Statistical Analysis Plan

Protocol Number and 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 (SERES 201)**

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I confirm that I have reviewed this document and agree with the content.

APPROVALS
Author
[redacted]

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
3CMMS	Three-Component Modified Mayo Score
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
CI	Confidence Interval
cm	Centimeter
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CSR	Clinical Study Report
D	Day
dL	Deciliter
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eDiary	Electronic diary
EIA	Enzyme Immunoassay
EOT	End of treatment
ES	Endoscopic subscore

Abbreviation	Description
FDA	Food and Drug Administration
FMT	Fecal Microbiota Transplant
g	Grams
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference to Harmonisation
ITT	Intent-To-Treat
IXRS	Interactive Voice or Web Response System
JAK	Janus kinase
K-M	Kaplan-Meier
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
mm^3	Cubic millimeter
mmHg	Millimeters of Mercury
Pbo	Placebo
PGA	Physician Global Assessment
PI	Principal Investigator
PP	Per Protocol population
PT	Preferred Term
QD	Once a day
QID	Four (4) times a day
QoL	Quality of Life
RB	Rectal bleeding subscore

Abbreviation	Description
RHI	Robarts Histopathological Index
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	Standard Deviation
SF	Stool frequency subscore
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLF	Table, Listing and Figure
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
Vanco.	Vancomycin
WHO	World Health Organization

1. STUDY DESIGN

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 UC. 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 (3CMMS), which sums patient-reported rectal bleeding (RB) and stool frequency (SF) sub-scores, collected daily using an electronic diary (eDiary), with endoscopic subscore (ES). The ES 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 ES.

This study will enroll subjects with a total 3CMMS of 3 to 7, inclusive, with inclusion requiring a SF $\geq$ 1 and an ES $\geq$ 1.

Subjects will be randomized to 1 of 3 study arms (Table 1), each of which contain a 6-day pre-treatment period (vancomycin or matching placebo) and a 10-week Induction Treatment period (SER-287 or matching placebo).

Table 1: 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 1 of 2 Maintenance Treatment study arms (Table 2):
  - 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 2).

Table 2: 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.

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on SER-287-SERES-201Protocol Amendment 3, dated 08 October 2019 and its associated electronic case report forms (eCRF) Version 4.0, dated 14 Feb 2020.

2.1. TIMINGS OF ANALYSES

2.1.1. At the end of the Induction Treatment period

Seres will conduct an unblinded analysis of the primary and key secondary efficacy and selected 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 treatment prematurely prior to the Week 11 [Visit 7].

Key unblinded efficacy and safety summary tables will be generated at this time. An unblinded separate pre-defined team will have access to the unblinded tables, listings and figures (TLFs). A detailed unblinding plan will be implemented concurrently with the SAP.

All clinical data generated during the induction treatment 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 the primary and key secondary efficacy data in the database will be permitted, unless deemed to be highly warranted (in such case, the decision, justification and the change will be documented). Therefore, all primary and key secondary 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, so it is clear which data points have been updated after the end of the primary study period. An audit trail of any changes made to the locked data will be available.

2.1.2. At the end of the Maintenance Treatment and Open-Label Treatment periods, whichever is later

Seres will conduct an unblinded analysis of the safety and exploratory efficacy endpoints at the end of the maintenance treatment and open-label treatment periods whichever is later, specifically 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 treatment prematurely prior to Week 37 (Visit M-7)

and

- All subjects who entered the Open-Label Extension arm have completed their open-label extension treatment (OL-Week 0 through OL-Week 11 [Visit OL-5]), or have terminated the treatment prematurely prior to Open-Label-Week 11 (Visit OL-5)

whichever is later.

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

Relevant clinical data generated during the maintenance treatment period (Week 11 through Week 37 [Visit M-7]) and the open-label treatment period (OL-Week 0 through OL-Week 11 [Visit OL-5]) for all subjects enrolled in the maintenance arms and the open-label 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 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, so it is evident which data points have been updated after the end of the maintenance and the open-label treatment periods. An audit trail of any changes made to the locked data will be available.

2.1.3. 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 adverse event (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).

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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

3.2. KEY SECONDARY OBJECTIVE

- 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

3.3. 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

3.4. PRIMARY SAFETY OBJECTIVES

- To evaluate safety and tolerability of SER-287

3.5. 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 (QoL), 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

3.6. SUBJECT SELECTION

3.6.1. 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 Principal Investigator (PI)) and a minimum disease extent of 15 cm from the anal verge at the Screening endoscopy.
4. Active mild-to-moderate UC as determined by a 3CMMS 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- aminosalicylate (5-ASA) compounds, corticosteroids, 6-mercaptopurine (6-MP) or azathioprine (AZA), anti-TNFα, anti-integrin or tofacitinib.
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).

3.6.2. 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

3.7. 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' ES subscores. However, due to the inclusion of mild subjects and those with an ES 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 3CMMS between 3 and 7, inclusive, and a baseline SF ≥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).

3.8. METHOD 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 Interactive Voice or Web Response System (IXRS) to one (1) of the three (3) study arms.

Randomization will be stratified by subjects' baseline ES subscore (1-2 vs. 3), 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.

3.9. 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 (SOPs) 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 (SAE) reporting].

Investigators are not to break the study treatment blind except when information concerning the study drug is necessary for the medical treatment of the subject. If a medical emergency requiring unblinding occurs, the investigator (or designated physician) is strongly encouraged to contact the medical or safety monitor to assess the necessity of breaking the study drug blind. If unblinding is warranted, the investigator will obtain the treatment assignment information from the IXRS. Every effort is to be made to limit study site personnel unblinding only to those individuals providing direct care to that subject. Any intentional or unintentional breaking of the blind is to be reported immediately to the sponsor. The other circumstances in which unblinding may be necessary are at the request of a subject who becomes pregnant during the study or for regulatory reporting purposes.

If the blind is broken, the date, time, and reason must be recorded in the Electronic Data Capture (EDC) system and any associated SAE report.

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

After the 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 personnel at Seres and the unblinded statistical and programming team at a biostatistics and statistical programming vendor will have access to the treatment code when the study blind is broken at the end of the induction phase and at the end of the maintenance phase. The remaining study team personnel (majority), principal investigators and subjects will remain blinded until the study is completed. A detailed unblinding plan will be implemented concurrently with the SAP.

3.10. SCHEDULE OF EVENTS

For an updated schedule of events (induction treatment, maintenance treatment for remitters and open-label extension arm for non-remitters), please refer to Table 1, Table 2 and Table 3 of the SERES-201 clinical study protocol, Amendment 3 (08-October-2019).

4. ENDPOINTS

4.1. 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)

4.2. 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)

4.3. 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

4.4. 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 maintenance treatment and 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

4.5. SAFETY ENDPOINTS

- Incidence of AEs, SAEs and Adverse Events of Special Interest (AESIs) for each treatment and each SER-287 donor
- Laboratory evaluation results

- Vital sign measurements
- Physical examination findings

5. ANALYSIS POPULATIONS

For the induction phase (IP), there will be 5 analysis populations: the Intent-to-Treat (ITT_IP) population, the modified Intent-to-Treat 1 (mITT-1_IP) population, the modified Intent-to-Treat 2 (mITT-2_IP) population, the Per-Protocol (PP_IP) population, and the Safety population (Safety_IP).

For the maintenance phase (MP), there will be 5 analysis populations: the ITT population (ITT_MP), the mITT-1 population (mITT-1_MP), the mITT-2 population (mITT-2_MP), the PP population (PP_MP), and the Safety population (Safety_MP).

For the open-label phase (OL), there will be 4 analysis populations: the ITT population (ITT_OL), the mITT-1 population (mITT-1_OL), the mITT-2 population (mITT-2_OL), the PP population (PP_OL), and the Safety population (Safety_OL).

5.1.1. Intent-to-Treat (ITT) Populations

The 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.

Specifically, the definitions for each study phase are listed below:

- For the induction phase, the ITT population (ITT_IP) is defined as all subjects who are randomly assigned to the induction phase, including those who are not exposed to any study drug during the induction phase.
- For the maintenance phase, the ITT population (ITT_MP) is defined as all subjects who enter the maintenance phase, and then are re-randomized in the maintenance phase, including those who are not exposed to any study drug during the maintenance phase.
- For the open-label phase, the ITT population (ITT_OL) is defined as all subjects who are assigned to the open-label phase (as indicated in the “Status” CRF page), including those who are not exposed to any study drug during the open-label phase.

The ITT_IP, ITT_MP, and ITT_OL populations will be the primary analysis populations for all efficacy endpoints for the induction, maintenance and open-label phases of the study, respectively. All analyses conducted in these populations will be analyzed based on the treatment to which subjects were randomized or assigned.

5.1.2. Modified Intent-to-Treat 1 (mITT-1) Populations

The 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.

Specifically, the definitions for each study phase are listed below:

- For the induction phase, the mITT-1 population (mITT-1_IP) is defined as all randomized subjects with a baseline evaluation for the induction phase, who have active mild-to-moderate UC when the induction phase starts, and receive any amount of study drug during the induction phase.
- For the maintenance phase, the mITT-1 population (mITT-1_MP) is defined as all subjects who were mITT-1 population during the induction phase, enter the maintenance phase, are re-randomized in the maintenance phase, and receive any amount of study drug during the maintenance phase.
- For the open-label phase, the mITT-1 population (mITT-1_OL) is defined as all subjects who were mITT-1 population during the induction phase, assigned to the open-label phase (as indicated in the "Status" CRF page), and receive any amount of study drug during the open-label phase.

All analyses in the mITT-1_IP, mITT-1_MP, and mITT-1_OL populations will be analyzed based on the treatment to which subjects were randomized or assigned.

5.1.3. Modified Intent-to-Treat 2 (mITT-2) Populations

The 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. Normal histology is defined as baseline Robarts Histopathological Index (RHI) score ≤3.

Specifically, the definitions for each study phase are listed below:

- For the induction phase, the mITT-2 population (mITT-2_IP) is defined as all randomized subjects with a baseline evaluation for the induction phase, who are confirmed to have normal histology at baseline for the induction phase, who have active mild-to-moderate UC when the induction phase starts, and receive any amount of study drug during the induction phase.
- For the maintenance phase, the mITT-2 population (mITT-2_MP) is defined as all subjects who were mITT-2 population during the induction phase, enter the maintenance phase, are re-randomized in the maintenance phase, and receive any amount of study drug during the maintenance phase.
- For the open-label phase, the mITT-2 population (mITT-2_OL) is defined as all subjects who were mITT-2 population during the induction phase, assigned to the open-label phase (as indicated in the "Status" CRF page), and receive any amount of study drug during the open-label phase.

All analyses in the mITT-2_IP, mITT-2_MP, and mITT-2_OL populations will be analyzed based on the treatment to which subjects were randomized or assigned.

5.1.4. Per Protocol (PP) Populations

The PP population will consist of subjects from the mITT-2 Population who do not have any major protocol deviations. This definition will be applied to each study phase. The subjects excluded from the PP_IP, PP_MP, and PP_OL population will be determined and documented before the study is unblinded. Specifically, Seres has defined the following criteria as major deviations excluding subjects from the Per Protocol Population:

1. Subject does not meet eligibility criteria which may impact subject safety or data integrity, including randomization >28 days from signing informed consent.
2. Subject does not have documented informed consent prior to screening and enrollment.
3. Subjects' Induction Treatment Week 11 endoscopies were missing or not performed in compliance with protocol, i.e. >7 days outside of protocol specified window; endoscopy video performed in black and white (or other method not in line with protocol).
4. Subject non-compliance with e-diary entry during Induction Treatment Week 11 and Induction Treatment Week 12 such that 3CMMS could not be calculated.
5. Subject received prohibited concomitant medication(s) which may impact the validity of the primary endpoint assessment.
6. Non-compliance with investigational product (<80% compliance in any treatment phase).
7. Other: deviations which may impact the validity of the primary endpoint assessment.

All analyses in the PP_IP, PP_MP, and PP_OL populations will be analyzed based on the treatment to which subjects were actually received.

5.1.5. Safety Populations

The Safety population will consist of all subjects who receive any amount of study drug. Subjects will be analyzed according to the treatment they actually received, rather than the treatment to which they are randomly assigned. This definition will be applied to each study phase.

All safety analyses will be conducted based on the Safety population. All analyses in the Safety_IP, Safety_MP, and Safety_OL populations will be analyzed based on the treatment to which subjects were actually received.

5.1.6. Microbiome Modified Intent-to-Treat (mcITT) Populations

The 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. Microbiome analysis populations will be described in a separate microbiome SAP which will be written to address the microbiome endpoints.

5.2. PROTOCOL DEVIATIONS

Protocol deviations are entered into the [redacted] Clinical Trial Management System (CTMS). The protocol deviations will be further classified as major vs. minor in CTMS and reviewed by the medical monitors on an ongoing basis. This listing of [redacted]-defined major and minor protocol deviations is reviewed by a Seres team including the Medical Monitor, Clinical Operations, Data Management, and statistical team prior to unblinding to identify deviations as either Major or Minor based on their impact to the primary efficacy analysis. Exclusion from the Per Protocol populations will be based on the occurrence of these major deviations.

Protocol deviations will be presented by sponsor-defined major/minor category and deviation category within each major/minor category and summarized in 2 tables as follows: 1) with frequencies and percentages of subjects with at least one deviation in each major/minor category. Subjects with multiple deviations will only be counted once for a given major/minor category and once for the specific protocol deviation category within the major/minor category; and 2) with all

incidences of the protocol deviations counted separately in each category. The total count of protocol deviations will be used as the denominator for percentages in this table.

A special COVID-19 related protocol deviation category was created during the study. The protocol deviations summary will present the number and percentage of subjects with COVID-19 related deviations and the type of deviations.

A listing of all protocol deviations by subject and deviation category will be provided.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All statistical procedures will be completed using SAS® version 9.4.

Hypothesis testing generally will be conducted at the two-sided α=0.05 level. Ninety-five percent (95%) confidence intervals (CIs) will be presented, where specified. All P-values will be reported to three decimal places. P-values less than 0.001 will be reported as '<0.001' and P-values greater than 0.999 will be reported as '>0.999'.

All summaries will be presented for each study phase separately. Within each phase, the summaries will be presented by treatment group, unless otherwise specified. For SER-287 treatment groups, in addition to the induction dose and step-down induction dose arms, a "Total SER-287" column will also be added, combining the summaries from both SER-287 active treatment groups. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation (SD), minimum, and maximum. For categorical variables, statistical summaries will include number of subjects and percentages.

Supporting listing will be provided for each analysis parameter.

6.2. KEY DEFINITIONS

6.2.1. Study Endpoints

6.2.1.1. Clinical Remission

a) Clinical Remission for the Induction and Open-Label Treatment Periods:

- SF = 0 or 1, with at least one-point decrease from baseline
- RB = 0
- ES = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline
- No occurrence of UC Flare during the treatment period

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

- SF = 0 or 1
- RB = 0
- ES = 0 or 1 on modified Mayo Score
- No occurrence of UC Flare during the treatment periods

c) Clinical Remission including normalization of stool frequency:

- SF = 0
- RB = 0
- ES = 0 or 1 on modified Mayo Score, with at least one-point decrease from baseline
- No occurrence of UC Flare during the treatment period

6.2.1.2. Symptomatic Remission:

- SF = 0 or 1
- RB = 0

For the derivation of symptomatic remission over time as mentioned in Section 8.3.5, based on data from the included study days within each time point, the average of the 3 most recent scores for the SF subscore and the most severe RB subscore among the 3 most recent scores will be used to derive symptomatic remission. If only one score or less is available from the included study days, the subscore(s) will be considered missing. If one or both subscores are missing, symptomatic remission will be considered missing.

6.2.1.3. Endoscopic Improvement

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

6.2.1.4. Endoscopic Remission

a) Endoscopic Remission for the Induction and Open-Label Treatment Periods

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

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

   - ES = 0 or 1 on modified Mayo Score, as assessed by flexible sigmoidoscopy or colonoscopy

6.2.1.5. Histological Mucosal Healing

Statistically significant decrease from baseline, using the RHI scoring system. The RHI score is computed based on Geboes score using the following formula (based on Mosli et al., 2017):

RHI = 1 X chronic inflammatory infiltrate level (Geboes score item 1, 4 levels)
+ 2 X lamina propria neutrophils (Geboes score item 2B, 4 levels)
+ 3 X neutrophils in epithelium (Geboes score item 3, 4 levels)
+ 5 X (erosion or ulceration (4 levels after combining Geboes score Item 5.1 and 5.2)

The Geboes scores are defined as below:

- 0: Structural - architectural change
- 1: Chronic Inflammatory infiltrate
- 2a: Lamina propria eosinophils

- 2b: Lamina propria neutrophils
- 3: Neutrophils in epithelium
- 4: Crypt destruction
- 5: Erosion or ulceration

For Geboes score Item 1, 2B and 3, the original scores are obtained from the histopathology data by removing the leading question index. For example, for Item 1, if the value in the histopathology data is 1.2, then the Geboes score Item 1 is 2 As another example, for Item 2B, if the value in the histopathology data is 2B.3, then the Geboes score Item 2B is 3.

For Geboes score Item 5, the original scores are obtained from the histopathology data based on the following rules:

- If histopathology data is 5.0, then Geboes score Item 5 is 0;
- If histopathology data is 5.1, then Geboes score Item 5 is 1;
- If histopathology data is 5.2, then Geboes score Item 5 is 1;
- If histopathology data is 5.3, then Geboes score Item 5 is 2;
- If histopathology data is 5.4, then Geboes score Item 5 is 3.

6.2.1.6. Three-Component Modified Mayo Score

Sum of the below three (3) subscores:

1. ES (modified Mayo)
2. SF
3. RB

6.2.1.7. 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 (SF and RB subscores) of the modified Mayo score,

- Compared to baseline score 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

6.2.1.8. 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

6.2.1.9. Engraftment

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

6.2.2. Study Day

For the induction phase, Study Day 1 is defined as the first dosing day of induction study drug. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Before the day of study drug administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

For the maintenance phase, Study Day 1_MP is defined as the first dosing day of maintenance study drug, subsequent days are numbered consecutively (Day 2_MP, Day 3_MP, etc.).

For the open-label phase, Study Day 1_OL is defined as the first dosing day of open-label study drug, subsequent days are numbered consecutively (Day 1_OL, Day 2_OL, etc.).

6.2.3. Baseline Values

Baseline values for SF, RB and ES are calculated in the following manner:

SF

1. Baseline of the induction and the open-label phases (at screening prior to induction treatment)

    a. The scores from the three (3) most recent days, within the last seven (7) days prior to the day of the bowel preparation for endoscopy, will be averaged and rounded to the nearest integer.
    b. If only two (2) scores are available within the last seven (7) days prior to the day of the bowel preparation for endoscopy, the SF subscore will be considered missing and the subject will be ineligible for enrollment.

2. Baseline of the maintenance (at the end of induction treatment)

    a. The scores from the three (3) most recent days, within the last seven (7) days prior to the day of the bowel preparation for endoscopy, will be averaged and rounded to the nearest integer.
    b. If only two (2) scores or less are available within the last seven (7) days prior to the day of the bowel preparation, then additional scores from three (3) to seven (7) days after the endoscopy procedure, choosing the scores closest to the day of endoscopy, can be used to obtain three (3) scores. These three (3) scores will be averaged and rounded to the nearest integer. Scores available prior to the bowel preparation should be included in the calculation of the average SF subscore first, before using any scores after the endoscopy procedure.
    c. If three (3) scores from the two (2) preceding scenarios are not available, then the SF subscore will be considered missing and the subject will be assigned an outcome of failure for all endpoints which are derived using the SF subscore.

RB

The RB subscores are derived in the same manner as outlined in the preceding section for the calculation of the SF subscores. However, instead of using the average of three (3) scores, the most severe RB score among the three (3) scores will be used to obtain the RB subscores.

ES

Endoscopic subscores are determined by qualified gastroenterologists – first locally, and then by an independent, blinded central reader. The endoscopy central readers were blinded to subjects' treatment assignments throughout the entire study. If the local and central scores were discordant, a second independent, blinded central reader scored the video (adjudication). If all of the scores were different from one another, then the median of the 3 scores is used as the final ES. The baseline ES for the induction phase and the open-label phase is calculated from the Screening Visit 2 data. The baseline ES of the maintenance phase is calculated from the last ES assessment prior to the dosing of any maintenance study drug (generally this will be assessed at Week 11, at the end of the induction treatment period).

If a subject discontinued the maintenance treatment and entered the open-label phase, baseline ES values would be at the time of discontinuation of the maintenance treatment prior to dosing of any open-label study drug, if available. If ES data is not available at the time of discontinuation at the end of maintenance treatment, baseline ES would be based from the Screening Visit 2 data.

Other Endpoints

In general, the baseline values for other endpoints (e.g. laboratory assessments) for different phases of the study are defined as follows, unless otherwise specified:

- For the induction phase and the open-label phase, baseline values are assessments done at screening or pre-dose assessments on Day 1, using the timepoint that is closest to but prior to dosing of any induction treatment study drug.

- For the maintenance phase, baseline values are the last assessments prior to dosing of any maintenance study drug (i.e. in general, these will be taken at Week 11, at the end of induction treatment period).

- For the open-label phase, if subject discontinued the maintenance treatment and entered open-label phase, baseline values would be at the time of discontinuation of the maintenance treatment prior to dosing of any open-label study drug. If data is not available at the time of discontinuation at the end of maintenance treatment, baseline values would be based on assessments done at screening or pre-dose assessments on Day 1.

6.2.4. End of Treatment (EOT) Values

SF

1. At the end of induction treatment (at Week 11 visit date, or the date of last visit if the subject early discontinued from the period)

    a. The scores from the three (3) most recent days, within the last seven (7) days prior to the day of the bowel preparation for endoscopy, will be averaged and rounded to the nearest integer.
    b. If only two (2) scores or less are available within the last seven (7) days prior to the day of the bowel preparation, then additional scores from three (3) to seven (7) days after the endoscopy procedure, choosing the scores closest to the day of endoscopy, can be used to obtain three (3) scores. These three (3) scores will be averaged and rounded to the nearest integer. Scores available prior to the bowel preparation should be included in the calculation of the average SF subscore first, before using any scores after the endoscopy procedure.
    c. If three (3) scores from the two (2) preceding scenarios are not available, then the SF subscore will be considered missing and the subject will be assigned an outcome of failure for all endpoints which are derived using the SF subscore.

2. At the end of the maintenance treatment (at M-Week 37 visit date, or the date of last visit if the subject early discontinued from the period) and open-label treatment (at OL-Week 11 visit date, or the date of last visit if the subject early discontinued from the period),

    a. The scores from the three (3) most recent days, within the last seven (7) days prior to the day of the bowel preparation for endoscopy, will be averaged and rounded to the nearest integer.
    b. However, if only two (2) scores are available within the last seven (7) days prior to the day of the bowel preparation for endoscopy, the SF subscore will be calculated as the average of these two (2) scores and rounded to the nearest integer.
    c. If one (1) score or less is available within the last seven (7) days prior to the day of the bowel preparation for endoscopy, the SF subscore will be considered missing and the subject will be assigned an outcome of failure for all endpoints which are derived using the SF subscore.

RB

The RB subscores are derived in the same manner as outlined in the preceding section for the calculation of the SF subscores. However, instead of using the average of three (3) scores, the most severe RB score among the three (3) scores will be used to obtain the RB subscores.

ES

The end of treatment ES is calculated from the last available data on or before the date of last visit for the period.

Due to onsite visit restrictions and closures of endoscopy facilities during the COVID-19 pandemic, the Week 11 endoscopy visits for some subjects may be performed outside of the visit window as defined in the study protocol. At the onset of the COVID-19 pandemic, a guidance document was issued to the sites, IRBs, and FDA to allow flexibility of the visit windows for endoscopies, including how to document delayed endoscopy visits.

For the purpose of this analysis, endoscopies at the end of the induction, maintenance, and open label phases will be considered valid as long as the endoscopy was performed within 30 days of last dose of IP taken in each treatment phase.

See Section 8.1.2.4 for sensitivity analyses related to the endoscopy visit window.

Other Endpoints

In general, the end of treatment values for other endpoints are defined as the last available data on or before the date of last visit for the period.

6.3. MISSING DATA

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

6.3.1. General Binary Efficacy Endpoint

In general, unless otherwise specified, missing data will be imputed based on non-responder imputation (NRI), that is subjects with missing values such that the clinical binary efficacy endpoint cannot be calculated, the outcome will be assigned as a failure for the endpoint. In another words, subjects with missing value of a binary efficacy endpoint will be assigned an outcome of failure for the endpoint, if

- The subject did not have a post-baseline endoscopy done during the induction period, OR
- 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.

6.3.2. Mayo Score, Stool Frequency and Rectal Bleeding Subscores

The description of the handling of missing data for individual components of the 3CMMS, specifically SF and RB subscores, are described in Section6.2.

6.3.3. Imputation of Missing Data Using Last Observation Carries Forward (LOCF) Approach

The primary endpoint and the key secondary endpoint will also be analyzed based on the LOCF approach. The values before the last available visit of the period will be used when the subject early discontinued from the period. The end of treatment values, as discussed in Section 6.2, will be used.

Subjects who only have baseline values will be treated as failures for the endpoint in the LOCF analysis.

Note that when a subject had an increasing dose in UC medication including the use of new UC treatment medication, use of UC surgery, indicates that a subject had a UC flare based on the definition of UC flare in this study. Therefore, since no occurrence of a UC flare is one of the criteria for achieving clinical remission, a value of failure will be assigned for this intercurrent event regardless of treatment arm in all the sensitivity analyses.

6.3.4. Observed-Case Analyses

For the observed-case analyses, the missing values will not be imputed.

6.3.5. Robarts Histopathological Index

When evaluating the change from baseline RHI score (as described in Section 8.2.3), two different approaches for RHI score imputation will be used:

1) A multiple imputation approach using Markov Chain Monte Carlo (MCMC) method (Schafer, 1997) will be used to impute the missing values for RHI score at Week 11 [Visit 7] using the distribution within each treatment group.

2) As a sensitivity analysis approach, Baseline Observation Carried Forward (BOCF) will also be used for the imputation for RHI score at Week 11 [Visit 7].: Missing post-baseline data will be imputed to their respective baseline RHI scores. This assumes disease activity as measured by RHI scores remained at baseline value for subjects with early withdrawal, i.e. subject does not, in the long-term, derive benefit nor harm from treatment.

6.3.6. Conventions for Missing AE Dates

For AEs or SAEs, a missing or incomplete onset date will be imputed according to the following conventions:

3) If an onset date is completely missing, the derived onset date will be calculated as the first non-missing date from the following list in the following order;
    - First study medication date
    - Date of informed consent
4) If an onset date is partially missing, the derived onset date will be calculated following:
    - Missing day, but month and year present: the day will be imputed as the 15th of the month. If the month and year are equal to the month and year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
    - Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the year is equal to the year of the first study medication dose, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
    - If the imputed AE onset date occurs after the database lock date, the imputed AE onset date will be imputed as the database lock date.

For AEs or SAEs which are not ongoing at the end of the study, a missing or incomplete end date will be imputed according to the following conventions:

1) If an end date is missing, the derived end date will be imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.

2) If an end date is incomplete, the derived end date will be calculated following:
    - Missing day, but month and year present: the day will be imputed as the last date (for example February 2019 will be imputed as 28 February 2019) of the month
    - Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.
    - If the imputed AE end date occurs after the database lock date, the imputed AE end date will be imputed as the database lock date.

6.3.7. Conventions of Missing Concomitant Medications Dates

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is missing or partial:

- If the day is missing, the start day will be the first day of the month
- If the month is missing, the start month will be the month of the randomization visit
- If the year is missing, the start year will be the year of the randomization visit
- If the entire date is missing, the start date will be the date of first study drug administration

If the stop date is missing, partial and the medication is not "ongoing":

- If the day is missing, the stop day will be the last day of the month reported
- If the month is missing, the stop month will be the month during which the last assessment occurred
- If the year or the entire date is missing, the date will be the date of the last assessment.

6.4. VISIT WINDOWS

Nominal visits will be used for all by visit analyses. The study visits scheduled after randomization should occur at the times delineated in the Schedule of Events.

6.5. POOLING OF CENTERS

Data from all investigational centers/sites will be pooled for analyses since analyses will not be adjusted for investigator site.

6.6. MULTIPLICITY ADJUSTMENTS

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 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.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Summary tables for demographics (e.g., age, race, ethnicity, sex), baseline characteristics (e.g., weight, height, body mass index), UC medical history, treatment history, and other baseline disease characteristics will be summarized by treatment group for specified analysis populations outlined below.

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

The following will be presented by treatment group: number of subjects who were screened; number and percentage of subjects who failed screening; number and percentage of subjects who were randomized; completion status for each period (pre-treatment, induction treatment,

maintenance treatment, open-label treatment, and safety follow-up period); primary reason for premature discontinuation during each period (pre-treatment, induction treatment, maintenance treatment, open-label treatment, and safety follow-up period).

The number and percentage of subjects included in each of the analysis populations will be presented.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be used to summarize demographics and other baseline characteristics. The summary will be presented by treatment group and overall for each study population.

Demographics information includes the following:

- Age at informed consent (Year)
- Sex at birth
- Race
- Ethnicity

Baseline characteristics information includes the following:

- Weight (kg)
- Height (m)
- Body mass index (BMI), calculated as BMI (kg/m^2) = (Weight (kg)) / [Height (m)]^2
- Stratification information:
  - Baseline ES (1-2 vs. 3), based on IXRS.
  - Concomitant use of UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none), based on IXRS and based on actual CRF information.
  - Concomitant use of UC medications at baseline (collapsed categories: 5-ASA or immunomodulators vs. none), based on IXRS and based on actual CRF information.

The following variables will be summarized for smoking history:

- Number of subjects who never smoked, were former smokers, and current smokers

- Number of years smoked for former smokers
- Number of years smoked for current smokers
- Time since the date stopped smoking for former smoker (from the date stopped to date of informed consent (months))

The following variables will be summarized for ulcerative colitis disease history information:

- Time since symptoms began, calculated from date symptoms began to date of informed consent (months)
- Time since UC diagnosis, calculated from date for diagnosis by physician to date of informed consent (months)
- Number of patients with at least one (1) acute exacerbation within the past 12 months (including screening), number of acute exacerbations, status of last exacerbations
- Number of patients with at least one (1) hospitalization for ulcerative colitis within the past 12 months (not including screening), number of hospitalizations
- Number of patients who had at least one (1) colonoscopy or sigmoidoscopy within the last 18 months (not including screening), time since last colonoscopy or sigmoidoscopy
- Location and extent of patient's disease: Proctosigmoiditis, Left sided colitis, Extensive colitis, Pancolitis
- Number of patients who had surgery for ulcerative colitis (not including screening), number of surgeries
- Number of patients who had any extraintestinal manifestations (not including screening) and number of extraintestinal manifestations for each category (e.g. Arthritis/Arthralgia, Iritis/Uveitis etc.)
- Number of weeks of corticosteroid use over the last 12 months

7.3. MEDICAL AND SURGICAL HISTORY

A by-treatment summary table of the number and percentage of subjects with medical and surgical history by system organ class (SOC) and preferred term (PT) will be produced for subjects in the Safety_IP. Medical history and surgical history will be sorted in alphabetical order of SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, V21.0. For the summary tables, a subject may appear more than once if he has more than one medical history/surgical history finding coded under different SOC terms or more than one medical

history/surgical history finding with a different PT under the same SOC term. However, the subject will be counted only once in the overall category.

A by-subject listing with coded SOC and PT along with verbatim eCRF term will also be provided.

7.4. PRIOR THERAPY FOR ULCERATIVE COLITIS

Prior therapy for Ulcerative Colitis will be summarized by treatment arm in the ITT_IP and ITT_MP population for the following therapies as outlined in the CRF. The summary table if applicable will also include status (ongoing/discontinued), duration of prior therapy (for ongoing/discontinued) and patient experience of the prior ongoing and prior discontinued therapy.

- Systematic Corticosteroids
- Immunomodulator: 6-Mercaptopurine, Azathioprine, Methotrexate
- Anti-TNF biologics (approved and non-approved)
- Anti-integrin biologics (approved and non-approved)
- Anti-IL biologics (approved and non-approved)
- Other orally active immunosuppressants (approved and non-approved)
- Rectal Corticosteroids (enemas or suppositories)
- Oral 5-ASA/Mesalamine/Mesalazine
- Sulfasalazine
- Balsalazide
- Rectal 5-ASA (enemas or suppositories)
- Probiotics
- Antidiarrheals
- Cyclosporine/Tacrolimus (FK506)
- Enteral Feeds
- Parenteral Nutrition

A by-subject listing of prior therapy for ulcerative colitis will also be provided.

7.5. PRIOR AND CONCOMITANT MEDICATION

Prior medications are defined as medications that started before the date of dosing. Any medication that started on the date of dosing will not be considered prior. Concomitant medications are defined as all medications (excluding study treatment) taken on or after the date of dosing. This also

includes medications ongoing on the dosing date. Medications that started before the date of dosing and are ongoing after the date of dosing will be considered as both prior and concomitant.

Separate summary tables will be provided for prior and concomitant medications in the Safety_IP population, presenting the number and percentage of subjects by treatment group, and will be sorted in alphabetical order of Anatomic Therapeutic Chemical (ATC) classification level 2 and then Preferred Term (PT) in the overall column. For concomitant medications, the summary will be presented for each phase (pre-treatment, induction treatment, maintenance treatment, open-label treatment, and safety follow-up period). For each subject, the medication will be counted only once within a given ATC level 2 and only once within a given preferred drug name level. A subject may appear more than once if he/she has more than one concomitant medication coded under different ATC categories, however, the subject will be counted only once in the overall category.

Prior and concomitant medications will be included in separate listings, coded by using the ATC classification codes and preferred drug name according to the World Health Organization (WHO) Drug Dictionary Global, (01SEP2018).

8. EFFICACY

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1. Primary Analysis of the Primary 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 (placebo after pre-treatment placebo – Arm A). The number and percentage of subjects with clinical remission will be presented by treatment group.

The primary efficacy endpoint analysis will be based on the Cochran-Mantel-Haenszel (CMH) test, stratified only by the ES score at baseline (1-2 vs. 3) and UC medications at baseline (collapsed categories based on IXRS: 5-ASA or immunomodulators vs. none). The CMH test p-value, the adjusted treatment difference with CMH weight (Treatment B vs. Treatment A) along with its 2-sided 95% CI will be presented. The Breslow-Day Test of Homogeneity will be used to assess the homogeneity of the risk differences across the strata.

As a supportive analysis, exact 2-sided Clopper Pearson binomial CIs will be computed for each treatment group. The difference of the clinical remission rate without adjustment for other

covariates between treatment groups will be computed. Asymptotic 2-sided 95% CIs will be computed using un-pooled variance estimates and approximation using Normal distribution.

For the primary efficacy analysis, end of treatment values will be taken from Week 11 visit date, as discussed in Section 6.2.

The primary efficacy analysis will be performed in the ITT_IP, mITT-1_IP, mITT-2_IP, and PP_IP Population. The results from the ITT_IP population will be deemed as the primary.

8.1.2. Sensitivity Analyses of the Primary Endpoint

8.1.2.1. Last Observation Carried Forward

To assess the robustness of missing data imputation in the primary efficacy analysis, an additional sensitivity analysis will be performed for the primary endpoint while the missing data is imputed based on the last observation carried forward (LOCF) approach. Details of LOCF approach are described in Section 6.3.3.

8.1.2.2. Re-randomization Test

Following Han et al. 2013, we will also carry out a "Re-randomization Test" to evaluate the impact of the adaptive randomization algorithm used in the treatment allocation. This will be done through a Monte Carlo simulation process:

1. Run 10000 simulation with the same treatment allocation algorithm (this will be done in SAS) for the enrolled subjects.
2. Assign the observed primary endpoint results to each subject regardless of the treatment allocated in step 1.
3. Calculate the CMH test statistic in each simulation. This will give us a null-distribution of the CMH test statistic
4. Apply the observed CMH test statistic obtained in the primary efficacy analysis.
5. Report the P-Value based on the quantiles of the observed CMH test statistic among the simulated CMH test statistics. P-Value will be defined as the proportion of CMH test statistic results that are more extreme than the observed CMH test statistic.

Additionally, a 2-sided 95% interval estimate of treatment effect will be obtained by identifying a shift that leads to relevant p-values (0.025 and 0.975) using the same simulation approach as above.

A grid search around the end point of this interval will be performed. This will be done in ITT_IP population.

8.1.2.3 Logistic Regression Model

For the ITT population, a multiple logistic regression model based on the binary clinical remission event (Yes, No) after 10 weeks of induction treatment between SER-287 (Induction Dose after pre-treatment with vancomycin – Arm B) and placebo (placebo after pre-treatment placebo – Arm A). This model will contain as main effects the treatment factor (B vs A), and the stratification factors baseline ES strata, baseline UC medication strata (based on IXRS), and donor. The model will also contain the 2-factor interactions treatment by ES strata, treatment by UC medication strata, and treatment by donor. After fitting the full model, the best fitting reduced model will be obtained by first removing interaction terms having little effect (using entry α=0.2) on the log odds ratio, then removing any main effect stratification factors having little effect. The resulting reduced model should fit the data as well as the full model. Conclusions regarding the comparison of B versus A from the reduced model will be compared with the conclusion resulting from the primary CMH analysis. The remission rate difference will be estimated using the difference in predicted rates from the logistic regression model. The confidence interval of the remission rate difference will be constructed by applying Delta Method to the results from logistic regression.

8.1.2.4 Sensitivity Analyses for COVID-19 Related Protocol Deviations.

Additional sensitivity analyses based on the type of COVID-19 related protocol deviations and their impact to the primary analysis may also be conducted. Subjects with Week 11 endoscopies conducted > 7 days outside of the protocol specified visit window will be assessed as non-remitters. As the protocol allows a Week 11 +3 day window, the maximum number of days that a subject can be outside of the protocol specified window is 10 days for this sensitivity analysis.

8.2. SECONDARY EFFICACY ANALYSES

8.2.1. Analysis of Key Secondary Endpoint

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

8.2.2. Sensitivity Analyses

Similarly, a sensitivity analyses will be performed based on the LOCF imputation of the missing data. Sensitivity analyses adjusting for COVID-19 related protocol deviations and their impact to the secondary endpoints may also be conducted.

8.2.3. 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. In general, the analyses are performed in the mITT-1_IP as well as mITT-2_IP population, unless otherwise stated.

Histological mucosal healing will be analyzed using the RHI. The analysis will be based on the change from baseline RHI score (Mosli et al., 2017) and analyzed by an analysis of covariance (ANCOVA) test, with treatment, ES at baseline, UC medications at baseline (based on CRF) as factors and baseline score as a covariate in the model. Two different imputation methods as described in Section 6.3.5 will be used in this analysis. For imputation by using multiple imputation, 100 imputed data sets will be generated. And PROC MIANALYZE will be used to combine the results based on different imputed data sets. The analysis population for this endpoint will be the mITT-1 and mITT-2_IP population.

In addition, histological mucosal healing will also be analyzed using a complete-case analysis in mITT-1. In this case, subjects with missing baseline or post-baseline data such that the change from baseline in RHI score cannot be calculated will be excluded from the analysis. This is assuming that the missing data is completely at random.

Normalization status of post-baseline histological mucosal healing from baseline normalization status will be evaluated using a shift table.

A by-subject listing with secondary efficacy data will also be provided.

For the analysis of the engraftment of SER-287 bacteria over time, this will be provided in the microbiome SAP.

8.3. EXPLORATORY EFFICACY ANALYSES

8.3.1. Additional Efficacy Analysis

Unless specified, all dichotomous exploratory efficacy endpoints will be analyzed using the same method used for the primary efficacy endpoint. The analyses are performed in the mITT-1 unless specified. It will be done for the induction, maintenance or the open-label periods, respectively, as appropriate.

8.3.2. Clinical Remission by Donor at the End of Induction

To evaluate the clinical remission rate of SER-287 by donor after 10 weeks of induction treatment, the primary analysis of the clinical remission rate of SER-287 by donor will be presented. This will be done for ITT_IP and mITT-1_IP populations only.

8.3.3. Clinical Remission by Histology at the End of Induction

To evaluate the clinical remission rate of SER-287 by histology after 10 weeks of induction treatment, the primary analysis of the clinical remission rate of SER-287 by histology will be presented. This will be done for ITT_IP and mITT-1_IP populations only.

8.3.4. Clinical Remission, Endoscopic Improvement, Endoscopic Remission, Histological Mucosal Healing at the End of Maintenance Treatment and at the End of Open-Label Treatment

Clinical remission at the end of maintenance and open-label treatment will be analyzed using the same method used for the primary efficacy endpoint.

Additionally, clinical remission at the end of open-label treatment will also be presented descriptively separating by their previous treatment in induction period and maintenance period.

Endoscopic improvement, endoscopic remission, histological mucosal healing at the end of maintenance and open-label treatment will be analyzed using the same approach.

8.3.5. Symptomatic Remission Over Time

Symptomatic remission over time will be calculated weekly based on the SF and RB subscores as defined in Section 6.2.1. The table below specifies the study days that will be included in the calculation of the SF and RB subscores for each time point:

Induction Phase

Time Point (Induction)	Study Days Included in SF and RB Calculations
Day 7	1-7
Day 14	8 -14
Day 21	15- 21
Day 28	22-28
Day 35	29-35
Day 42	36-42
Day 49	43-49
Day 56	50-56
Day 63	57-63
Day 70	64-70
Day 77	71-77

Maintenance Phase

Time Point (Maintenance: MP)	Study Days Included in SF and RB Calculations
Day 7_MP	1_MP-7_MP
Day 14_MP	8_MP -14_MP
Day 21_MP	15_MP - 21_MP
Day 28_MP	22_MP -28_MP
Day 35_MP	29_MP -35_MP
Day 42_MP	36_MP -42_MP
Day 49_MP	43_MP -49_MP
Day 56_MP	50_MP -56_MP
Day 63_MP	57_MP -63_MP
Day 70_MP	64_MP -70_MP
Day 77_MP	71_MP -77_MP
Day 84_MP	78_MP -84_MP
Day 91_MP	85_MP -91_MP
Day 98_MP	92_MP -98_MP
Day 105_MP	99_MP -105_MP
Day 112_MP	106_MP -112_MP
Day 119_MP	113_MP -119_MP

Time Point (Maintenance: MP)	Study Days Included in SF and RB Calculations
Day 126_MP	120_MP -126_MP
Day 133_MP	127_MP -133_MP
Day 140_MP	134_MP -140_MP
Day 147_MP	141_MP -147_MP
Day 154_MP	148_MP -154_MP
Day 161_MP	155_MP -161_MP
Day 168_MP	162_MP -168_MP
Day 175_MP	169_MP -175_MP
Day 182_MP	176_MP -182_MP

Open-Label Phase

Time Point (Open-Label: OL)	Study Days Included in SF and RB Calculations
Day 7_OL	1_OL - 7_OL
Day 14_OL	8_OL -14_OL
Day 21_OL	15_OL - 21_OL
Day 28_OL	22_OL -28_OL
Day 35_OL	29_OL -35_OL

Time Point (Open-Label: OL)	Study Days Included in SF and RB Calculations
Day 42_OL	36_OL -42_OL
Day 49_OL	43_OL -49_OL
Day 56_OL	50_OL -56_OL
Day 63_OL	57_OL -63_OL
Day 70_OL	64_OL -70_OL
Day 77_OL	71_OL -77_OL

Symptomatic remission over time will be analyzed by generalized linear mixed effect model using the logit link and with treatment, visit, ES at baseline, UC medications at baseline, treatment group by visit interactions as fixed effects and subjects as random effect.

A by-subject listing with symptomatic remission over time will also be provided.

8.3.6. Time to Symptomatic Remission (Symptom Scores), during the Induction Treatment

For the induction treatment period, Kaplan-Meier (K-M) plots of the time to symptomatic remission from the date of randomization will be produced for each treatment group, overall and by stratification factor. The median time to symptomatic remission and the corresponding 2-sided 95% CI will be summarized for each treatment group. Time to symptomatic remission will be tested between each treatment arm and placebo overall using a stratified log-rank test and separately within stratification factor level by the log-rank test. This will be done for ITT_IP and mITT-1_IP populations only.

For subjects with symptomatic remission during the induction treatment period, the date of symptomatic remission will be used as the event date. For subjects without symptomatic remission during the induction treatment period, the following censoring rules will be used:

- Subjects who are lost to follow-up or discontinued the trial prematurely during the induction treatment period are censored on the last date of contact during this period.
- Subjects who die during the induction treatment period are censored on the date of death.
- Subjects who complete the induction treatment period are censored on the date of last eDiary entry for SF/RB scores, or the date before entering Open-Label or Maintenance period, whichever is earlier.

8.3.7. Time to UC flare during Maintenance Phase

K-M plots of the time to UC flare from the date of re-randomization (maintenance treatment period) will be produced for each treatment group and overall. The median time to UC flare and the corresponding 2-sided 95% CI will be summarized for each treatment group. Time to UC flare will be tested between the treatment arm and placebo by the log rank test. This will be done for mITT-1_MP population only.

For subjects with UC flare during the maintenance treatment period, the date of UC flare will be used as the event date. For subjects without UC flare during the induction treatment period, the following censoring rules will be used:

- Subjects who are lost to follow-up or discontinued during the maintenance treatment period are censored on the last date of contact during this period.
- Subjects who die during the maintenance treatment period are censored on the date of death.
- Subjects who complete the maintenance treatment period are censored on the last date of contact during this period.

8.3.8. Inflammatory Bowel Disease Questionnaire (IBDQ)

Changes from baseline in IBDQ scores (total and sub-scale scores) will be assessed at the end of induction treatment, at the end of maintenance treatment and at the end of open-label treatment. Appropriate baseline values as defined in Section 6.2.3 will be used for each phase of the study. Descriptive statistics will be provided for the value and change from baseline in IBDQ scores. An ANCOVA model will be used with the change from baseline in IBDQ scores as the response variable, treatment group and stratification factors as the factors, and baseline IBDQ scores as a covariate. The least square means along with their 95% 2-sided CIs will be presented for the change from baseline in IBDQ scores for each treatment arm. The least square means along with

their 95% 2-sided CIs for the differences between treatment groups in changes from baseline in IBDQ scores will also be presented.

The IBDQ 32-item questionnaire is summarized as a total score ranging from 32 to 224. The items are grouped into the following sub-scale scores:

- IBDQ Bowel symptoms score = sum of (Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, Q29), ranging from 10 to 70, 10 questions
- IBDQ Emotional function score = sum of (Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, Q32), ranging from 12 to 84, 12 questions
- IBDQ Social function score = sum of (Q4, Q8, Q12, Q16, Q28), ranging from 5 to 35, 5 questions
- IBDQ Systemic symptoms score = sum of (Q2, Q6, Q10, Q14, Q18), ranging from 5 to 35, 5 questions

A by-subject listing with IBDQ scores will also be provided.

8.3.9. Biomarker Analysis

CRP change from baseline will be analyzed using the same method as for IBDQ scores. Both observed case and LOCF imputation for missing values will be used. It will be presented for mITT-1 population only.

Changes in fecal calprotectin will be summarized in a similar manner as CRP. In addition, normalization status (as evaluated by lab normal range) of post-baseline fecal calprotectin from baseline normalization status will be evaluated using a shift table.

A by-subject listing with biomarker data will also be provided.

8.3.10. Microbiome Outcome Analysis

A separate Microbiome SAP will be provided by Seres Therapeutics for the following microbiome endpoints:

- Engraftment of SER-287 bacteria over time
- 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. SUBGROUP ANALYSES

There are specific subgroups of interest which will be performed for the primary endpoint and key secondary endpoints in induction phase. All subgroup analyses will be conducted for mITT-1 population only. Endpoints will be summarized by treatment group and overall for the subgroups defined based on the categorized variables listed below:

- Age (< 65 and ≥ 65 years and < 35 and ≥ 35 years)
- Gender (Female, Male)
- Race (Asian, Black of African American, White and Other)
- Duration of UC (years from date of diagnosis to date of informed consent): < 1 years, ≥ 1 - < 3 years, ≥ 3 - < 7 years, ≥ 7 years)
- Country (US, Canada)
- ES subscore (1-2 vs. 3) and (1 vs. 2 vs. 3)
- Baseline UC Medication (collapsed categories based on IXRS: 5-ASA or immunomodulators vs. None)
- Disease severity (Mild vs. Moderate)
  - Mild (Modified Mayo Score of 3-4) vs. Moderate (Modified Mayo Score of 5-7)
  - Mild (Modified Mayo Score of 3-5) vs. Moderate (Modified Mayo Score of 6-7)
- Baseline RHI score: missing, 0-3 (normal); 4-6 (mild); >6 Stratification factor levels:
  - 1 = ES 1 or 2 and 5-ASA or immunomodulators
  - 2 = ES 1 or 2 and none
  - 3 = ES 3 and 5-ASA or immunomodulators
  - 4 = ES 3 and none
- Screening fecal calprotectin (≤ 500 and > 500 ug/g, ≤ 250 and > 250 ug/g)
- Extent and location of disease localization (Proctosigmoiditis, Left sided colitis, Extensive colitis, Pancolitis)
- Status of biologics therapy prior to entering the study (Yes vs. No, and Failed vs. Naïve or received and did not fail).
  - Anti-TNF
  - Anti-integrin
  - Anti-IL

- Status of non-biologics therapy prior to entering the study (Yes vs. No, Failed vs. Naïve or received and did not fail)
  - Non-biologics (e.g. tofacitinib, filgotinib, upadacitinib, apremilast, ameselimod, ozanimod, etrasimod)
- Status of advanced therapy (including biologic therapy or non-biologic therapy) prior to entering the study (Yes. Vs. No., Failed at least one of the therapies vs. Naïve or received and did not fail).

In addition, clinical remission and endoscopic improvement at the end of maintenance will be summarized by treatment group and overall for the subgroup defined below:

- Subject's treatment assignment in the induction phase (Arm A: Placebo/Placebo, Arm B: Vancomycin/SER-287 Induction Dose, Arm C: Vancomycin/SER-287 Step-Down Induction Dose)

If the value of the grouping variable cannot be determined, the patient will be excluded from the corresponding subgroup analysis.

10. SAFETY

All safety analyses will be conducted in the Safety populations, unless specified otherwise. Subjects will be analyzed according to the treatment they receive, rather than that to which they are randomized.

Safety endpoints will be summarized for each treatment period (pre-treatment, induction treatment, maintenance treatment, open-label treatment, and safety follow-up period).

Each Safety table will have a variable identify the period. The total number (N) of subjects at each period will be:

- For pre-treatment: N = # of subjects in Safety_IP
- For induction treatment: N = # of subjects in Safety_IP
- For maintenance treatment: N= # of subjects in Safety_MP
- For open-label: N= # of subjects in Safety_OL
- For safety follow-up: N= # of subjects entering follow-up period

Note that, during the first four (4) weeks of the long-term safety follow-up period, AEs/SAEs/AESIs will be collected. Only SAEs/AESIs will be collected starting from the four (4) week follow-up call through the End of Study. For this period, summaries will be presented for subjects who enter the follow-up period from induction treatment, from maintenance treatment, and from open-label treatment. A total combining the numbers from all these 3 groups will also be provided.

10.1. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Duration of study drug exposure includes the study drug exposure during pre-treatment period, induction treatment period, maintenance treatment period, and open-label treatment period. The duration of exposure is computed as the following:

- Duration of Exposure during Pre-Treatment Period = Last Dose Date during Pre-Treatment Period (from "End of Treatment" CRF Page) – First Dose Date during Pre-Treatment Period (from "Status" CRF page) + 1.
- Duration of Exposure during Induction Treatment Period = Last Dose Date during Induction Treatment Period (from "End of Treatment" CRF Page) – First Dose Date during Induction Treatment Period (from "Status" CRF page) + 1.
- Duration of Exposure during Maintenance Treatment Period = Last Dose Date during Maintenance Treatment Period (from "End of Treatment" CRF Page) – First Dose Date during Maintenance Treatment Period (from "Status" CRF page) + 1.
- Duration of Exposure during Open-Label Treatment Period = Last Dose Date during Open-Label Treatment Period (from "End of Treatment" CRF Page) – First Dose Date during Open-Label Treatment Period (from "Status" CRF page) + 1.

Duration of study drug exposure will be summarized by descriptive statistics by treatment group for each period.

Compliance rates defined below will be summarized by treatment groups for induction, maintenance and open-label treatment periods.

Compliance rate (capsules) = (number of capsules dispensed – number of capsules returned) / capsules expected to be taken) * 100

The number of capsules dispensed and returned are documented in the Cenduit Interactive Response Technology system in each period.

The capsules expected to be taken is calculated by # of capsules expected for each day x # of days in each period. For the pre-treatment period, # of capsules will be capped at 24 capsules.

The compliance rate will be summarized descriptively by treatment group for each period. The Total # of subjects (N) will be the # of subjects entering each corresponding period.

10.2. ADVERSE EVENTS

AEs will be coded by using the MedDRA V21.0. A Treatment-Emergent Adverse Event (TEAE) is any AE that newly appeared, increased in frequency, or worsened in severity after initiation of study drug (including the pre-treatment period).

AE summaries will be presented by treatment group for each period.

An overall summary of AEs will be presented by treatment group, including the number and percentage of subjects, and the number of events for:

- Any TEAEs
- Study drug related (including related and possibly related) TEAEs
- Serious TEAEs
- Treatment-emergent AESIs
- Severe TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to death

The overall summary of AEs will also be presented by treatment group and by baseline ES and baseline UC medication (collapsed categories based on CRF) stratum.

The number and percentage of subjects with TEAEs will be tabulated by system organ class (SOC) and preferred term (PT) for each treatment group and stratum. Serious TEAEs, AESIs and TEAEs leading to study discontinuation will be similarly tabulated. For this study, UC Flare and invasive

infections (e.g., bacteremia, abscess, meningitis) have been designated as AESIs. Summaries of TEAEs by maximum severity and by maximum relationship to study drug will also be summarized by SOC and PT.

The overall summary of AEs, TEAE by SOC and PT and Serious TEAE by SOC and PT will also be provided by SER-287 donor. It will be for the induction period.

A listing of all TEAEs and listings of deaths will be provided.

10.3. LABORATORY EVALUATIONS

Quantitative chemistry and hematology tests (observed values and change from baseline) will be summarized descriptively in tabular format by visit and treatment period. For pre-treatment and induction treatment period, the baseline value before the first pre-treatment dose is used. For maintenance and open-label treatment periods, the value before the subject entering the period will be used as the baseline of the period, and a summary for the pre-treatment baseline will also be included in the summary. A shift table will be presented for chemistry, hematology and urinalysis tests shift from baseline to each post-baseline visit

10.4. VITAL SIGNS

Descriptive statistics of the vital signs will be presented by treatment group by visit and treatment period. The change from baseline to each post-baseline visit will also be summarized by treatment group. For pre-treatment and induction treatment period, the baseline value before the first pre-treatment dose is used. For maintenance and open-label treatment periods, the value before the subject entering the period will be used as the baseline.

10.5. PHYSICAL EXAMINATION

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

A by-subject listing of physical examination will also be provided.

11. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

11.1. STRATIFICATION FACTORS THAT ARE USED IN THE ANALYSIS

For the analysis for efficacy endpoints using CMH method, the stratification factors as defined by the study protocol was by ES at baseline (1-2 vs. 3), and UC medications at baseline (5-ASA alone vs. immunomodulators with or without 5-ASA vs. none). Because there are few subjects in the category of "immunomodulators with or without 5-ASA", the stratification factors for UC medications at baseline are collapsed to "5-ASA or immunomodulators" vs. "none" in the analysis.

11.2. SENSITIVITY ANALYSES ON SAFETY POPULATION

In protocol section 9.5.5, the following is stated:

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

Since the Safety population is not relevant for efficacy analysis, the efficacy analysis will not be performed for Safety population.

12. REFERENCE LIST

Food and Drug Administration Center for Drugs Evaluation Research (CDER). (2016). Guidance for Industry: Ulcerative Colitis: Clinical Trial Endpoints (FDA Maryland).

Han, B., Yu M., and McEntegart D., (2013), Weighted re-randomization tests for minimization with unbalanced allocation, Pharmaceut. Statist., 12 243–253.

Lachin John M (2011). Biostatistical methods: the assessment of relative risks. New York, NY: John Wiley & Sons.

Mosli, M.H., Feagan, B.G., Zou, G., Sandborn W.J., D'Haens, G.D., Khanna, R., Shackelton, L.M., Walker, C.W., Nelson, S., Vandervoort, M.K., et al. (2017). Development and validation of a histological index for UC. Gut *66*, 50-58.

Schafer, J. L. (1997). Analysis of Incomplete Multivariate Data. New York: Chapman & Hall.

Sandborn, W.J., Ghosh, S., Panes, J., Vranic, I., Su, C., Rousell, S., and Niezychowski, W. (2012). Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis. N. Engl. J. Med. *367*, 616-624.

Sandborn, W.J., Feagan, B.G., Wolf, D.C., D'Haens, G., Vermeire, S., Hanauer, S.B., Ghosh, S., Smith, H., Cravets, M., Frohna, P.A., et al. (2016). Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. N. Engl. J. Med. *374*, 1754-1762.

Sandborn, W.J., Su, C., Sands, B.E., D'Haens, G.R., Vermeire, S., Schreiber, S., Danese, S., Feagan, B.G., Reinisch, W., Niezychowski, W., et. al. (2017). Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N. Engl. J. Med. *376*, 1723-1736.

13. PROGRAMMING SPECIFICATIONS

The Specification for analysis data sets will be presented in a separate document.

14. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

The mock TLFs will be presented in a separate document.