SERES-101 Treatment Arms**

| Arm | Pre-Treatment (QID for 6 days) | Induction Treatment (8 weeks) |
|---|---|---|
| A | Placebo | SER-287 weekly: [redacted] |
| B | Placebo | Placebo daily |
| C | Vancomycin | SER-287 daily: [redacted] |
| D | Vancomycin | SER-287 weekly: [redacted] |

[redacted]

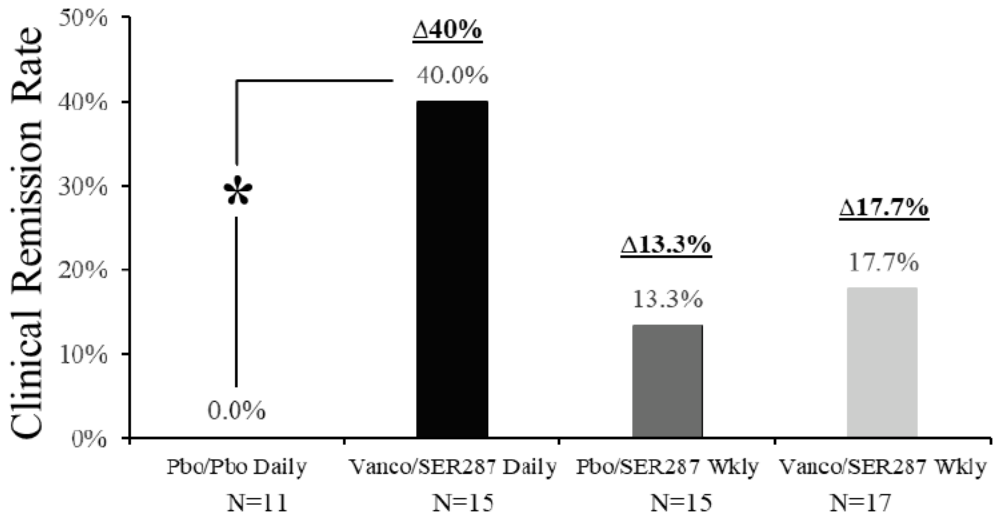
Results were analyzed using the intent-to-treat (ITT) "worst case" analysis method, which includes all randomized subjects in the analysis. Subjects who had incalculable clinical endpoints due to missing data, added a UC medication due to UC flare during the

treatment period or discontinued from the study prior to Day 48 were considered not to have achieved any clinical endpoints (worst outcome). However, if the end-of-study endoscopy at Day 48, or later, was available, and the subject didn't take any additional UC medication due to UC flare, then the Mayo score including endoscopy after Day 48 was used to define success or failure for that subject.

In the "worst case" analysis, a statistically significant clinical remission improvement was observed in the vancomycin pre-treatment / SER-287 once-daily dosing arm as compared to the placebo arm: 40% (6 of 15 in SER-287) vs. 0% (0 of 11 in placebo); difference from placebo (SER-287 - placebo) 40.0% (95% CI: 15.2%, 64.8%; p=0.0237) (Figure 3).

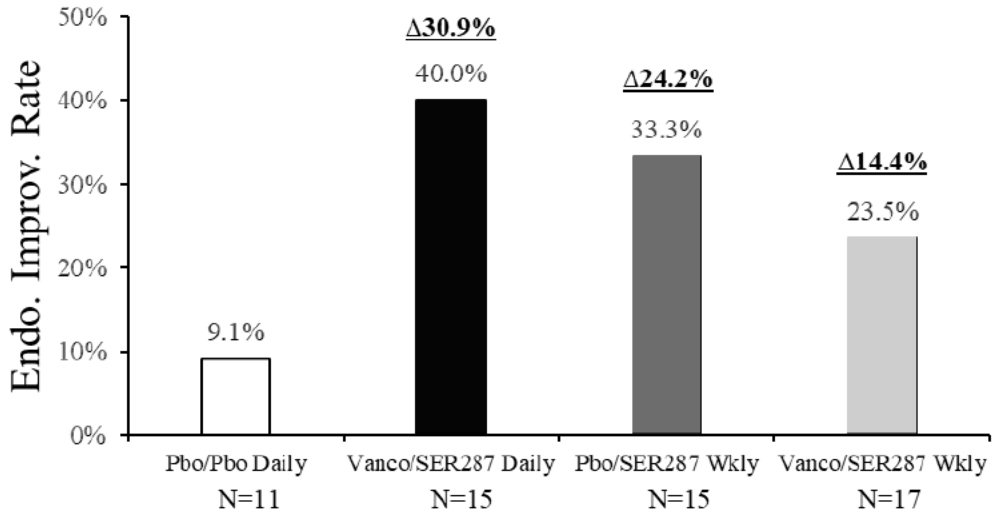
**Figure 3: SERES-101 Efficacy Data – ITT**

A. Clinical Remission




Legend: * = statistically significant; Δ = change from placebo; pbo = placebo; Vanco = vancomycin; wkly = weekly; Clinical remission was defined as a total modified Mayo score of less than or equal to 2, and an endoscopic subscore of 0 or 1; Endoscopy measures were analyzed by a central reader.

B. Endoscopic Improvement




Legend: Δ = change from placebo; pbo = placebo; Vanco = vancomycin; wkly = weekly; Endoscopic improvement was defined as a decrease in endoscopic subscore of greater than or equal to 1 point. Endoscopy measures were analyzed by a central reader.

The SER-287 weekly treatment arms also showed an improvement over placebo in both clinical remission and endoscopic improvement, but the effect was less than with the daily dosing regimen, demonstrating a dose-response to SER-287 in both the rate of clinical remission (Figure 3A) and the rate of endoscopic improvement (Figure 3B). Addition of vancomycin to the SER-287 weekly dosing regimen did not clearly alter efficacy effects; however, effects of vancomycin were seen on microbiome engraftment (Section 1.2.4, Microbiome Engraftment and Post-Baseline Composition).

### *1.2.2 Clinical Safety*

The primary safety objective (short-term safety) was to evaluate the safety and tolerability of SER-287 in adults with active mild-to-moderate ulcerative colitis up to 92 days after randomization as determined by clinical and laboratory safety assessments.

The Treatment-emergent Adverse Events (TEAEs) were balanced across all the treatment arms. There was one (1) serious AE (SAE), suicidal ideation in a subject with a history of depression, which was considered not to be related to study drug by the investigator. All AEs were considered mild to moderate in intensity. Gastrointestinal (GI) disorders had the greatest number of AEs compared to other System Organ Classes, with the most efficacious treatment arm (vancomycin/SER-287 Daily) experiencing the lowest percentage of GI AEs.

All SER-287 treatment arms, following a pre-treatment period with vancomycin or placebo, were safe and tolerable, with safety equivalent to placebo. The safety profile, when evaluating GI AEs, showed an improvement in the SER-287 daily treatment arm

compared to placebo or the SER-287 weekly treatment arms. This finding provides an independent assessment of efficacy as the GI AEs likely reflect ulcerative colitis disease activity.

### *1.2.3 Baseline Microbiome Composition*

Comparison of the baseline microbiome of UC subjects enrolled in the SERES-101 Phase 1B study to 202 healthy individuals characterized as part of the Human Microbiome Project (Lloyd-Price et al., 2017), based on high-resolution WMS genomics, demonstrates features of UC dysbiosis comparable to that reported in the literature.

First, minimal differences in total diversity were observed between UC and healthy subjects; this is similar to findings in recent large cohort studies of the UC microbiome (Imhann et al., 2018, Halfverson et al., 2017, Schirmer et al., 2018). Notably, since the SERES-101 subject population consists of subjects with mild-to-moderate disease, the expected baseline dysbiosis is less than observed in cohort studies which include subjects with severe disease. Second, microbiomes from SERES-101 subjects at baseline tended to have a higher abundance of taxa from the family *Enterobacteriaceae* than healthy subjects ($p=0.110$, 2-tailed t-test), consistent with the findings of a meta-analysis of cohort studies conducted by Seres. Additionally, the mean abundance of *Enterobacteriaceae* was higher in subjects with more severe disease at baseline (baseline endoscopic subscore [ES] $\geq 2$), with the highest abundance in subjects with baseline ES of 3. The mean abundance of *Enterobacteriaceae* was 2.2-fold higher in subjects with baseline ES of 3 than in subjects with baseline ES of 1. Notably, several publications implicate an increased abundance of *Enterobacteriaceae* taxa with increased oxidative stress in the gastrointestinal tract, related to increased host inflammatory response (Winter et al., 2013; Caballero and Pamer, 2015; Morgan et al., 2012; Lawley and Walker, 2013).

### *1.2.4 Microbiome Engraftment and Post-Baseline Composition*

The two microbiome primary objectives of the SERES-101 study were to (1) determine the engraftment of SER-287 bacteria into each of the treatment arms, relative to placebo, and (2) to compare the baseline composition of the intestinal microbiome to the post-baseline composition after treatment with SER-287, or placebo. The fecal microbiome of SERES-101 subjects and SER-287 drug product were characterized using WMS, a high-resolution and widely utilized methodology (e.g. Lloyd-Price et al., 2017) which enables species-level taxonomic identifications (Truong et al., 2015).

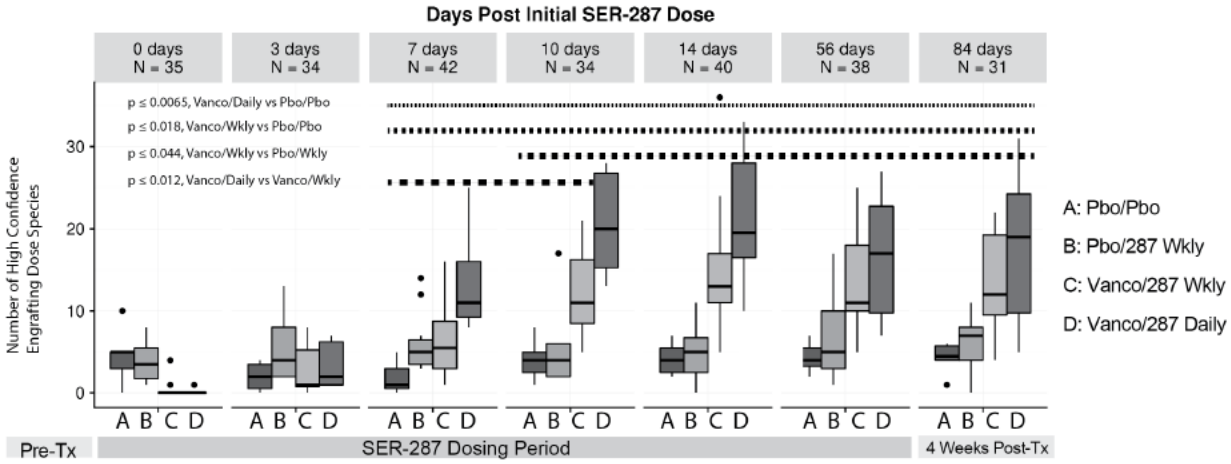
A statistically significant signal of engraftment of SER-287 bacteria in SERES-101 subjects was observed following treatment with SER-287, which led to a rapid and durable change in subject microbiomes (Figure 4). Vancomycin pre-treatment was associated with significantly higher levels of engraftment of SER-287 relative to placebo pre-treatment in subjects receiving a weekly dose of SER-287, starting at one (1) week after the start of dosing ($p<0.007$ for Vanco/SER287 Daily vs. Pbo/Pbo Daily, $p<0.018$ for Vanco/SER287 Wkly vs. Pbo/Pbo Daily, one-sided Mann-Whitney U test). Engraftment was dose-dependent within vancomycin pre-treatment arms; the daily dosing arm showed significantly faster engraftment than the weekly dosing arm ($p<0.012$ for Vanco/SER287 Wkly vs. Vanco/SER287 Daily). Significant engraftment of

SER-287 in the vancomycin pre-treatment arms was observed as early as one (1) week after the initial SER-287 dose (p=0.004 for Vanco/SER287 Daily vs. Pbo/Pbo Daily, p=0.025 for Vanco/SER287 Wkly vs. Pbo/Pbo Daily). Additionally, engraftment of SER-287 bacteria in the vancomycin pre-treatment arms was detectable four (4) weeks after the completion of SER-287 dosing (p=0.005 for Vanco/SER287 Daily vs. Pbo/Pbo Daily, p=0.007 for Vanco/SER287 Wkly vs. Pbo/Pbo Daily), at levels comparable to those observed during the dosing period, suggesting that SER-287 taxa can durably persist in subjects for at least four (4) weeks following cessation of drug administration (Figure 4).

Treatment with SER-287 led to changes in the overall composition of the microbiome. The microbiome of subjects in the Vanco/SER-287 Daily dosing arm shifted and exhibited significantly greater similarity to SER-287 drug product one (1) week after the start of treatment (p=0.001); subjects in the SER-287 weekly dosing arm shifted, but did not show comparable similarity to the SER-287 dose until the study endpoint (p=0.016) (Figure 4).

Notably, the composition of the microbiome in subjects in the daily dosing arm was stable from one (1) week after the start of treatment through four (4) weeks after the end of the dosing period. Subjects in the daily dosing arm also showed significantly higher richness of spore-forming taxa at the end of the treatment period (p=0.037) relative to baseline, indicating that treatment with SER-287 was effective in shifting the composition of subject microbiomes. Notably, comparison of the microbiomes from subjects who achieved clinical remission in the Vanco/SER-287 Daily arm to those who did not, revealed distinct patterns in microbial composition – subjects who achieved remission tended to demonstrate an increased prevalence of certain commensal species, including both species present and absent in SER-287 (Figure 4).

**Figure 4: SERES-101 High-Confidence Engraftment of SER-287**




Summary: High-confidence engraftment of SER-287 species genomically detected in SER-287 drug product and absent in subjects at baseline is significant and dose-dependent starting at seven (7) days after the start of dosing and continuing through the end of the treatment period, when all available samples and subjects are considered. Comparable statistical significance was also achieved for both populations pre-defined in the SERES-101 SAP.

Legend: pbo = placebo; Vanco = vancomycin; wkly = weekly; The y-axis shows the number of high-confidence engrafting dose species, and the x-axis shows the visit date. The first row on the top of the x-axis shows the number of days after the start of SER-287 dosing, and the second row indicates the total subjects across all arms available in the analysis for a given timepoint. The dashed lines indicate statistical significance for the comparisons indicated. Treatment arms are labeled below the figure for each timepoint; from left to right within each timepoint, arms shown are: Pbo/Pbo (A), Pbo/SER-287 Weekly (B), Vanco/SER-287 Weekly (C), and Vanco/SER-287 Daily (D).

## 1.3 Phase 2B Overview

SERES-201 is a Phase 2B randomized, double-blind, placebo-controlled, multiple dose, multicenter study designed to evaluate the efficacy, safety and microbiome alterations associated with a regimen of pre-treatment with vancomycin followed by treatment with two (2) dose levels of SER-287, in adult subjects, age 18-80, with active mild-to-moderate UC.

The primary objective of the study is to assess the efficacy of once-daily dosing of SER-287 (Induction Dose) for 10 weeks, after pre-treatment with vancomycin, to achieve clinical remission in subjects with active mild-to-moderate ulcerative colitis. In addition, the study will evaluate multiple dosing regimens of SER-287, the safety and efficacy of SER-287, subjects' microbiome dynamics throughout treatment, and post-treatment effects of SER-287.

Enrollment in this trial, as well as the clinical endpoints, will be based upon a composite Three-Component Modified Mayo Score, which sums patient-reported rectal bleeding and stool frequency subscores, collected daily using an eDiary, with endoscopy subscore. Endoscopic subscores will be determined by qualified gastroenterologists – first locally, and then by an independent, blinded central reader. The endoscopy central readers will remain blinded to subjects' treatment assignments throughout the entire study. If the local and central scores are discordant, a second independent, blinded central reader will

score the video (adjudication). If all of the scores are different from one another, then the median of the three (3) scores will be used as the final endoscopic subscore.

This study will enroll subjects with a total Three-Component Modified Mayo Score of 3 to 7, inclusive, with inclusion requiring a stool frequency subscore $\geq 1$ and an endoscopic subscore $\geq 1$.

This Three-Component Modified Mayo Score is adapted from the overall Mayo scoring system (Schroeder et al., 1987, shown in Appendix 1), a measure of UC disease activity which ranges from 0 to 12 points, which consists of four (4) subscores (stool frequency, rectal bleeding, endoscopy, and physician global assessment [PGA]), each graded from 0 to 3, with higher scores indicating more severe disease. The composite Three-Component Modified Mayo Score is a recommended measure (FDA CDER, 2016) which omits the PGA subscore, excludes friability from an endoscopic subscore of 1, and ranges from 0 to 9 points.

Subjects will be randomized to one (1) of three (3) study arms (Table 5), each of which contain a six-day pre-treatment period (vancomycin or matching placebo) and a 10-week Induction Treatment period (SER-287 or matching placebo).

**Table 5: SERES-201 Induction Treatment Arms**

| Arm | Pre-Treatment (QID for 6 days) | Induction Treatment (QD for 10 weeks) |
|---|---|---|
| A | Placebo | Placebo |
| B | Vancomycin | SER-287 Induction Dose |
| C | Vancomycin | SER-287 Step-Down Induction Dose |

[redacted]

Subjects will be assessed for clinical remission status following 10 weeks of Induction Treatment.

- Remitters will be re-randomized to one (1) of two (2) Maintenance Treatment study arms (Table 6):
  - Arm D, treatment with placebo, to assess durability of clinical remission, and serve as a control
  - Arm E, treatment with a SER-287 Maintenance Dose, to assess maintenance of clinical remission with a once-weekly dosing regimen
- Non-Remitters will enter the Open-Label Extension arm, Arm F (Table 6).

**Table 6: SERES-201 Post-Induction Treatment Arms**

| Arm | Study Phase | Pre-Treatment (QID for 6 days) | Treatment | Frequency of Treatment | Treatment Duration |
|---|---|---|---|---|---|
| D | Maintenance Treatment | N/A | Placebo | Once-Weekly | 26 weeks |
| E | | N/A | SER-287 Maintenance Dose | Once-Weekly | 26 weeks |
| F | Open-Label Extension | Vancomycin | SER-287 Induction Dose | Once-Daily | 10 weeks |

[redacted]

All subjects will be followed for long-term safety for 26 weeks following their last treatment dose.

The study duration, from Screening through last follow-up, will be up to 67 weeks.

## 1.4 Rationale

### *1.4.1 Rationale for Induction Dosing Regimen*

This study will evaluate the efficacy of daily dosing of SER-287 for 10 weeks to induce clinical remission, as supported by the efficacy results from the eight (8) weeks of induction treatment in the SERES-101 Phase 1B study, in active mild-to-moderate UC subjects. The daily dosing arm from the SERES-101 study was more efficacious than weekly dosing (Figure 3) and was safe and well tolerated at all tested dose regimens.

Two (2) once-daily SER-287 induction dosing regimens will be examined in this study:

[redacted]

### *1.4.2 Rationale for Maintenance Dosing Regimen*

Subjects who achieve clinical remission after 10 weeks of induction treatment will enter the placebo-controlled, 26-week Maintenance Treatment phase, [redacted]. There are two (2) objectives of the maintenance phase:

a. To test durability of the clinical remission: In the SERES-101 Phase 1B study, there were no flares after 26 weeks of safety follow-up among 11 SER-287-treated subjects who achieved clinical remission at the end of treatment. In addition, it was observed that microbiome engraftment changes were stable for one (1) month after stopping SER-287 dosing,

consistent with the properties of a live biological drug. The placebo arm of the maintenance treatment phase of SERES-201 will, therefore, explore this sustained clinical remission, as well as enable assessment of time-to-flare/disease worsening, within a larger subject population.

b. To explore whether intermittent dosing of SER-287 after induction treatment can maintain clinical remission, comparing a weekly Maintenance Dose of SER-287 to placebo, over 26 weeks.

### *1.4.3 Rationale for Open-Label Extension Dosing Regimen*

Subjects who do not achieve clinical remission after 10 weeks of induction treatment will enter the Open-Label Extension arm, where they will receive pre-treatment with vancomycin, followed by 10 weeks of daily SER-287 (Induction Dose).

The Open-Label Extension will allow Non-Remitters who were assigned to the placebo or the Step-Down Induction Dose regimen during the Induction Treatment phase, to receive the Induction Dose of SER-287. For those who were on the SER-287 Induction Dose during the Induction Treatment Period, the Open-Label Extension will test whether an additional Induction Treatment Period with daily dosing of SER-287 will induce clinical remission.

### *1.4.4 Rationale for Antibiotic Pre-Treatment*

The pre-treatment vancomycin regimen in SERES-101 is hypothesized to create a niche in the intestinal microbiota to facilitate engraftment of the SER-287 dose. Data from the SERES-101 study demonstrated that vancomycin pre-treatment reduces the presence of spore forming Firmicutes immediately prior to SER-287 dosing. In addition, significantly higher engraftment with weekly SER-287 dosing was observed following vancomycin pre-treatment compared to placebo pre-treatment. Finally, the treatment arm with greatest clinical remission and endoscopic improvement rates in the SERES-101 study included pre-treatment with vancomycin and daily treatment with SER-287 [redacted] for eight (8) weeks.

The value of antibiotics in IBD, both UC and Crohn's disease (CD), have been examined in many studies using a variety of antibiotics, both monotherapy and combination therapy. The authors of a 2016 meta-analysis (Nitzan, 2016) concluded that antibiotics may play a role in CD patients with pouchitis and may prevent post-operative recurrence of CD; however, the data on the role of antibiotics in UC are sparse and most studies do not demonstrate a clear benefit. Society guidelines do not recommend antibiotics for treatment of UC (Bressler et al., 2015, Kornbluth et al., 2010).

### *1.4.5 Rationale for Endpoints*

The Mayo score is a widely utilized tool for UC drug development; it measures UC disease activity based on clinical signs and symptoms of UC (FDA CDER, 2016). This study will utilize a Three-Component Modified Mayo Score (composed of patient reported outcomes using a daily diary and an endoscopy subscore). The Three-Component Modified Mayo score, as proposed herein, is recommended by the 2016 FDA Guidance for Industry on UC Clinical Trial Endpoints (FDA CDER, 2016). The

efficacy endpoints in this study include clinical remission (primary), endoscopic remission and endoscopic improvement (secondary). In this study, clinical remission is based on the Three-Component Modified Mayo Scoring system and is defined as a stool frequency subscore of 0 or 1 with at least a one-point decrease from baseline, rectal bleeding subscore of 0 and endoscopic subscore of 0 or 1 (modified, excludes friability), with at least a one-point decrease from baseline. All endpoints will be measured at 1) baseline (Screening Visit 2) prior to randomization, 2) after 10 weeks of induction treatment and 3) after Maintenance or Open-Label treatment.

Symptoms of disease will be assessed throughout the study via the patient reported outcome components of the Mayo score, rectal bleeding and stool frequency, using daily data from subjects' electronic diary (eDiary) entries.

Drug effects on mucosal healing will be assessed using lower endoscopy and histologic assessment of biopsies:

1. Appearance of the mucosa will be assessed using lower endoscopy and the Mayo scoring system
2. Histological mucosal healing will be assessed using Robarts Histopathological Index (RHI; Mosli et al., 2017) and Geboes Score (Geboes et al., 2000)

Safety and tolerability will be evaluated by comparing safety parameters across treatment arms, including incidence of AEs, laboratory evaluations, vital sign measurements and physical examination findings, before and after treatment.

SERES-101 provided safety on 47 subjects who received up to eight (8) weekly doses (32 subjects) or up to 56 daily doses (15 subjects) of SER-287. The current study will add safety data for 67 subjects at approximately the same dose as the SERES-101 study (Arm B, Table 5), and for 67 subjects at a lower dose (Arm C, Table 5).

This study will also evaluate microbiome changes. Engraftment (a secondary endpoint) is defined as the outgrowth of bacteria that comprise the SER-287 drug product in a subject's gastrointestinal tract, post-treatment. This study will evaluate the engraftment of SER-287 bacteria in each treatment arm and will evaluate mechanism of action data for SER-287.

There are several additional exploratory endpoints.

# 2 OBJECTIVES

## 2.1 Primary Objective

- To demonstrate the efficacy of SER-287, after 10 weeks of induction dosing (following vancomycin pre-treatment), in achieving clinical remission

## 2.2 Key Secondary Objectives

- To demonstrate the efficacy of SER-287, after 10 weeks of step-down induction dosing (following vancomycin pre-treatment), in achieving clinical remission
- To demonstrate the efficacy of SER-287, after 10 weeks of induction dosing (following vancomycin pre-treatment), in achieving endoscopic improvement
- To demonstrate the efficacy of SER-287, after 10 weeks of step-down induction dosing (following vancomycin pre-treatment), in achieving endoscopic improvement

## 2.3 Other Secondary Objectives

- To demonstrate the efficacy of each SER-287 treatment arm in achieving endoscopic remission after 10 weeks of induction treatment
- To demonstrate the efficacy of each SER-287 treatment arm in achieving histological mucosal healing after 10 weeks of induction treatment
- To demonstrate the efficacy of each SER-287 treatment arm in achieving clinical remission with normalization of stool frequency after 10 weeks of induction treatment
- To evaluate the efficacy of each SER-287 treatment arm on symptomatic remission (rectal bleeding and stool frequency) after 10 weeks of induction treatment
- To evaluate the engraftment of SER-287 bacteria from each SER-287 treatment arm into the intestinal microbial community over time
- For EMA consideration only (see Section 3, Definitions):
    - To demonstrate the efficacy of SER-287 to induce clinical remission, using less stringent definition
    - To demonstrate the efficacy of SER-287 to induce clinical remission, using more stringent definition
    - To demonstrate the efficacy of SER-287 to induce symptomatic remission and endoscopic remission as co-endpoints

## 2.4 Safety Objective

To evaluate safety and tolerability of SER-287

## 2.5 Exploratory Objectives

- To evaluate clinical remission at the end of maintenance treatment
- To evaluate endoscopic remission at the end of maintenance treatment
- To evaluate histological mucosal healing at the end of maintenance treatment
- To evaluate clinical remission at the end of open-label treatment
- To evaluate endoscopic improvement at the end of open-label treatment

- To evaluate endoscopic remission at the end of open-label treatment
- To evaluate histological mucosal healing at the end of open-label treatment
- To evaluate the effect of SER-287 treatment on symptomatic remission (rectal bleeding and stool frequency) over time
- To evaluate the clinical remission rate of SER-287, by donor, after 10 weeks of induction treatment
- To assess improvement in quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ)
- To assess changes in serum biomarkers (C-reactive protein [CRP]) and fecal biomarkers (fecal calprotectin)
- To evaluate changes in the composition of the intestinal microbiome over time
- To evaluate changes in signatures of host and microbial functional responses over time

# 3 DEFINITIONS

## 3.1 Clinical Remission

Due to the differences in the definition of clinical remission in the U.S. FDA Guidance Ulcerative Colitis: Clinical Trial Endpoints (FDA CDER 2016) and the EMA "Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis" (EMA/CHMP, 2018), the definitions for clinical remission, as well as associated endpoints, to be used for the U.S. FDA and the EMA analyses, are provided below.

### *3.1.1 U.S. FDA*

*3.1.1.1 Clinical Remission for the Induction and Open-Label Treatment Periods:*

- Stool Frequency subscore = 0 or 1, with at least one-point decrease from baseline
- Rectal Bleeding subscore = 0
- Endoscopic subscore = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline
- No occurrence of UC Flare during the treatment period

*3.1.1.2 Clinical Remission for the Maintenance Treatment Period (Sustained from Week 11 through M-Week 37):*

- Stool Frequency subscore = 0 or 1
- Rectal Bleeding subscore = 0
- Endoscopic subscore = 0 or 1 on modified Mayo Score
- No occurrence of UC Flare during the treatment periods

*3.1.1.3 Clinical Remission including normalization of stool frequency:*

- Stool Frequency subscore = 0
- Rectal Bleeding subscore = 0
- Endoscopic subscore = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline
- No occurrence of UC Flare during the treatment period

### *3.1.2 EMA*

*3.1.2.1 Clinical Remission – Less stringent:*

- Stool Frequency subscore = 0 or 1
- Rectal Bleeding subscore = 0
- Endoscopic subscore = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline
- No occurrence of UC Flare during the treatment period

*3.1.2.2 Clinical Remission – More stringent:*

- Stool Frequency subscore = 0 or 1
- Rectal Bleeding subscore = 0

- Endoscopic subscore = 0 on modified Mayo Score
- No occurrence of UC Flare during the treatment period

*3.1.2.3 Co-endpoints:*

- Symptomatic remission:
    a. Stool Frequency subscore = 0 or 1
    b. Rectal Bleeding subscore = 0
- Endoscopic remission
    a. Endoscopic subscore = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline

## 3.2 Endoscopic Improvement

Endoscopic subscore decrease from baseline of at least one (1) point, as assessed by flexible sigmoidoscopy or colonoscopy

## 3.3 Endoscopic Remission

### *3.3.1 Endoscopic Remission for the Induction and Open-Label Treatment Periods*

Endoscopic subscore = 0 or 1 on modified Mayo Score, with at least one (1) point decrease from baseline, as assessed by flexible sigmoidoscopy or colonoscopy

### *3.3.2 Endoscopic Remission for the Maintenance Treatment Period (from Week 11 through M-Week 37)*

Endoscopic subscore = 0 or 1 on modified Mayo Score, as assessed by flexible sigmoidoscopy or colonoscopy

## 3.4 Histological Mucosal Healing

Statistically significant decrease from baseline, using the Robarts Histopathological Index (RHI) scoring system

## 3.5 Three-Component Modified Mayo Score

Sum of the below three (3) subscores:

1. Endoscopic subscore
2. Stool frequency subscore
3. Rectal bleeding subscore

## 3.6 Disease Worsening

An increase by two (2) or more points, on two (2) days within a three (3) day period, of the patient reported outcomes (stool frequency and rectal bleeding) of the modified Mayo score,

- Compared to baseline score (Visit 2) if disease worsening is during the Induction Treatment period, or

- Compared to the post-10-week induction treatment score if disease worsening is after the Induction Treatment period

### 3.7 UC Flare

UC symptom changes (which may include disease worsening, as defined above), as determined by the principal investigator to be significant enough to warrant addition of a new UC medication, an increase in dose of a baseline UC medication, or surgery

### 3.8 Engraftment

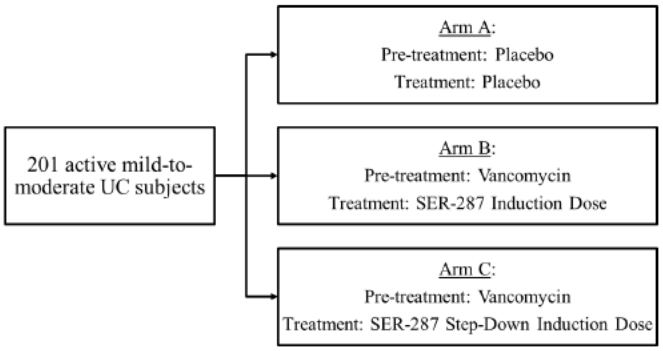
Outgrowth of bacteria that comprise the SER-287 drug product in a subject's gastrointestinal tract, post-treatment

# 4 STUDY DESIGN

## 4.1 Overview

This is a Phase 2B randomized, double-blind, placebo-controlled, multiple dose, multicenter study designed to evaluate the efficacy and safety of SER-287 in adult subjects 18-80 years of age, inclusive, with active mild-to-moderate ulcerative colitis. Approximately 201 subjects will be enrolled and randomized to one (1) of three (3) study treatment arms (approximately 67 per arm), each of which contains a six-day, daily pre-treatment period (vancomycin or matching placebo), and a 10-week, daily treatment period (SER-287 or matching placebo) (Figure 5).

**Figure 5: SERES-201 Treatment Arms**




Randomization will be stratified by subjects' baseline endoscopic subscore (ES, 1-2 vs. 3) and by subjects' concomitant use of UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none).

## 4.2 Study Periods

This study will be conducted over a total period of up to 67 weeks (includes Screening), as detailed below:

### *4.2.1 Screening (Weeks -4 to -1; four [4] weeks)*

Screening (Figure 1) includes two (2) visits:

- Visit 1: Subjects will be assessed for inclusion/exclusion criteria, medical history and demographic information. They will be instructed to complete an electronic diary (eDiary) for documenting stool frequency (SF) & rectal bleeding (RB) subscores daily during the Screening period. A minimum of seven (7) days between Visit 1 and Visit 2 are required to ensure there are a sufficient quantity of eDiary entries to calculate the SF subscore. Subjects with SF $\geq$ 1 will be eligible for endoscopic assessment at Visit 2. Sites will receive a preliminary notification from the interactive web/voice response system (IXRS) two days prior to the scheduled endoscopy that the subject meets, or does not meet, this requirement thus far. Sites must then check the IXRS Stool Frequency Report one day prior to the scheduled endoscopy to confirm the subject has a SF $\geq$ 1.

- Visit 2: Eligible subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies from the area of worst disease prior to Randomization at Week 0. Subjects with ES $\geq$ 1 will be eligible for randomization. Sites will receive a notification from the IXRS that the subject meets, or does not meet, this requirement, as well as if their Three-Component Modified Mayo Score meets the study inclusion requirement (score of 3 to 7, inclusive). There will be a maximum time of seven (7) business days between the Screening endoscopy and randomization. This measurement at Visit 2 will be utilized for a baseline assessment, as the visit is closest to randomization.

Endoscopy videos will be obtained during the endoscopy procedure and scored by qualified gastroenterologists – first locally, and then by an independent, blinded central reader. If the scores are discordant, a second independent, blinded central reader will score the video (adjudication). If all of the scores are different from one another, then the median of the three (3) scores will be used as the final endoscopic subscore. The central reading laboratory will provide a detailed endoscopy charter which will outline the procedures for endoscopy, video recordings (using a storage medium provided by the sponsor or designee), and appropriate equipment for video capture and transmission of endoscopic recordings.

Enrollment in this trial, as well as the clinical endpoints, will be based upon three (3) components of the modified Mayo scoring criteria – endoscopic, stool frequency, and rectal bleeding subscores, as described in the Inclusion Criteria.

### *4.2.2 Pre-Treatment (Week 0; six [6] days)*

Eligible subjects will be randomized using the IXRS to one (1) of the three (3) treatment groups at Week 0 and will initiate the pre-treatment regimen of oral vancomycin, 125 mg four (4) times a day (qid), or matching placebo, for six (6) days (Figure 1). Subjects will begin pre-treatment drug dosing on-site at the clinic and thereafter continue dosing independently. Subjects will document SF and RB subscores daily, via eDiary.

Subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening) during Pre-Treatment or beyond (Induction, Maintenance or Open-Label Treatment Periods) will have an assessment by the principal investigator (PI) to determine if the subject is experiencing a UC flare. If the subject is experiencing a UC flare, they will discontinue study drug, and will be followed for safety for 26 weeks. Subjects will undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy) and biopsies prior to a change in UC treatment medication, and discontinuation from study drug, if possible.

### *4.2.3 Induction Treatment (Week 1 – Week 11; 10 weeks)*

Subjects who complete the Pre-Treatment will receive 10 weeks of once-daily treatment with SER-287 [redacted], each following vancomycin pre-treatment, or matching placebo (following placebo pre-treatment) (Figure 1). Subjects will receive a supply of SER-287, or matching placebo, according to the treatment group to which they have been assigned and the Schedule of

Events (SOE, Table 1). Subjects will begin Induction Treatment drug dosing on-site at the clinic and thereafter continue daily dosing independently. Subjects will visit the clinic four (4) times during this period and will be asked to provide blood and stool samples. They will continue to document SF and RB subscores daily, via eDiary, and will undergo a lower endoscopy and biopsies after 10 weeks of induction treatment, or early termination. Biopsy samples will be collected from subjects who complete the Induction Treatment period, from the same area as the Screening biopsies.

#### *4.2.4 Maintenance Treatment (Week 11 – Week 37; 26 weeks)*

Remitters (subjects who have a SF subscore of 0 or 1, with at least one-point decrease from baseline, a RB subscore of 0 and ES of 0 or 1, with at least one-point decrease from baseline, and had no occurrence of a UC flare during the treatment period) will be re-randomized to receive a once-weekly SER-287 Maintenance Dose regimen, [redacted], or matching placebo, for 26 weeks. Subjects will visit the clinic seven (7) times during this period. Subjects will continue to document SF and RB subscores daily, via eDiary.

After the end of the 26-week Maintenance Treatment period, subjects will undergo a lower endoscopy and biopsies at Week 37, or early termination. Biopsy samples will be collected from subjects from the same area as the Screening and Induction Treatment biopsies. Subjects who experience a UC flare during the first 13 weeks of Maintenance Treatment (prior to M-Week 24) will have the option to enter the Open-Label Extension arm; those who do not enter Open-Label will be followed for safety for 26 weeks.

#### *4.2.5 Open-Label Extension (OL-Week-0 – OL-Week-11; 11 weeks)*

Non-Remitters (subjects who do not meet the remitter criteria) will enter the Open-Label Extension arm, where they will receive six (6) days of vancomycin pre-treatment and 10 weeks of once-daily SER-287 (Induction Dose). Subjects will visit the clinic four (4) times during this period. Subjects will continue to document SF and RB subscores daily, via eDiary. After 10 weeks of daily treatment, subjects will undergo a lower endoscopy and biopsies at Open-Label Week 11. The endoscopy central reader will remain blinded to treatment assignment. Biopsy samples will be collected from subjects from the same area as the Screening and Induction Treatment biopsies. Subjects who experience a UC flare during the Open-Label treatment period will discontinue study drug and be followed for safety for 26 weeks.

#### *4.2.6 Long-Term Safety Follow-Up (26 weeks)*

All subjects will be followed for long-term safety for 26 weeks following their last treatment dose. Follow-up phone calls will occur every four (4) weeks. During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected. During subsequent follow-up phone calls, subjects will be asked about any SAEs/AESIs, and any concomitant medications associated with the treatment of SAEs/AESIs. Concomitant UC medications, and UC procedures, any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period. No office visits are required.

# 5 STUDY POPULATION

Subjects must meet all the inclusion criteria and none of the exclusion criteria.

## 5.1 Inclusion Criteria

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

1. Signed informed consent prior to initiation of any study-specific procedure or treatment. The subject must be willing to provide written informed consent and understand the potential risks and benefits from study enrollment and treatment. The subject must also be willing and able to comply with the scheduled visits, treatment plan, laboratory tests, daily eDiary and other study procedures.
2. Male or female (non-lactating), 18-80 years of age, inclusive
3. Documented diagnosis of ulcerative colitis at least three (3) months prior to Screening. Documentation should include lower endoscopic (flexible sigmoidoscopy or colonoscopy) evidence or histological evidence (biopsy report) of UC; however, UC medical treatment records may be sufficient, as determined by the PI. Subjects must also have a minimum disease extent of 15 cm from the anal verge, as determined at the Screening endoscopy.
4. Active mild-to-moderate UC as determined by a Three-Component Modified Mayo Score of 3 to 7, inclusive, composed of endoscopic subscore (≥ 1, as determined by local and central reader scores, with adjudication by a second central reader, if necessary), stool frequency subscore (≥ 1) and rectal bleeding subscore (no eligibility requirement). There will be a maximum time of seven (7) business days between the Screening endoscopy and randomization.
5. Subjects must be willing to undergo a lower endoscopy (flexible sigmoidoscopy or colonoscopy), including biopsy sample collection, at all specified timepoints.
6. Subjects with an inadequate response to, loss of response to, or intolerance of, at least one (1) of the following conventional therapies: 5-ASA compounds, corticosteroids, 6-mercaptopurine (6-MP) or azathioprine (AZA), anti-TNFα, anti-integrin or tofacitinib (note full definition later within Section 5.1)
7. If female, is either:
    a. Not of childbearing potential, defined as postmenopausal (≥ 12 continuous months of amenorrhea with no other cause than menopause) or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy
    b. Of childbearing potential and participates in any activity associated with risk of pregnancy: is practicing at least one (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 one (1) of the above methods for the duration of the study.
8. If male and partner is of childbearing potential, subject agrees to practice at least one (1) highly effective method of birth control for the duration of the study.

**Note definition for Inclusion Criterion #6:** Subjects who have demonstrated, over the previous five (5) year period, an inadequate response to, loss of response to, or intolerance of, at least one (1) of the following agents, as defined below:

- 5-ASA compounds:
  - Signs and symptoms of persistently active disease despite taking a therapeutic dose of a 5-ASA compound (based on the product label for each compound, per PI judgement) for a minimum of four (4) weeks, or
  - History of intolerance to at least one (1) 5-ASA (discontinuation due to side effects)

- Corticosteroids:
  - Signs and symptoms of persistently active disease despite a history of at least one (1) four-week induction regimen that included a dose equivalent to prednisone ≥ 30 mg or budesonide ≥ 9 mg daily, orally for at least two (2) weeks, or intravenously for at least one (1) week, or
  - Two (2) failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily, orally, on two (2) separate occasions, or
  - History of intolerance of corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, or neuropsychiatric side-effects, including insomnia, associated with corticosteroid treatment)

- Immunomodulators:
  - Signs and/or symptoms of persistently active disease despite at least three (3) months of treatment with one (1) of the following:
    - oral AZA (≥ 1.5 mg/kg/day) or 6-MP (≥ 0.75 mg/kg/day), or
    - oral AZA or 6-MP within a therapeutic range, as judged by thioguanine metabolite testing, or
    - a combination of a thiopurine and allopurinol within a therapeutic range, as judged by thioguanine metabolite testing, or
    - history of intolerance to at least one (1) immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities and lymphopenia)

- Pathway specific drugs for UC treatment, including anti-TNF antibodies, anti-integrin antibodies, or janus kinase (JAK) inhibitors (such as tofacitinib):
  - Signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing that was indicated in the product label at the time of use, or
  - Loss of response: Recurrence of signs and symptoms of active disease during approved maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC biologic therapy), or

- Intolerance: History of intolerance to infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or other approved biologics or JAK inhibitors (including but not limited to infusion-related event, demyelination, congestive heart failure, serious infection, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication).

## 5.2 Exclusion Criteria

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

1. Known history of Crohn's disease
2. No previous history of treatment for UC (treatment-naïve subjects should not be enrolled)
3. Subjects on steroid medication (e.g. prednisone, budesonide, budesonide MMX®) who are unable to have steroids tapered, and be completely off steroids at least two (2) weeks prior to Screening
4. Subjects who have received any investigational or approved biologic therapy (e.g. infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, natalizumab) within eight (8) weeks prior to Screening or five (5) half-lives prior to Screening (whichever is longer)
5. Subjects who have received any investigational or approved non-biologic therapy (e.g. cyclosporine, tacrolimus, thalidomide, methotrexate, tofacitinib), except for those specifically listed in the Permitted Concomitant Medications (e.g. stable dose of 6-mercaptopurine, azathioprine, methotrexate for ≥ 12 weeks prior to Screening), for the treatment of underlying disease, within 30 days or five (5) half-lives prior to Screening (whichever is longer)
6. Major gastrointestinal surgery (not including appendectomy or cholecystectomy) within two (2) months before Screening, or any history of total colectomy
7. Subjects with active celiac disease (i.e., active diarrhea due to documented celiac disease)
8. Subjects with evidence of, or treatment for, *Clostridium difficile* infection, or other intestinal pathogen, within 30 days prior to Screening
9. Subjects with *Clostridium difficile* positive stool, performed with a toxin enzyme immunoassay (EIA) by the Central Laboratory. Subjects who test positive for *C. difficile* can be treated with standard of care antibiotics and rescreened for the study after 30 days, as per Exclusion Criterion #8.
10. Oral antibiotic use within 30 days before Screening
11. Expected to receive antibiotics (i.e., for planned/anticipated procedure) within the Induction Treatment period
12. Received an investigational drug or live vaccine within two (2) months before Screening
13. Previously enrolled in a Seres Therapeutics SER-109 or SER-287 study
14. Received a fecal microbiota transplant (FMT; includes human microbiota-based therapeutics) within three (3) months prior to Screening
15. 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. Known hypogammaglobulinemia
b. Known severe immunodeficiency
c. Underlying liver function test (LFT) [Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] abnormalities greater than 3x upper limit of normal (ULN)
d. Absolute neutrophil count (ANC) < 500 cells/$mm^3$
e. Hemoglobin levels < 9 g/dL

16. Subjects with anatomic or medical contraindications to lower endoscopy (flexible sigmoidoscopy or colonoscopy), including but not necessarily limited to toxic megacolon, gastrointestinal 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)
17. Unable to stop steroid enemas or suppositories, or 5-ASA enemas or suppositories, at least two (2) weeks prior to Screening
18. Unable to stop probiotic treatment at least one (1) week prior to Screening. Note: food containing probiotics are permitted.
19. Known active malignancy, except for basal cell skin cancer or squamous cell skin cancer, or concurrent intensive induction chemotherapy, radiotherapy, or biologic treatment for active malignancy (subjects on maintenance chemotherapy may only be enrolled after consultation with medical monitor)
20. Unable to comply with the protocol requirements, including the ability to take oral drugs; or any condition that, in the opinion of the investigator, might interfere with study objectives or compromise patient safety, including if the subject is likely to require surgery for UC during the study period
21. Known allergy or intolerance to oral vancomycin
22. Current or recent history (six [6] months prior to Screening) of drug or alcohol abuse

## 5.3 Subject Withdrawal and Replacement

### *5.3.1 Reasons for Discontinuation of Treatment*

A subject may discontinue treatment after discussion with the investigator and/or medical monitor for the following reasons:

- Pregnancy (see Section 7.1.5, Pregnancy)
- Adverse event(s)
- At the discretion of the Investigator
- Subject choice (withdrawal of consent by subject; investigator will attempt to ascertain reason)
- Protocol violation
- Non-compliance with study drug
- Non-compliance with eDiary entries

Subjects should continue to be followed for safety assessments up to 26 weeks after last study drug dose. However, a subject may withdraw from the study at any time for any reason, without any consequence.

### *5.3.2 Handling of Withdrawals and Discontinuation of Treatment*

Subjects who discontinue from treatment early will enter the long-term safety follow-up period. The primary reason for discontinuation of treatment will be recorded in the subject's clinical records and in the electronic data capture (EDC) system. If a subject discontinues treatment, the Investigator must make every effort to perform the End of Treatment Visit, as described in Section 8.2.26, End of Treatment Visit.

Subjects who withdraw from the study will have the reason for withdrawal documented in the EDC system. 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, three [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).

## 5.4 Termination of Study

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study at any time for clinical or administrative reasons.

## 5.5 Planned Sample Size and Number of Study Centers

Approximately 201 subjects will be enrolled at approximately 104 sites in North America.

## 5.6 Subject Identification and Randomization

### *5.6.1 Subject Identification*

All screened subjects will be assigned a unique subject identification (SID) number that will be used through Screening, Pre-Treatment, Treatment and Follow-Up periods.

### *5.6.2 Methods of Assigning Subjects 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 Week 0 (Visit 3), after all screening procedures have been performed and eligibility for the study is confirmed. Subjects will be

randomized via the IXRS to one (1) of the three (3) study arms (Figure 5). Randomization will be stratified by subjects' baseline endoscopic subscore (1-2 vs. 3) and by subjects' concomitant use of UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none). An adaptive subject randomization algorithm will be employed to facilitate balance among the different donors within each of the SER-287 arms.

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, the following people will remain blinded to the treatment assignment: subjects, investigators, other study site personnel, clinical staff, medical monitor, study site monitors and other sponsor representatives involved in the clinical aspects of study conduct.

### *5.6.3 Maintaining the Randomization Codes and Breaking the Study Blind*

A designated randomization administrator from an external, independent vendor will maintain the randomization codes in accordance with standard operating procedures to ensure that the blind is properly maintained and that only personnel who require knowledge of treatment assignments will be unblinded [e.g., staff involved in serious adverse event 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 EDC system and any associated SAE 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 (Week 0 [Visit 3] to Week 11 [Visit 7]) data is declared complete and final, the study blind codes will be broken for the induction period efficacy analyses. The Maintenance Treatment period will remain blinded until all data collected through M-Week 37 (Visit M-7) has been entered, cleaned and declared complete and final. Only limited study personnel will

have the access to the treatment code. The remaining study team personnel (majority), PIs and subjects will remain blinded until the study is completed.

# 6 INVESTIGATIONAL PRODUCT

## 6.1 SER-287 Drug Product Capsules

### *6.1.1 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.

### *6.1.2 SER-287 Manufacturing*

SER-287 is manufactured using current Good Manufacturing Practice (GMP) -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), [redacted]. Full details can be found in the Investigator's Brochure (IB).

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

## 6.2 Vancomycin HCl Hard Gelatin Capsules ("Vancomycin")

[redacted]

## 6.3 SER-287 Placebo Capsules

### *6.3.1 SER-287 Placebo Manufacturing*

Placebo will be identical to the Investigational Product (IP) SER-287 but will not contain product spores or non-spore solids. [redacted]

[redacted] Full details can be found in the IB.

## 6.4 Vancomycin HCl Placebo Capsules ("Vancomycin Placebo")

### *6.4.1 Vancomycin HCl Placebo Manufacturing and Storage*

Vancomycin HCl Placebo is manufactured [redacted]

## 6.5 Storage

### *6.5.1 SER-287 and SER-287 Placebo Storage*

SER-287 or SER-287 Placebo bottles are assembled into kits which will be shipped in temperature-controlled containers to clinical sites, [redacted]. More information can be found in the study manual.

## 6.6 Study Drug Administration

The doses, route, and schedule of study drug administration are shown in Table 7.

**Table 7: Doses, Route, and Schedule of Study Drug Administration**

| Treatment Arm | Pre-Treatment Period (6 days) | | Induction Treatment Period (10 weeks) | |
|---|---|---|---|---|
| | Pre-Treatment | Administration | Induction Treatment | Administration |
| A | Placebo | [redacted] 4x, daily | Placebo | [redacted] 1x, daily |
| B | Vancomycin | [redacted] 4x, daily | SER-287 Induction Dose | [redacted] 1x, daily |
| C | Vancomycin | [redacted] 4x, daily | SER-287 Step-Down Induction Dose | [redacted] 1x, daily |

[redacted]

When the randomization code is broken, the record of randomization will include study arm assignment and the association of treatment kit number with donor lot.

## 6.7 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 [redacted]. Each bottle should be stored unopened and intact until dispensed to the subject. The seal on a given bottle should be punctured at the time of subject randomization, for drug accountability at the capsule level.

SER-287 or SER-287 Placebo are provided in sealed bottles [redacted]. Each bottle should be stored unopened and intact until time-of-use. The seal on a given bottle should only be removed at the time of administration. Drug accountability at the clinical site should be done both at the kit level and at the individual unit-dose bottle level.

## 6.8 Prior and Concomitant Medications

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 UC medications they have taken, as well as all medications taken during the last six (6) months which are non-UC-related. At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

### 6.8.1 *Permitted Concomitant Medications*

The below medications are allowed at study entry. Doses must remain stable during the study treatment period.

- Oral aminosalicylates (if taken for at least six [6] weeks prior to Screening, 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)
- Pain medication (stable dose), including low-dose aspirin (81 mg); Note: temporary use of pain medication is permitted during the treatment period (e.g. for minor surgery), and is defined as no more than 48 hours. Temporary use of opiates should be discussed with the medical monitor.
- Inhaled steroids for non-UC-related treatment (taper-down is also acceptable)
- Inactivated influenza vaccine

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 to treat UC, the subject would then be discontinued from the study medication but continued to be followed for safety.

### *6.8.2 Prohibited Concomitant Medications and Nutritional Supplements*

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

- Oral, intravenous (IV) and rectal steroids (e.g. prednisone, budesonide, budesonide MMX®)
- 5-ASA enemas or suppositories
- Any investigational or approved biologic therapy (e.g. infliximab, adalimumab, golimumab, certolizumab, vedolizumab, ustekinumab, natalizumab)
- Any investigational or approved non-biologic therapy (e.g. cyclosporine, tacrolimus, thalidomide, methotrexate, tofacitinib)
- Anti-diarrheals (e.g. loperamide, diphenoxylate/atropine, or bile-salt sequestrant [cholestyramine, colesevelam])
- Probiotics (food containing probiotics are permitted)
- Use of any nutritional supplement which claims to support or promote gut health should be determined by medical monitor.

# 7 VARIABLES AND METHODS OF ASSESSMENT

## 7.1 Safety Variables

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

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 one (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.

The Investigator is responsible for:

- Informing the sponsor if a subject or a subject's partner becomes pregnant during the study. A "Pregnancy Report Form" will be generated, and the pregnancy will be documented in the safety database and outcome of the pregnancy will be documented.
- Evaluating subject safety including assessment of AEs for seriousness, severity, and causality.
- Informing the IRB/IEC of AEs as required, and SAEs as per IRB/IEC guidelines.

### *7.1.1 Treatment Emergent Adverse Events*

Collection of adverse events will begin following the first administration of study pre-treatment medication on Week 0 (Visit 3) and will be collected through the first four (4) weeks of the Long-Term Safety Follow-Up Period.

An adverse event 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 it is related to the study drug, or not.

A serious adverse event 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 inpatient 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 one (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 inpatient hospitalization, and the development of drug dependency or drug abuse.

### *7.1.2 Adverse Event of Special Interest*

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 communication by the investigator to the Medical Monitor is required. In this protocol, UC flares, as defined in Section 3.7, UC Flare, and invasive infections (e.g., bacteremia, abscess, meningitis) have been designated as AESIs, and as such, will be documented and reported on an AESI report form. AESIs will be reported and followed in the same manner as an SAE.

### *7.1.3 Reporting Serious Adverse Events*

The Investigator must report any SAEs to the [redacted] safety contact within 24 hours of becoming aware of the event by completing and transmitting the Serious Adverse Event report form by email to the [redacted] safety contact listed 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 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 REPORTING INSTRUCTIONS**

[redacted]

Telephone Number: [redacted]

Email: [redacted]

Fax Number: [redacted]

Email the SAE report form and any supporting documentation to the [redacted] safety contact within 24 hours of becoming aware of the event.

The SAE 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

Report Form and transmitted to the [redacted] 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 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 electronic Case Report Form (eCRF).

### *7.1.4 Follow-up of Serious Adverse Events and Adverse Events of Special Interest*

All SAEs/AESIs experienced by a subject, irrespective of the suspected causality, will be monitored until the SAE/AESI 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.

### *7.1.5 Pregnancy*

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug (including a female partner of a male study subject).

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 [redacted]/Sponsor on the initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The Investigator must document 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 [redacted]/Sponsor on the pregnancy outcome report form within 24 hours after he or she has gained knowledge of the pregnancy outcome.

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, 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 outcome of the pregnancy should be documented.

### *7.1.6 Laboratory Variables*

All hematology and blood chemistry laboratory tests will be performed by the central laboratory. The laboratory facilities for analysis of clinical laboratory samples obtained under this protocol will have adequate licensure and accreditation. Urine pregnancy tests will be performed at the sites. Details of sample handling, specific tests performed, and methodology will be provided in the laboratory manual.

Blood samples for hematology, blood chemistry, and biomedical research will be obtained according to the Schedule of Events (Table 1, Table 2, Table 3). Blood samples for hematology and blood chemistry obtained on Day 1 (pre-dose) will be used to determine baseline data but will not be used to confirm eligibility criteria.

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 the value is of clinical significance and should be recorded as an AE. Actual laboratory results will not be captured within the EDC system. However, if any laboratory results meet the reporting requirements for an AE, the event term (e.g., elevated transaminase) will be recorded within the EDC system as an AE or SAE, as applicable.

### *7.1.7 Stool Samples*

Stool samples will be collected by the subjects, as detailed in Section 8, Study Conduct. Stool sample collection, handling, storage and processing procedures will be defined in stool sample manuals for sites and study subjects. When lower endoscopies are being performed, stool samples will be collected prior to the start of the clear liquid diet, in preparation for endoscopy.

### *7.1.8 Biopsy Samples*

Four (4) biopsies will be obtained from the area of worst disease, with a minimum disease extent of 15 cm from the anal verge, before and after treatment, as detailed in Section 8, Study Conduct. The biopsies collected after treatment will be from the same location as those collected before treatment. Three (3) of the four (4) biopsy samples per visit will be placed in formalin, for histopathology, and one (1) will be placed in RNALater, for mucosal genomic analyses. Samples will be processed at the clinical site, and then shipped to the central laboratory, according to the procedures defined in the endoscopy and histopathology charters. Refer to the endoscopy and histopathology charters for full details.

#### *7.1.9 Vital Signs*

The following vital signs will be assessed in accordance with the Schedule of Events (Table 1, Table 2, Table 3):

- Blood pressure (BP; systolic and diastolic; mmHg)
- Heart rate (HR; beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute)

The Investigator or designee will indicate whether a value is of clinical significance and should be recorded as an AE.

#### *7.1.10 Physical Examinations*

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

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

### 7.2 Demographics and Baseline Characteristics

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

#### *7.2.1 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)

#### *7.2.2 Disease History*

- UC history

#### *7.2.3 Baseline Characteristics*

- General medical history
- General surgical history
- Smoking history

#### *7.2.4 Medical History*

Any previous and concomitant diseases before Screening will be documented as medical history. Medical history will be obtained by interviewing the subject and by inspecting his/her medical records.

#### *7.2.5 Prior and Concomitant Medications*

Prior and concomitant medication will be documented as described in Section 6.8, Prior and Concomitant Medications. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior UC medications are of particular interest, as well as reason for stoppage – lack of efficacy or intolerance.

### 7.3 Three-Component Modified Mayo Score

To be eligible for enrollment, a subject must have active mild-to-moderate UC as determined by a Three-Component Modified Mayo Score of 3 to 7, inclusive. The total Three-Component Modified Mayo Score is the sum of the below three (3) subscores, which will be calculated electronically from subject eDiary entries and central endoscopy reads.

#### *7.3.1 Stool Frequency Subscore*

To be eligible for enrollment, a subject must have a stool frequency subscore $\geq 1$. Stool frequency will be recorded daily by enrolled subjects using an eDiary. Subscore calculation guidelines can be found in Appendix 2.

#### *7.3.2 Rectal Bleeding Subscore*

There is no rectal bleeding subscore requirement for enrollment. Rectal bleeding will be recorded daily by enrolled subjects using an eDiary. Subscore calculation guidelines can be found in Appendix 2.

#### *7.3.3 Endoscopic Subscore*

To be eligible for enrollment, a subject must have an endoscopic subscore $\geq 1$. Endoscopic subscores will be determined by qualified gastroenterologists – first locally, and then by an independent, blinded central reader. If the scores are discordant, a second independent, blinded central reader will score the image (adjudication). If all of the scores are different from one another, then the median of the three (3) scores will be used as the final endoscopic subscore.

If the endoscopic subscore is missing, the subject will be assigned an outcome of failure for all endpoints which are derived using the endoscopic subscore.

# 8 STUDY CONDUCT

## 8.1 Study Schedule

The study consists of the study periods listed within Table 8, and will be conducted over a period of up to 67 weeks (includes Screening).

**Table 8: Study Schedule**

| Study Period | Duration | Study Weeks |
|---|---|---|
| Screening | Up to 4 weeks | -4 to -1 |
| a. Visit 1 | | |
| b. Visit 2 for lower endoscopy | | |
| Pre-Treatment | 6 days | 0 |
| Induction Treatment | 10 weeks | 1-11 |

| Maintenance Treatment (Remitters) | | |
|---|---|---|
| Study Period | Duration | Study Weeks |
| Maintenance Treatment | 26 weeks | M-11-37 |
| Long-Term Safety Follow-Up | 26 weeks | M-37-63 |

| Open-Label Extension (Non-Remitters) | | |
|---|---|---|
| Study Period | Duration | Study Weeks |
| Pre-Treatment | 6 days | OL-0 |
| Induction Treatment | 10 weeks | OL-1-11 |
| Long-Term Safety Follow-Up | 26 weeks | OL-11-37 |

End-of-study is defined as the end of the Long-Term Safety Follow-Up, which is 26 weeks following the last treatment dose taken during the Induction Treatment, Maintenance Treatment or Open-Label Induction Treatment periods.

The Schedules of Events are presented in (Table 1, Table 2, and Table 3).

## 8.2 Procedures by Visit

### *8.2.1 Screening: Week -4 to -1 (Visit 1)*

- Obtain written informed consent for study
- Confirm subject meets all the inclusion criteria and none of the exclusion criteria
- Record medical history
- Record UC history
- Record prior medications and UC therapies
- Concomitant Medications
- Record Demographics

- Perform full physical exam
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Obtain height and weight
- Collect blood, urine and stool samples and ship to the central laboratory for evaluation of:
  - Blood chemistry
  - Hematology
  - Serum pregnancy test for women of childbearing potential (WOCBP)
  - Blood & Serum for Future Biomedical Research
  - Urinalysis: Urine dipstick performed at the study site; if positive for nitrates and/or leukocytes, send sample to central laboratory for analysis
- Subject should be asked to provide a stool sample on site, if possible, to be used for *Clostridum difficile* testing (toxin enzyme immunoassay [EIA]), microbiome and metabolomics. If unable to produce a stool sample on site, subject should be provided with a stool collection kit to take home. Stool collection done at home should be returned the next day by the subject or can be returned to the clinic via courier.
- Fecal calprotectin
- Obtain history of stool frequency and rectal bleeding
- Review subject eDiary Instructions with subject for recording of daily rectal bleeding & stool frequency
- Review stool collection handling and storage instructions with subject
- Provide stool collection kit to subject for next clinic visit
- Subject eDiary (daily rectal bleeding, stool frequency)

**Note:** A minimum of seven (7) days between Visit 1 and Visit 2 are required to ensure there are a sufficient quantity of daily eDiary entries to calculate the Stool Frequency subscore. The SF score will be calculated electronically, from subject eDiary entries. Sites will receive a notification from the IXRS that the subject meets the SF score requirement (SF $\geq$ 1) for performing the endoscopy at Screening Visit 2.

### *8.2.2 Screening: Week -4 to -1: Endoscopy Visit (Visit 2)*

- Verify subject meets all the inclusion criteria and none of the exclusion criteria
- Concomitant Medications
- Concomitant Procedures for UC
- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject performed bowel preparation at PI discretion (e.g., two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)

- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

**Note:** The Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read, to determine subject eligibility. Sites will receive an eligibility notification from the IXRS confirming if the subject is eligible to be randomized into the protocol (Three-Component Modified Mayo Score 3 to 7, inclusive), or is ineligible (screen failure).

### *8.2.3 Pre-Treatment: Week 0 (Visit 3)*

#### *8.2.3.1 Pre-dosing*

- Concomitant Medications
- Concomitant Procedures for UC
- Confirm eligibility review has been completed by Medical Monitor, pre-randomization, for final eligibility decision by PI
- Perform focused physical exam
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Obtain weight
- Obtain urine sample pre-dose for pregnancy testing; should be performed and reported as negative prior to dosing. (WOCBP only)
- Blood sampling pre-dose for hematology, blood chemistry
- Blood for CRP
- Perform IBDQ
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

#### *8.2.3.2 Dosing*

- Perform randomization in IXRS
- Dispense pre-treatment drug supply
- Begin pre-treatment drug dosing (observe subject one [1] hour post-dosing)
- Review stool sample collection, handling and storage instructions with subject
- Provide stool sample collection kit to subject
- Begin adverse event monitoring

### *8.2.4 Induction Treatment: Week 1 +/-1d (Visit 4)*

*8.2.4.1 Pre-dosing:*

- Concomitant medications
- Concomitant procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return any remaining pre-treatment drug and all bottles dispensed
- Review drug compliance
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Blood sampling pre-dose for hematology, blood chemistry
- Blood and Serum for future medical research
- Subject to return stool sample collected at home and ship to the central laboratory
- Review stool sample collection, handling and storage instructions with subject

*8.2.4.2 Dosing:*

- Begin treatment period drug dosing (observe subject one [1] hour post-dosing)
- Dispense study drug for daily dosing
- Continue adverse event monitoring
- Provide stool collection kit to subject for next clinic visit

### *8.2.5 Induction Treatment: Week 3 +3d (Visit 5)*

- Concomitant Medications
- Concomitant Procedures for UC
- Subject to return stool sample collected at home and ship to the central laboratory
- Provide stool sample collection kit to subject
- Obtain urine sample for pregnancy testing (WOCBP only)
- Dispense study drug for daily dosing
- Continue adverse event monitoring
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.6 Induction Treatment: Week 7 +3d (Visit 6)*

- Concomitant Medications
- Concomitant Procedures for UC

- Obtain urine sample for pregnancy testing (WOCBP only)
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Dispense study drug for daily dosing
- Continue adverse event monitoring
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review Subject eDiary for compliance

### *8.2.7 Induction Treatment: Week 11 +3d (End of Induction Treatment) (Visit 7)*

- Concomitant Medications
- Concomitant Procedures for UC
- Perform focused physical exam
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Obtain weight
- Obtain urine sample for pregnancy testing (WOCBP only)
- IBDQ
- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject has performed bowel preparation at PI discretion (e.g. two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Note: Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Collect blood and ship to the central laboratory for evaluation of:
  - Hematology
  - Blood Chemistry
  - CRP
  - Blood and Serum for Future Biomedical research
- Subject to return stool sample collected at home (pre-liquid diet for endoscopy) and ship to the central laboratory
- Fecal calprotectin

- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Provide stool collection kit to subject for next clinic visit
- Continue adverse event monitoring

### *8.2.8 Induction Treatment: Unscheduled Visit*

See Section 8.2.25, Unscheduled Visits.

## Determining Subjects' Remitter vs. Non-Remitter Status

The lower endoscopy performed at the Week 11 visit will be scored, and the Three-Component Modified Mayo Score will be calculated electronically from subject eDiary entries and endoscopic subscore to determine if the subject achieved clinical remission (See Section 3, Definitions) at the end of the 10-week Induction Treatment period.

Subjects who achieve clinical remission at the end of the 10-week Induction Treatment period will be re-randomized into the Maintenance Treatment period, to receive either a SER-287 Maintenance Dose, once-weekly, or matching placebo, for 26 weeks.

Subjects who did not achieve clinical remission at the end of the 10-week Induction Treatment period will enter the Open-Label Extension arm, where they will receive six (6) days of vancomycin pre-treatment followed by 10 weeks of SER-287 (Induction Dose), once-daily.

## Maintenance Treatment Period – Remitters

### *8.2.9 Maintenance Treatment: M-Week 12 +/-2d (Visit M-1)*

*8.2.9.1 Pre-dosing:*

- Concomitant medications
- Concomitant procedures for UC
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Provide stool collection kit to subject for next clinic visit

*8.2.9.2 Dosing:*

- Perform re-randomization in IXRS
- Begin treatment period drug dosing. Subject to take Week 12 dose on site (observe subject one [1] hour post-dosing)
- Dispense study drug for weekly dosing

- Continue adverse event monitoring

### *8.2.10 Maintenance Treatment:* **M-***Week 16 +3d (Visit M-2)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return all unused study drug and any bottles dispensed
- Review Study Drug Compliance
- Dispense study drug for weekly dosing
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory
- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.11 Maintenance Treatment: M-Week 20 +3d (Visit M-3)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Dispense study drug for weekly dosing
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Continue adverse event monitoring

### *8.2.12 Maintenance Treatment:* **M-***Week 24 +3d (Visit M-4)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Perform focused physical exam
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Dispense study drug for weekly dosing
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory

- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.13 Maintenance Treatment:* M-*Week 28 +3d (Visit M-5)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Dispense study drug for weekly dosing
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory
- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.14 Maintenance Treatment:* M-*Week 32 +3d (Visit M-6)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Dispense study drug for weekly dosing
- Provide stool collection kit to subject for next clinic visit
- Subject to return stool sample collected at home and ship to the central laboratory
- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.15 Maintenance Treatment:* M-*Week 37 +3d (Visit M-7)*

- Concomitant Medications
- Concomitant Procedures for UC
- Perform focused physical exam
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Obtain urine sample for pregnancy testing (WOCBP only)
- IBDQ

- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject has performed bowel preparation at PI discretion (e.g. two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Note: Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read
- Obtain weight
- Return all unused study drug and any bottles dispensed
- Review drug compliance
- Subject to return stool sample collected at home and ship to the central laboratory
- Fecal calprotectin
- Collect blood and ship to the central laboratory for evaluation of:
    - Hematology
    - Blood chemistry
    - CRP
    - Blood and Serum for Future Biomedical Research
- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- End of eDiary completion; subject to leave eDiary device on-site

**NOTE:** If a subject in the Maintenance Treatment Arm experiences a UC flare during the first 13 weeks of Maintenance Treatment (prior to M-Week 24), the subject will have the option to enter the Open-Label Extension Arm of the study and receive pre-treatment with vancomycin followed by 10 weeks of open-label treatment with SER-287.

### *8.2.16 Maintenance Treatment – Long-Term Safety Follow-Up: Phone Calls Every Four (4) Weeks +/-3d (Visits M-8 – M-13)*

- During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected.
- Continue adverse event monitoring; only SAEs/AESIs and concomitant medications associated with SAEs/AESIs will be collected for the remainder of the long-term safety follow-up period. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period.

### *8.2.17 Maintenance Treatment: Unscheduled Visit*

See Section 8.2.25, Unscheduled Visits.

## Open-Label Extension Arm – Non-Remitters

### *8.2.18 Open-Label Extension: OL-Week 0 +/-2d (Visit OL-1)*

- Concomitant Medications
- Concomitant Procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Register subject in IXRS for Open-Label Extension arm
- Dispense pre-treatment medication to subject
- Administer first dose of vancomycin pre-treatment in clinic
- Dispense two (2) weeks of Open-Label study drug for **daily** dosing and provide instructions to subject to start study drug after completing pre-treatment medication
- Provide stool collection kit to subject for next clinic visit
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Continue adverse event monitoring

### *8.2.19 Open-Label Extension: OL-Week 1 +/-1d (Visit OL-2)*

- Provide stool collection kit to subject for next clinic visit
- Subject eDiary (daily rectal bleeding, stool frequency)
- Subject to return stool sample collected at home and ship to the central laboratory. The stool sample may be returned to clinical site via courier or by the subject.

### *8.2.20 Open-Label Extension: OL-Week 3 +3d (Visit OL-3)*

- Concomitant medications
- Concomitant procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return any remaining pre-treatment and study drug and all bottles dispensed
- Review drug compliance
- Dispense study drug for daily dosing
- Subject to return stool sample collected at home and ship to the central laboratory
- Provide stool collection kit to subject for next clinic visits
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Continue adverse event monitoring

### *8.2.21 Open-Label Extension: OL-Week 7 +3d (Visit OL-4)*

- Concomitant medications
- Concomitant procedures for UC
- Obtain urine sample for pregnancy testing (WOCBP only)
- Return any remaining Open-Label study drug and all bottles dispensed
- Review study drug compliance
- Provide stool collection kit to subject for next clinic visits
- Dispense study drug for **daily** dosing
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- Continue adverse event monitoring

### *8.2.22 Open-Label Extension: OL-Week 11 +3d (Visit OL-5)*

- Concomitant Medications
- Concomitant Procedures for UC
- Perform focused physical exam
- IBDQ
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Subject to return stool sample collected at home and ship to the central laboratory
- Obtain urine sample for pregnancy testing (WOCBP only)
- Obtain weight
- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject has performed bowel preparation at PI discretion (e.g. two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Note: Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read
- Return all unused study drug and any bottles dispensed
- Review study drug compliance
- Collect blood and ship to the central laboratory for evaluation of:
    - Hematology
    - Blood chemistry
    - CRP
- Blood and serum for future biomedical research

- Continue adverse event monitoring
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance
- End of eDiary completion; subject to leave eDiary device on-site

#### *8.2.23 Open-Label Extension – Long-Term Safety Follow-Up: Phone Calls Every Four (4) Weeks for 26 Weeks/EoS +/-3d (Visits OL-6 – OL-11)*

- During the first four (4) weeks of the Long-Term Safety Follow-Up Period, AEs/SAEs/AESIs, concomitant procedures, and concomitant medications will be collected
- Continue adverse event monitoring; only SAEs/AESIs and concomitant medications associated with the treatment of SAEs/AESIs will be collected for the remainder of the long-term safety follow-up period. Concomitant UC medications and UC procedures, and any changes to these, will be collected throughout the entirety of the Long-Term Safety Follow-Up Period.

#### *8.2.24 Open-Label Extension: Unscheduled Visit*

See Section 8.2.25, Unscheduled Visits.

#### *8.2.25 Unscheduled Visits*

To accommodate scheduling of clinic visits and/or endoscopies, assessments & procedures for an Unscheduled Visit do not need to take place during one (1) clinic visit. The Unscheduled Visit may be used for dispensation of study drug, as needed.

For subjects who experience disease worsening (as defined in Section 3.6, Disease Worsening), an Unscheduled Visit may be used by the PI to determine if the subject is experiencing a UC flare.

The Unscheduled Visit can serve as an 'End of Treatment' visit for a subject who ends treatment early in the study but will continue to be followed for safety, or for subjects who decide to leave the study early and not be followed for safety. If subjects decide to end treatment early or early terminate from the study, all study IP should be returned by the subject.

##### *8.2.25.1 Unscheduled Visit for Reasons Other than UC Flare Assessment or EoT (Pre-Treatment, Induction, Maintenance and Open-Label)*

- Concomitant Medications
- Concomitant Procedures for UC
- Continue Adverse Event Monitoring
- Focused Physical Exam
- IBDQ
- Assess Vital Signs (systolic and diastolic pressure, heart rate, respiratory rate, temperature)
- Collect blood and ship to the central laboratory for evaluation of:

  - Hematology
  - Blood Chemistry
  - Blood and Serum for Future Biomedical research
- Subject to return stool sample collected at home and ship to the central laboratory
- Fecal calprotectin

*8.2.25.2 Unscheduled Visit for UC Flare Assessment (Pre-Treatment, Induction, Maintenance and Open-Label)*

- Concomitant Medications
- Concomitant Procedures for UC
- Continue Adverse Event Monitoring
- Focused Physical Exam
- IBDQ
- Obtain urine sample for pregnancy testing (WOCBP only)
- Assess Vital Signs (systolic and diastolic pressure, heart rate, respiratory rate, temperature)
- Obtain weight
- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject has performed bowel preparation at PI discretion (e.g. two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Note: Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read
- Collect blood and ship to the central laboratory for evaluation of:
  - Hematology
  - Blood Chemistry
  - CRP
  - Blood and Serum for Future Biomedical research
- Subject to return stool sample collected at home (pre-liquid diet for endoscopy) and ship to the central laboratory
- Fecal calprotectin
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.26 End of Treatment Visit*

Perform the following assessments and procedures:

- Concomitant Medications
- Concomitant Procedures for UC

- Perform focused physical exam
- Assess vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature)
- Obtain weight
- IBDQ
- Obtain urine sample for pregnancy testing (WOCBP only)
- Confirm subject has had no liquids six (6) hours prior to lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Confirm subject has performed bowel preparation at PI discretion (e.g. two [2] Fleet enemas 1.5 hours before procedure)
- Perform lower endoscopy (flexible sigmoidoscopy or colonoscopy)
- Obtain biopsy for histopathology (3 samples)
- Obtain biopsy for mucosal genomic analyses (1 sample)
- Note: Three-Component Modified Mayo Score will be calculated electronically, from subject eDiary entries and central endoscopy read
- Return all unused study drug and any bottles dispensed
- Review study drug compliance
- Collect blood and ship to the central laboratory for evaluation of:
  - Hematology
  - Blood Chemistry
  - CRP
  - Blood and Serum for Future Biomedical research
- Subject to return stool sample collected at home (pre-liquid diet for endoscopy) and ship to the central laboratory
- Subject eDiary (daily rectal bleeding, stool frequency)
- Review subject eDiary for compliance

### *8.2.27 Handling of Withdrawals and Discontinuations of Treatment*

The primary reason for withdrawal from study treatment and/or withdrawal from the study will be recorded in an electronic case report form (eCRF).

Subjects who voluntarily withdraw, or who are withdrawn from the study during treatment (Pre-Treatment/Induction/Maintenance/Open-Label) will be encouraged to complete the End of Treatment Visit. The End of Treatment Visit procedures are listed in Section 8.2.26, End of Treatment Visit. Although subjects are free to withdraw at any time, subjects will be encouraged to remain in the study for long term follow-up safety evaluation.

# 9 STATISTICAL METHODS

The primary study period for this study is from Screening Visit 1 through Week 11 (Visit 7). The primary study period will be conducted as a double-blind study. The database for the primary study period will remain blinded until all data collected through Week 11 (Visit 7) has been entered, cleaned and declared complete and final.

The Maintenance Treatment period will remain blinded until all data collected through M-Week 37 (Visit M-7) has been entered, cleaned and declared complete and final.

Before the primary study period data is declared complete and final, and before any data unblinding, an 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.

## 9.1 Study Endpoints

### *9.1.1 Primary Efficacy Endpoint*

- Clinical remission with SER-287, after 10 weeks of induction dosing, following vancomycin pre-treatment (Treatment Arm B), compared to placebo, following placebo pre-treatment (Treatment Arm A)

### *9.1.2 Key Secondary Efficacy Endpoints*

- Clinical remission with SER-287, after 10 weeks of step-down induction dosing, following vancomycin pre-treatment (Treatment Arm C), compared to placebo, following placebo pre-treatment (Treatment Arm A)
- Endoscopic improvement with SER-287, after 10 weeks of induction dosing, following vancomycin pre-treatment (Treatment Arm B), compared to placebo, following placebo pre-treatment (Treatment Arm A)
- Endoscopic improvement with SER-287, after 10 weeks of step-down induction dosing, following vancomycin pre-treatment (Treatment Arm C), compared to placebo, following placebo pre-treatment (Treatment Arm A)

### *9.1.3 Other Secondary Efficacy Endpoints*

- Endoscopic remission after 10 weeks of induction treatment
- Histological mucosal healing after 10 weeks of induction treatment
- Clinical remission with normalization of stool frequency after 10 weeks of induction treatment
- Symptomatic remission (rectal bleeding and stool frequency) after 10 weeks of induction treatment
- Engraftment of SER-287 bacteria over time
- For EMA consideration only (see Section 3, Definitions):
    - Clinical remission (less stringent criteria) after 10 weeks of induction treatment
    - Clinical remission (more stringent criteria) after 10 weeks of induction treatment

- Clinical remission co-endpoints: symptomatic remission and endoscopic remission after 10 weeks of induction treatment

### *9.1.4 Exploratory Efficacy Endpoints*

- Clinical remission at the end of maintenance treatment and at the end of open-label treatment
- Endoscopic improvement at the end of open-label treatment
- Endoscopic remission at the end of maintenance treatment and at the end of open-label treatment
- Histological mucosal healing at the end of maintenance treatment and at the end of open-label treatment
- Symptomatic remission (rectal bleeding and stool frequency) over time
- Clinical remission after 10 weeks of induction treatment for each SER-287 donor used in the induction treatment period
- IBDQ scores after 10 weeks of induction treatment, at the end of maintenance treatment and at the end of open-label treatment
- Serum biomarkers: CRP after 10 weeks of induction treatment (Week 11), at the end of maintenance treatment and at the end of open-label treatment
- Fecal biomarkers: fecal calprotectin levels after 10 weeks of induction treatment (Week 11), at the end of maintenance treatment and at the end of open-label treatment
- Composition of the intestinal microbiome through the end of the maintenance treatment and open-label treatment periods
- Signatures of host and microbial functional responses through the end of the maintenance treatment and open-label treatment periods

### *9.1.5 Safety Endpoints*

- Incidence of AEs, SAEs and AESIs for each treatment and each SER-287 donor
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

## 9.2 Study Subjects

### *9.2.1 Disposition of Subjects*

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

### *9.2.2 Protocol Deviations*

Protocol deviations will be listed by subject.

### *9.2.3 Analysis Populations*

Intent-to-Treat Analysis Population: The Intent-to-Treat (ITT) Population will consist of all subjects who are randomly assigned, including those who are not exposed to any study drug, and

will be analyzed based on the treatment to which they were randomized. The ITT population will be the primary analysis population for all efficacy endpoints.

Modified Intent-to-Treat 1 Population: The Modified Intent-to-Treat 1 (mITT-1) Population will consist of all randomized subjects with a baseline evaluation, who have active mild-to-moderate UC and receive any amount of study drug, and will be analyzed based on the treatment to which they were randomized.

Modified Intent-to-Treat 2 Population: The Modified Intent-to-Treat 2 (mITT-2) Population will consist of all randomized subjects with a baseline evaluation, who have active mild-to-moderate UC and receive any amount of study drug, and will be analyzed based on the treatment to which they are randomized. Subjects who are confirmed to have normal histology at baseline will be excluded from this analysis population.

Per Protocol Population: The Per Protocol (PP) Population will consist of subjects from the mITT-2 Population who do not have any major protocol deviations. The details of the PP Population will be provided in the SAP and defined before unblinding of the data.

Microbiome Modified Intent-to-Treat: The Microbiome Modified Intent-to-Treat (mcITT) Population will be used for analysis of microbiome data. It will consist of all randomized subjects with an evaluable stool sample collected at baseline, and at least one (1) evaluable stool sample collected after the start of dosing, who are exposed to any amount of study drug, and will be analyzed based on the treatment to which they are randomized.

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 are randomly assigned. All safety analyses will be conducted based on the Safety Population.

All clinical efficacy analyses will be conducted in the ITT population, and in the mITT-1, mITT-2, PP and Safety populations as sensitivity analyses, as appropriate.

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

## 9.3 Multiplicity Adjustment

Adjustments for multiple testing will be made to test the primary efficacy and key secondary efficacy endpoints. A fixed-sequence method will be used to maintain a study-wide 2-sided Type I error rate of 0.05. Testing of the key hypotheses will be conducted in the following order, all at the same significance level (2-sided $\alpha = 0.05$):

1. $H_{01}$: No difference in clinical remission rates after 10 weeks of induction treatment between Arm B (SER-287 at Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
2. $H_{02}$: No difference in clinical remission rates after 10 weeks of induction treatment between Arm C (SER-287 at Step-Down Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
3. $H_{03}$: No difference in endoscopic improvement rates after 10 weeks of induction treatment between Arm B (SER-287 at Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population
4. $H_{04}$: No difference in endoscopic improvement rates after 10 weeks of induction treatment between Arm C (SER-287 at Step-Down Induction Dose after pre-treatment with vancomycin) vs. Arm A (pre-treatment with placebo followed by treatment with placebo) in the ITT population

Testing of later hypotheses in the sequence stops as soon as failure to show statistical significance at the 2-sided 0.05 level is observed in a hypothesis earlier in the sequence.

## 9.4 General Considerations

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

Selected clinical efficacy and biomarker data will be presented in treatment mean (+/- standard deviation [SD]) profile plots.

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

## 9.5 Efficacy Analyses

### *9.5.1 Timing of Analyses*

#### *9.5.1.1 At the end of the Induction Treatment period*

Seres will conduct an unblinded analysis of the efficacy and safety endpoints when all planned subjects in the study are enrolled, have been evaluated for the primary/key

secondary efficacy endpoints and have completed their Induction Treatment (Week 11 [Visit 7]) or have terminated from the study prematurely prior to the Week 11 [Visit 7].

Key unblinded efficacy and safety summary tables will be generated at this time. Limited personnel at Seres will have access to the unblinded tables, listings and figures (TLFs). A detailed unblinding plan will be drafted and finalized at the same time that the SAP is finalized.

All clinical data generated during the primary study period (Screening Visit 1 through Week 11 [Visit 7]) for all subjects enrolled in the study will be entered in the database, cleaned and locked prior to the unblinding. No changes to any locked data in the database will be permitted, unless deemed to be highly warranted. Therefore, all efficacy results evaluated up until this primary study period will be considered final. A comparison of the data at the time of this unblinding and at the end of the study will be performed. An audit trail of any changes made to the locked data will be available.

#### *9.5.1.2 At the end of the Maintenance Treatment period*

Seres will conduct an unblinded analysis of the safety and exploratory efficacy endpoints when all subjects who were re-randomized in the maintenance arm have been evaluated for the exploratory efficacy endpoints, and have completed their maintenance treatment, or have terminated the study prematurely prior to Week 37 (Visit M-7).

Key unblinded efficacy and safety summary tables will be generated at this time. Limited personnel at Seres will have access to the unblinded tables, listings and figures (TLFs).

All clinical data generated during the maintenance period (Week 11 through Week 37 [Visit M-7]) for all subjects enrolled in the maintenance arm will be entered in the database, cleaned and locked prior to the unblinding. No changes to any locked data in the database will be permitted, unless deemed to be highly warranted. Therefore, all efficacy results evaluated up until this time for the maintenance arm will be considered final at the time of the analysis. A comparison of the data at the time of this unblinding and at the end of the study will be performed. An audit trail of any changes made to the locked data will be available.

#### *9.5.1.3 At the end of the Long-Term Safety Follow-Up period*

At the end of the Long-Term Safety Follow-Up period, after final database lock, all AE summary tables will be re-generated to include any additional safety findings from this period. All other TLFs will also be re-run to ensure that any changes to the database that may have occurred since the earlier analyses are reflected in the final TLFs. All changes in the efficacy results from the previous analyses will be described in the Clinical Study Report (CSR).

### *9.5.2 Statistical Analysis and Significance Level*

Statistical significance tests, if reported, will be two-sided and will be presented as relative measures of the strength of association to the active SER-287 treatment arm (Arms B and C) for comparison with the placebo arm (Arm A) among study endpoints.

Details of the statistical analysis will be addressed in the SAP, finalized prior to the time the primary study period data is declared complete and final and any study unblinding.

### *9.5.3 Missing or Spurious Data*

Every effort will be made to collect all data at specified timepoints, according to the schedule of study events.

For analysis of the binary efficacy endpoints (i.e. clinical remission, endoscopic remission and clinical remission with normalization of stool frequency during the induction period), subjects with missing values will be assigned an outcome of failure for the endpoint, if

(i) the subject discontinued study treatment prior to Study Day 48, OR

(ii) did not have a post-baseline endoscopy done during the induction period, OR

(iii) if data is missing for any of the subscores needed for the Week 11 assessments at the end of the induction period, such that the endpoint cannot be calculated.

The description of the handling of missing data for individual components of the Three-Component Modified Mayo Score, specifically stool frequency and rectal bleeding, are described in Appendix 2.

As sensitivity analyses, the primary endpoint and the key secondary endpoint will also be analyzed based on the last observation carried forward (LOCF) approach. Subjects who only have baseline values will be treated as failures for the endpoint in the LOCF analysis. The observed-case analyses will also be conducted where missing values will be excluded in the analyses.

For continuous secondary endpoints, such as histological mucosal healing, missing values will not be imputed. The analyses will be based on the observed-case data where missing values will be excluded in the analyses.

Handling of missing data for other endpoints will be specified in the SAP.

### *9.5.4 Analysis of the Primary Efficacy Endpoint*

The primary efficacy outcome measure for this study will be the difference in clinical remission rates after 10 weeks of induction treatment between SER-287 (Induction Dose after pre-treatment with vancomycin – Arm B) and placebo (Arm A). The primary efficacy endpoint analysis will be based on the CMH test, stratified by endoscopic score at baseline (1-2 vs. 3), and UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none) in the ITT population.

### *9.5.5 Analysis of the Key Secondary Efficacy Endpoints*

The key secondary efficacy endpoints will be analyzed using the same method used for the primary efficacy endpoint.

Sensitivity Analyses for the primary and key secondary efficacy endpoint will be performed in the mITT-1, mITT-2, Safety and PP populations.

### *9.5.6 Analyses of Other Secondary Efficacy Endpoints*

All other dichotomous secondary efficacy endpoints will be analyzed using the same method used for the primary efficacy endpoint.

For histological mucosal healing, analysis will be based on the change from baseline score using RHI (Mosli et al., 2017) and analyzed by an analysis of covariance (ANCOVA) test, with treatment, endoscopic score at baseline and UC medications at baseline as factors in the model. The primary analysis population for this endpoint will be the mITT-2 population.

All clinical efficacy analyses will be conducted in the ITT population, unless otherwise stated, and in the mITT-1, mITT-2 and PP populations as sensitivity analyses, as appropriate.

### *9.5.7 Analyses of Exploratory Endpoints*

Details of the methods used for the analyses of the exploratory endpoints will be provided in the SAP.

## 9.6 Safety Analyses

### *9.6.1 Adverse Events*

A TEAE is any adverse event (AE) that newly appeared, increased in frequency, or worsened in severity after initiation of study drug (including the pre-treatment period).

Safety summaries of TEAEs will be presented by treatment group at the end of the pre-treatment period (Week 1), Week 3, Week 7, after 10 weeks of induction treatment (Week 11), at the end of Maintenance Treatment or Open-Label Treatment and at end-of-study, with selected safety summaries also presented by baseline endoscopic subscore and baseline UC medication stratum. The number and percentage of subjects with TEAEs will be tabulated by system organ class and preferred term (PT) for each treatment group and stratum. Serious TEAEs, AESIs and TEAEs leading to study discontinuation will be similarly tabulated. Summaries of TEAEs by maximum severity and by maximum relationship to study drug will also be summarized by system organ class and PT.

Selected safety summaries will also be provided by SER-287 donor.

A listing of all TEAEs will be provided.

All safety analyses will be conducted in the Safety Population, unless specified otherwise. Subjects will be analyzed according to the treatment they actually received, rather than that to which they are randomly assigned. Adverse events will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA).

### *9.6.2 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.

### *9.6.3 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.

### *9.6.4 Physical Examination Findings*

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

### *9.6.5 Pharmacokinetic Analyses*

Not applicable

## 9.7 Gastrointestinal Tract Microbiome

The gastrointestinal microbiome of subjects will be characterized using genomic data sets generated from stool collected at the time points defined above in the Schedule of Events. 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 phylogenetic clade and/or species and further, to define the relative proportion of each species or taxon relative to all other species or taxa in a given sample. Engraftment of SER-287 taxa will be measured and analyzed as defined in Section 9.7.1, Microbiome Secondary Endpoint Data Analysis.

### *9.7.1 Microbiome Secondary Endpoint Data Analysis*

Engraftment of spore-forming bacteria in SER-287 will be assessed by examining the richness of spore-forming taxa found in drug product lots which appear newly in subject stool at one (1) or more timepoints after the initiation of treatment with SER-287 (ΔSobs_spore_dose). The nonparametric one-sided Mann-Whitney U test will be used to determine if there is a greater change in ΔSobs_spore_dose in subjects receiving SER-287 relative to subjects receiving placebo.

Further details will be included in the microbiome SAP.

## 9.8 Interim Analyses

Two unblinded analyses will be conducted prior to the completion of the entire study, specifically at the end of the induction period and at the end of the maintenance period. Please refer to Section 9.5.1, Timing of Analyses, for further details on these analyses.

## 9.9 Determination of Sample Size

The planned sample size for this study is 67 subjects per treatment arm for a total sample size of 201 subjects. Assuming a clinical remission rate of 29% in the SER-287 arms and a clinical remission rate of 9% in the placebo arm, this sample size will provide 86% power to detect a difference of 20% in clinical remission rates between SER-287 to placebo, using a 2-sided significance level of 0.05.

A placebo rate of 7% was derived from the weighted average of the placebo rates observed in the tofacitinib Phase 2 (Sandborn et al., 2012), 3A and 3B (Sandborn et al., 2017) studies, and the ozanimod induction studies (Sandborn et al., 2016). These four (4) studies were chosen as the basis for the placebo rate because each utilized a central reader to determine subjects' endoscopic subscores. However, due to the inclusion of mild subjects and those with an endoscopic subscore of 1 in the SERES-201 study, who may have a higher placebo response rate, the assumed placebo rate was increased to 9%. The clinical remission rate that was used for the SER-287 arm was based on the re-analysis of the clinical remission rate in the vancomycin/SER-287 daily arm in the SERES-101 Phase 1B study, and applying the definition of clinical remission for the SERES-201 study; additionally, only subjects with a baseline Three-Component Modified Mayo Score between 3 and 7, inclusive, and a baseline stool frequency subscore ≥1 were included, (38.5% with 95% CI: 15.1%, 67.7%). The clinical remission rate was decreased to 29% to account for the small sample size in this SERES-101 arm (n=13).

# 10 ADMINISTRATIVE REQUIREMENTS

## 10.1 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.

## 10.2 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, informed consent form (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.

## 10.3 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.

### 10.4 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.

### 10.5 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.

### 10.6 Future Use of Stored Specimens

The sponsor may, where permitted by local regulations, conduct future biomedical research on specimens (including blood, serum, stool and biopsies) 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.

### 10.7 Study Monitoring

Regular monitoring is defined in ICH Guidance for Industry E6 R2 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, GCP, and the applicable regulatory requirement(s)." The purpose of monitoring is to verify that:

- Rights and wellbeing 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.

### 10.8 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 must be 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 will allow for application of electronic signatures. The Investigator or designated Sub-Investigator, 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.

## 10.9 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 End-of-Study
- 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)

# 11 REFERENCE LIST

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# 12 APPENDICES

## 12.1 Appendix 1: Mayo Score (Schroeder et al., 1987)

**Stool frequency***

0= Normal no. of stools for this patient

1= 1-2 stools more than normal

2= 3-4 stools more than normal

3= 5 or more stools more than normal

**Rectal bleeding****

0= No blood seen

1= Streaks of blood with stool less than half the time

2= Obvious blood with stool most of the time

3= Blood alone passed

**Findings of flexible proctosigmoidoscopy**

0= Normal or inactive disease

1= Mild disease (erythema, decreased vascular pattern, mild friability)

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

3= Severe disease (spontaneous bleeding, ulceration)

**Physician's global assessment*****

0= Normal

1= Mild disease

2= Moderate disease

3= Severe disease

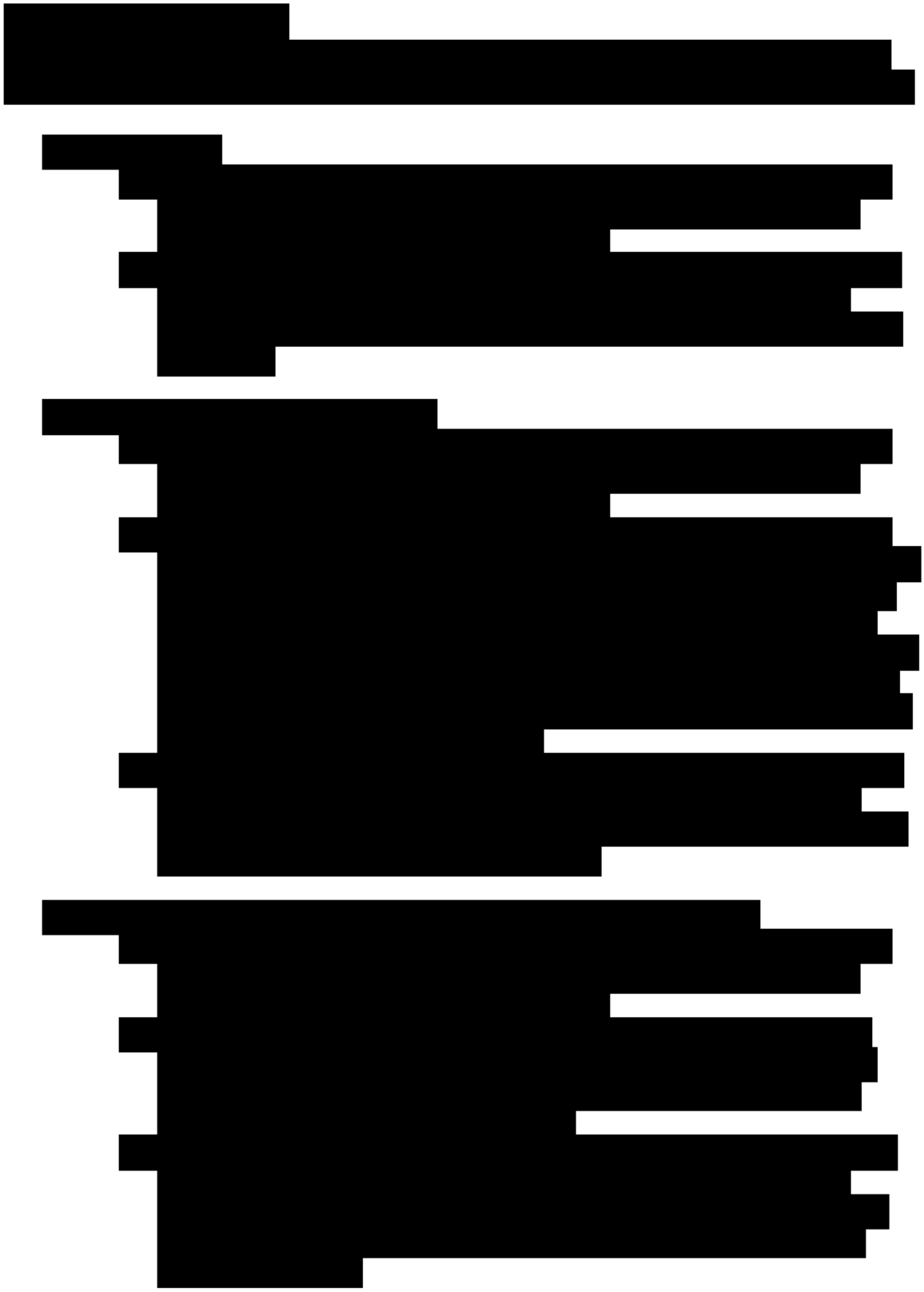
* Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.

** The daily bleeding score represented the most severe bleeding of the day.

*** The physician's global assessment acknowledged the three other criteria, the patient's record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Schroeder, K.W., Tremaine, W.J., Ilstrup, D.M., (1987). Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. N. Engl. J. Med. 317(26), 1625-1629.

## 12.2 Appendix 2: Stool Frequency and Rectal Bleeding Subscore Calculation Guidelines



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## 12.3 Appendix 3: Inflammatory Bowel Disease Questionnaire (Guyatt et al., 1989)

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from I through 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, STOP for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

**QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)**

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem. Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at. Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED



Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. (1989). A New Measure of Health Status for Clinical Trials in Inflammatory Bowel Disease. Gastroenterology. 96(3), 804-10.