Statistical Analysis Plan

Protocol Number and Title:	**SERES-012** ECOSPOR III: A Phase 3 Multicenter, Randomized, DoubleBlind, -Placebo-Controlled, ParallelGroup Study to Evaluate the Safety, Tolerability, and Efficacy of -SER-109 -vs. Placebo to Reduce Recurrence of *ClOstRidium difficile* Infection (CDI) in Adults Who Have Received Antibacterial Drug Treatment for Recurrent CDI (RCDI)
Protocol Version and Date:	**Amendment 8.0** **13 April 2020**
Author(s):	[redacted]
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I confirm that I have reviewed this document and agree with the content.

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TABLE OF CONTENTS

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CD4	Cluster of Differentiation 4
CDI	*Clostridium difficile* infection
CI	Confidence Interval
cm	Centimeter
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DSMC	Data and Safety Monitoring Committee
EAIR	Exposure-adjusted Incidence Rate
eCRF	Electronic Case Report Form
EIA	Enzyme Immunoassay
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FDA	Food and Drug Administration
FMT	Fecal Microbiota Transplantation
GDH	Glutamate Dehydrogenase Antigen
ICF	Informed Consent Form
ICH	International Conference to Harmonisation
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
IXRS	Interactive Voice or Web Response System
kg	Kilogram
K-M	Kaplan-Meier
mg	Milligram
MITT	Modified Intent-to-Treat
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of Mercury
NAAT	Nucleic Acid Amplification
PCR	Polymerase Chain Reaction

Abbreviation	Description
PP	Per Protocol population
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TLF	Table, Listing and Figure
UBM	Unformed Bowel Movement
WHO	World Health Organization

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 SERES-012 Protocol Amendment 8 dated 13 April 2020 and electronic case report form (eCRF) Version 4.0 dated 25 May 2018.

2.1. TIMINGS OF ANALYSES

Unblinded safety and efficacy analyses will be performed after all subjects have completed the 24-week follow-up period, or otherwise terminated from the study.

8-Week Efficacy and Safety Data Analysis: An unblinded safety and efficacy analyses will be performed after all subjects have completed the 8-week efficacy visit (Day 58) or otherwise terminated from the study, but before all subjects have completed the safety follow-up period at 24 weeks. At the time of unblinding, approximately 80% of subjects will have completed their 24-week safety follow-up contact.

3. STUDY OBJECTIVES

3.1. PRIMARY EFFICACY OBJECTIVE

- To demonstrate the superiority of SER-109 versus Placebo in the reduction of CDI recurrence rates(%), determined by a toxin assay, up to 8 weeks after initiation of treatment.

3.2. SECONDARY EFFICACY OBJECTIVES

- To demonstrate the superiority of SER-109 versus placebo in the reduction of rates of CDI recurrence, determined by a PCR algorithm (see Laboratory Manual), up to 8 weeks after initiation of treatment
- To compare the time to CDI recurrence, determined by a toxin assay, in the SER-109 treatment group to the time to CDI recurrence in the placebo group after initiation of treatment
- To compare the time to CDI recurrence, determined using a PCR algorithm, in the SER-109 treatment group to the time to CDI recurrence in the placebo group after initiation of treatment
- To compare the proportion of subjects experiencing CDI recurrence, determined by a toxin assay, in subjects who receive SER-109 to the proportion of subjects experiencing CDI recurrence in subjects who receive placebo up to 4, 12, and 24 weeks after initiation of treatment
- To compare the proportion of subjects experiencing CDI recurrence, determined using a PCR algorithm, in subjects who receive SER-109 to the proportion of subjects experiencing CDI recurrence in subjects who receive placebo up to 4, 12, and 24 weeks after initiation of treatment
- To demonstrate clinical efficacy of each SER-109 lot as compared to placebo up to 8 weeks after initiation of treatment

3.3. PRIMARY SAFETY OBJECTIVES

- To evaluate the safety and tolerability of SER-109 versus placebo in adult subjects with recurrent CDI.

3.4. EXPLORATORY OBJECTIVES

- To compare changes in the composition of the gut microbiome in the SER-109 treatment group to changes in the composition of the gut microbiome in the placebo group from Baseline up to 1, 2, 8, and 24 weeks after initiation of treatment
- To compare changes in the fecal metabolome in the SER-109 treatment group versus in the placebo group from Baseline up to 1, 2, and 8 weeks after initiation of treatment
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups

- To determine the incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To determine, for subjects who are hospitalized, the total length of stay (days) of hospitalization, including days in the intensive care unit, up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To assess health outcomes, including Health Related Quality of Life (HRQOL), by using the EuroQol 5 Dimensions 5 Level (EQ-5D-5L) and the HRQOL survey for CDI (CDiff32) up to 24 and 8 weeks, respectively, after the initiation of treatment in each of the two treatment groups.

3.5. BRIEF DESCRIPTION

ECOSPOR III is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the safety, tolerability, and efficacy of SER-109 versus placebo in adult subjects 18 years of age or older with recurrent CDI (RCDI), defined as: a history of ≥ 3 CDI episodes within 12 months, inclusive of the current episode. This study is designed to demonstrate the superiority of SER-109 versus placebo to reduce recurrence of *Clostridium difficile* infection (CDI) in adults who have received antibacterial drug treatment for recurrent CDI, based on the proportion of subjects experiencing a CDI recurrence requiring antibiotic treatment up to 8 weeks after initiation of treatment.

This study will be conducted at approximately 100 study centers in North America. Subjects with a history of RCDI, diarrhea and a positive *C. difficile* stool sample tested by a toxin assay, preferably by a central laboratory, who have responded to 10 to 21 days of standard-of-care (SOC) antibiotic treatment (i.e., vancomycin [125 mg QID] or fidaxomicin [200 mg BID]). Subjects will be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment groups (Treatment Group I [SER-109] or Treatment Group II [Placebo]), and stratified by age (<65 years; ≥65 years), as well as antibiotic regimen for the qualifying episode (vancomycin; fidaxomicin).

Subjects will receive an oral dose of SER-109 ([redacted] in 4 capsules) once daily for 3 days in Treatment Group I or matching placebo once daily for 3 days in Treatment Group II.

The study duration is approximately 27 weeks, including a ~3-week Screening Period, an 8-week Efficacy Period, and a 16-week Follow-up Period from randomization on Day 1.

Favorable clinical outcome in this study will be determined by the absence of CDI recurrence up to 8 weeks after initiation of treatment of study drug, with CDI recurrence defined as ≥ 3 unformed stools per day over 2 consecutive days and the requirement that patients must continue to have diarrhea until antibiotic treatment is initiated, with a positive *C. difficile* test on a stool sample determined by a toxin assay and a decision by the investigator (based on clinical assessment), that antibiotic treatment is needed. Data from the *C. difficile* toxin assay (either enzyme immunoassay [EIA] or cell cytotoxicity neutralization assay [CCNA]), performed at the central laboratory, will be used for the primary endpoint analysis. The central laboratory results will be communicated to the investigator and the decision to treat with antibiotics will be based upon the investigator's assessment. In this SAP, the favorable clinical outcome will be referred as the sustained clinical response which is a more commonly used terminology

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 able to provide written informed consent and understand the potential risks and benefits from study enrollment and treatment
2. Male or female subject ≥ 18 years of age.
3. A qualifying episode of CDI as defined by:
    a. ≥ 3 unformed stools per day for 2 consecutive days
    b. A positive *C. difficile* stool toxin assay. Documentation of a positive *C. difficile* stool test result preferably performed by a central laboratory (see Laboratory Manual) is required for subjects entering the study.
    c. The requirement of CDI SOC antibiotic therapy (defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]. Note: It is acceptable if subject was started on metronidazole, switched to vancomycin or fidaxomicin and is treated for a minimum of 10 days of vancomycin or fidaxomicin with a total treatment (including days on metronidazole) duration of up to a maximum of 21 days.
    d. An adequate clinical response following SOC antibiotic therapy, defined as <3 unformed stools in 24 hours) for 2 or more consecutive days before randomization.
    e. The requirement that the subject can be dosed with study drug within 4 days of SOC antibiotic completion.
4. ≥ 3 episodes of CDI within the previous 12 months, inclusive of the current episode, with documented history of ≥ 2 episodes, inclusive of the current (qualifying) episode, including:
    a. Dates, test results, and antibiotic treatments received. Efforts should be made to acquire history of additional CDI episodes (beyond the 2 required documented episodes) including dates, test results, and antibiotic treatments received.
5. If female, subject is non-lactating, and is either:
    a. Not of childbearing potential, defined as post-menopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.
    b. Of childbearing potential and is practicing at least 1 highly effective method of birth control including: the barrier method; oral or parenteral contraceptives; a vasectomized partner; or abstinence from sexual intercourse. The investigator will discuss with the subject the option of practicing more than 1 of the above methods for the duration of the study.
6. If male, and partner is of childbearing potential, subject agrees to practice at least 1 highly effective method of birth control for the duration of the study.

7. Is not taking probiotics, or discontinues probiotics prior to study start and will not take probiotics for the duration of the study.

3.6.2. Exclusion Criteria

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

1. Female subjects who are pregnant, breastfeeding, lactating, or planning to become pregnant during the study.
2. Known or suspected toxic megacolon and/or known small bowel ileus.
3. Admitted to or expected to be admitted to an intensive care unit for medical reasons (not just boarding). Note: nursing homes, rehabilitation, assisted living centers and acute care hospitals are acceptable.
4. Absolute neutrophil count of <500 cells/ml^3.
5. Taking antibacterial therapy other than SOC antibiotics for the most recent episode of CDI during the screening period (a single day- antibiotic prophylactic regimen is permitted), or projected to receive antibiotics during the 8-week period post-randomization.
6. Major gastrointestinal surgery (e.g., significant bowel resection or diversion) within 3 months before enrollment (this does not include appendectomy or cholecystectomy), or any history of total colectomy or bariatric surgery (bariatric surgery which does not disrupt the gastrointestinal lumen, i.e., restrictive procedures such as banding, are permitted).
7. History of active inflammatory bowel disease (ulcerative colitis, Crohn's disease, microscopic colitis) with diarrhea believed to be caused by active inflammatory bowel disease in the past 3 months.
8. Unable to stop loperamide, diphenoxylate/atropine, or cholestyramine prior to start of study.
9. Unable to stop opiate treatment unless on a stable dose, including PRN dosing, as of the onset of diarrhea and no increase in dose planned for the duration of the study. Note: Short term opiate use is permitted (e.g., for a dental extraction).
10. Known positive stool cultures for other enteropathogens including, but not limited to, Salmonella, Shigella, and Campylobacter within the 30 days before enrollment.
11. Known stool studies positive for ova and/or parasites within the 30 days before enrollment.
12. Poor concurrent medical risks with clinically significant co-morbid disease such that, in the opinion of the investigator, the subject should not be enrolled.
13. Received a human monoclonal antibody against *C. difficile* toxin within 3 months before study entry.
14. Received an investigational drug or vaccine, or participated in any experimental procedure within 1 month (3 months for monoclonal antibodies) before study entry.

15. Any history of immunoglobulin (IgG) replacement therapy within the past 3 months.
16. Any history of fecal microbiota transplantation (FMT) within the previous 3 months.
17. Previously enrolled in this study or any Seres Therapeutics, Inc. sponsored study.
18. Known active intravenous drug or alcohol abuse or use of other drugs of abuse.
19. Concurrent intensive induction chemotherapy, radiotherapy, or biologic treatment for active malignancy (subjects on maintenance chemotherapy may only be enrolled after consultation with the study 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.
21. Life expectancy is 24 weeks or less.

3.7. DETERMINATION OF SAMPLE SIZE

The original planned sample size for this study is 160 subjects per treatment group for a total sample size of 320 subjects. However, due to the competition for subjects because of preference for fecal microbiota transplants (FMT), the study enrollment for this study was much slower than anticipated. Potential subjects appear to choose FMT because they know they are 100% assured of getting a purported effective product rather than having only a 50% chance of receiving SER-109 in SERES-012.

[redacted].

The current sample size planned for this study is 94 subjects per treatment arm or 188 subjects total. This sample size was derived using recurrence rate assumptions based on available information at the time the sample size was re-estimated. A blinded assessment of the CDI recurrences observed in SERES-012 among subjects enrolled who have either experienced a recurrence prior to Day 58 or have been followed for at least 58 days as of March 24, 2019 yielded an estimated overall recurrence rate of 26%. From the open-label SERES-013 study, the SER-109 recurrence rate observed as of March 24, 2019 was 16%. Therefore, based on this accumulated information, the placebo recurrence rate was estimated to be 36%, since the randomization ratio for this study is 1:1.

Assuming a 36% recurrence rate for the control group and a 16% recurrence rate in the SER-109 group, the sample size for this study will provide the following power estimates based on the fixed sequence multiple testing strategy to be implemented for this study (see Section 6.6):to test the null hypothesis (H_1) that the relative risk (RR) of CDI recurrence of SER-109 to placebo is ≥ 1.0 vs the alternative hypothesis (H_{a1}) that the RR < 1.0 at a one-sided significance level of 0.025, the sample size will provide 83% power. If H_1 is found to be

statistically significant, then H_2: RR ≥ 0.833 vs H_{a2}: RR < 0.833 will be tested at a one-sided significance level of 0.025. The sample size will provide 62% power to test H_2.

The sample size and power estimates were computed based on a Cochran-Mantel-Haenszel (CMH) test of the RR stratified by age (<65 years; ≥65 years), as well as antibiotic regimen for the qualifying episode (vancomycin; fidaxomicin) using a customized version [redacted].

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-109 or placebo) and to increase the likelihood that known and unknown subject characteristics will be evenly distributed between the treatment groups. Randomization will be stratified by age (<65 years, ≥65 years) and type of antibiotic used to treat the qualifying episode of CDI (vancomycin, fidaxomicin).

Eligible subjects are to be randomly assigned to receive either a dose of SER-109 ([redacted] in 4 capsules) once daily for 3 days or matching placebo once daily for 3 days in a 1:1 fashion by using block randomization via an interactive voice and web response system (IxRS). Subjects who qualify for random assignment, will be assigned the treatment corresponding to the next sequentially available number within the appropriate age group and prior antibiotic regimen stratum of the computer-generated randomization schedule. A forced randomization algorithm will also be included in IxRS to avoid failed randomizations in the unlikely event that the assigned study medication is not available at the site. The number of forced randomizations will be limited and monitored by unblinded study personnel. Subjects are considered randomly assigned when the IxRS provides the randomization number to the investigator or investigator's designee regardless of whether the subject ultimately receives study drug.

The IxRS will also assign an appropriate kit number, which includes 3 bottles of double-blinded study medication, that will be available at the study site for that subject. 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 kit or bottle is returned unopened.

Subjects, the investigators and other study site personnel will remain blinded to the treatment assignment. The Sponsor, study site monitors, and other Sponsor representatives involved in the clinical aspects of the study conduct will also remain blinded to the treatment assignment.

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 to ensure that the blind is properly maintained.

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 subject's eCRF, and any associated SAE report, if applicable.

The study blind codes will be broken after the statistical analysis plan (SAP) is final and all clinical data up to the 12-week efficacy and safety visit for all subjects enrolled in the study have been entered in the database, cleaned and locked for the 8-week efficacy and safety data analysis. The 12-week efficacy and safety visit is used as the data cut-off point to accommodate the primary efficacy endpoint for the EMA, which is recurrence by 12 weeks post randomization (Day 86). At this time, all subjects will have completed their 8-week efficacy and safety visit, but not all subjects will have completed the safety follow-up period at 24 weeks. Only a small team at Seres, specifically the Vice President of Clinical Science and the Vice President of Regulatory Affairs and the Statistical Consulting CRO (Integrated Medical Development) will have access to the unblinded tables, listings and figures (TLFs) to allow them to assess the safety signals from the available safety data and assess the primary efficacy and interim safety endpoints to support the use of SER-109 in an expanded access clinical study.

An unblinded team from the biostatistics and statistical programming vendor [redacted], comprised of personnel distinct from the vendor study team assigned to this project, will provide unblinded datasets and generate the unblinded efficacy and safety TLFs. The unblinded datasets and TLFs will be accessed by Seres from the vendor's File Transfer Portal (sFTP). . The unblinded team at [redacted] will keep the unblinded information confidential and will not disclose the information to any investigative sites, subjects in the study, others at [redacted] or at Seres (except for the unblinded Seres team) or to the public until after all subjects have completed the study and the final 24-week database lock occurs.

The vendor study team from [redacted], who are working with Seres on operational aspects of the study, will remain blinded throughout the study and will continue to conduct the study until all subjects have completed their 24-week follow-up and the database has been locked. Appropriate blinded Seres personnel will continue to provide oversight until all subjects have completed the study.

No changes to any locked data in the database will be permitted, unless deemed to be highly warranted. Therefore, analyses of all efficacy endpoints evaluated up to the Week 8 timepoint will be considered final.

A comparison of the data at the time of the unblinding for the 8-week efficacy and safety data analysis and at the end of the study will be performed. An audit trail of any changes made to the locked data will be available. All other data collected beyond the 12-week efficacy and safety visit that has been entered in the database at the time of the 12-week visit of the last subject enrolled, will be included in the summary TLFs, but not necessarily cleaned and locked prior to unblinding.

At the time of unblinding, approximately 80% of subjects will have completed their 24-week safety follow-up period.

3.10. SCHEDULE OF ASSESSMENTS

Please refer to the protocol for the schedule of assessments.

4. ENDPOINTS

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is

- the recurrence of CDI in subjects who receive SER-109 or placebo as determined by a toxin assay up to 8 weeks after initiation of treatment in the ITT population.

A recurrence is defined as (i) ≥ 3 unformed stools per day for 2 consecutive days with the requirement that subjects continue to have diarrhea until antibiotic treatment is initiated, with (ii) a positive *C. difficile* test on a stool sample determined by a toxin assay, and (iii) assessment by the investigator that the clinical condition of the subject warrants antibiotic treatment. The requirement that *subjects continue to have diarrhea until antibiotic treatment is initiated* in (i) is met if the subject has ≥1 UBM each day during the period between having 2 consecutive days of ≥ 3 unformed stools and the start date of the CDI antibiotic treatment.

4.1.2. Secondary Efficacy Endpoints

The other secondary efficacy endpoints are

- Recurrence of CDI as determined by a PCR algorithm up to 8 weeks after initiation of treatment
- Time to recurrence of CDI from initiation of treatment as determined by a toxin assay
- Time to recurrence of CDI from initiation of treatment as determined by PCR algorithm
- Recurrence of CDI, as determined by a toxin assay, up to 4, 12 and 24 weeks after initiation of treatment in each treatment group
- Recurrence of CDI, as determined by a PCR algorithm, up to 4, 12 and 24 weeks after initiation of treatment in each treatment group
- Recurrence of CDI up to 8 weeks after initiation of treatment in each SER-109 donor lot and in the placebo group

4.1.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are

- Change in the composition of the gut microbiome from Baseline up to 1, 2, 8, and 24 weeks after initiation of treatment
- Change in the fecal metabolome from Baseline up to 1, 2, and 8 weeks after initiation of treatment
- Incidence of mortality from all causes up to 8 and 24 weeks after initiation of treatment
- Incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of treatment
- Incidence of all hospitalizations up to 8 and 24 weeks after initiation of treatment
- Total length of stay (days) of hospitalization, including days in the intensive care unit, up to 24 weeks after treatment initiation (for subjects hospitalized)

- Changes from Baseline in Health-Related Quality of Life (HRQoL) and health outcomes as assessed by the EQ-5D-5L from Day 1 through Weeks 8 and 24 and assessed by the Cdiff32 HRQoL from Day 1 to Week 1 and Week 8 or at the ET or Recurrence Visit prior to Week 8 after initiation of treatment

4.1.4. Safety Endpoints

The safety endpoints are

- Incidence of AEs
- Incidence of Solicited AEs on Days 4-10
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

5. ANALYSIS POPULATIONS

5.1.1. Intent-to-Treat (ITT) Population

The ITT Population will consist of all subjects who were randomized, including those who were not exposed to any study drug, and will be analyzed based on the treatment to which they were randomly assigned. Subjects randomized using forced randomization will be analyzed according to the original treatment arm they were randomized to and not the one based on the forced randomization algorithm. The primary efficacy population is the ITT Population.

5.1.2. Modified Intent-to-Treat (mITT) Population

The mITT Population will be composed of all subjects with recurrent CDI diagnosis who were randomized, received any amount of study drug, whose qualifying CDI episode was confirmed and clinically controlled by antibiotic treatment before receiving study drug, and who have at least one efficacy evaluation post baseline.

Subjects with a recurrent CDI diagnosis should have ≥3 CDI episodes in the previous 12 months prior to screening, inclusive of the current episode.

Confirmation of the qualifying CDI episode requires a positive *C. difficile* test based on a toxin assay.

Requirements for the qualifying CDI episode to be clinically controlled by antibiotic treatment include:

- ≤2 unformed bowel movements (UBM) at least 2 days prior to randomization
- Receipt of appropriate antibiotic, including adequate treatment duration, for the qualifying episode

Data from the mITT Population will be analyzed based on the treatment to which they were randomly assigned. Subjects randomized using forced randomization will be analyzed according to the original treatment arm they were randomized to and not the one based on the forced randomization algorithm.

5.1.3. Per Protocol 8 and Per Protocol 24 Populations

The Per Protocol 8 (PP8) and Per Protocol 24 (PP24) Populations will consist of subjects from the mITT Population who do not have any major protocol deviations or met the primary endpoint before any major protocol deviation occurred. . Subjects will be excluded from the PP8 and PP24 populations if the major protocol deviation occurred prior to the Week 8 (Day 58) primary endpoint assessment, but will only be excluded from the PP24 population if the protocol deviation occurred after the Week 8 primary endpoint assessment. Forced randomizations are considered to be major protocol deviations and therefore, subjects who are randomized using forced randomization will be excluded from both the PP8 and PP24 Populations. The PP8 and PP24 Populations will be defined before unblinding of the data.

5.1.4. Safety Population

The Safety Population consists of all randomly assigned subjects who receive any amount of study drug. Subjects will be analyzed according to the treatment they actually received, rather than that to which they were randomly assigned. In the same manner, subjects who are randomized using forced randomization will be analyzed according to the treatment they actually received. All safety analyses will be conducted based on the Safety Population.

5.2. PROTOCOL DEVIATIONS

Protocol deviations are collected in [redacted], the Clinical Trial Management System (CTMS), used by [redacted], the contract research organization employed for this study. Protocol deviations will be assigned to a deviation sub-type within one of the following deviation types: inclusion/exclusion criteria, informed consent form issues, procedures/tests, laboratory, visit schedule, study drug, concomitant medication, and other. The protocol deviations will be further classified as key vs. non-key in [redacted] Protocol Deviation Criteria document and reviewed by the medical monitors on an on-going basis.

The deviations entered in [redacted] are then transferred into a cumulative protocol deviation listing organized by severity, subject, site, deviation sub-type, and type. This listing of [redacted]-defined key and non-key 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. Exclusion from the Per Protocol populations will be based on the occurrence of these major deviations as outlined in Seres Work Instruction 012 Protocol Deviation Review:Population Categorization.

[redacted]

Protocol deviations will be presented by severity category of Major vs. Minor, deviation type and deviation sub-type and summarized in 2 tables as follows: 1) with frequencies and percentages of subjects with at least one deviation in each deviation sub-type and type. Subjects with multiple deviation sub-types will only be counted once for a given deviation type within the major/minor deviation category and once for the protocol deviation sub-type within a

deviation type; and 2) with all incidences of the protocol deviations counted separately in each deviation sub-type, type and severity category. The total count of protocol deviations will be used as the denominator for percentages in this table.

Although occurrences of forced randomization are not collected in [redacted], as these could be potentially unblinding, forced randomizations will be considered critical protocol deviations. Forced randomizations will be tracked in IxRS. Specifically, subject number, the skipped randomization number, the treatment assigned to skipped randomization number, the assigned randomization number and the treatment assigned to assigned randomization number will be saved in IxRS and exported after the database is unblinded.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- Unless otherwise specified, inferences, point estimates, and confidence intervals for efficacy analyses will be derived using methods for stratified analysis, where the stratification variable is age (< 65 years, ≥ 65 years) and prior antibiotic regimen (vancomycin, fidaxomicin). The α-level used for the 2-sided CIs will correspond to the α-level used for testing the primary endpoint, specified by the multiple testing algorithm for this study in Section 6.6. Similarly, all 2-sided CIs provided for the sensitivity analyses specified in Section 8.1.3 will use the α-level used for testing the primary endpoint, specified by the multiple testing algorithm for this study.
- Unless otherwise specified, summaries will be presented for each treatment (SER-109 and placebo).
- Separate summary tables will be included for analysis of subjects within each age and prior antibiotic regimen stratum.
- For all subgroup and by age and prior antibiotic regimen stratum summaries, the 95% CI will be provided.
- Continuous variables will be summarized using the number of subjects with evaluable data, mean, standard deviation (SD), median, minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD.
- Categorical variables will be summarized using the number of observations (n), frequency and percentage of subjects. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.
- Unless stated otherwise, the percentages will be based on the number of non-missing observations. The header will still contain the number of subjects in the treatment group. There will be a row for the number of non-missing observations in the table (at each time point, if required) for each variable being summarized.
- Unless otherwise stated, all formal tests of hypotheses will be conducted at the one-sided level of significance with alpha=0.025.
- Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as ‘p<0.001’ and p-values greater than 0.999 will be presented as ‘p>0.999’.
- All relevant subject data will be included in listings and sorted by treatment, Subject ID, and visit, as applicable, for all randomized subjects.
- Unscheduled or repeat assessments will not be included in summary tables unless specified otherwise (e.g., unscheduled CDI assessments will be summarized), but will be included in the subject listings.
- All tables, listings and figures will include footers that identify the name of the program that created the item, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

6.2. KEY DEFINITIONS

6.2.1. Study Day

Study Day 1 is defined as the first day of study drug administration. 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.

6.2.2. Baseline Values

Baseline values will be taken as the last assessments before dosing with study drug. In general, these will be taken from the pre-dose assessment on Day 1, unless otherwise specified.

6.3. MISSING DATA

Every effort will be made to collect all data required in this study, especially with regards to the primary endpoint. Contact with subjects is made weekly either by telephone or clinic visits up to Week 8, in which all the components of the CDI recurrence endpoint, specifically, (i) 2 or more consecutive days with ≥3 unformed stools, with the requirement that subjects continue to have diarrhea until antibiotic treatment is initiated, (ii) *Clostridium difficile* test on a stool sample determined by a toxin assay and (iii) assessment by investigator that the condition warrants antibiotic treatment, are assessed.

From the date of randomization to the end of study (Week 24) assessment, subjects are given 24 hours to enter the number of unformed bowel movements (UBMs) from the previous day in the electronic diarrhea log, including recording when no UBMs are experienced on any given day. Subjects are instructed to do this daily until the end of the study. However, some missing data can be expected. Handling of missing data for components of the CDI recurrence endpoint is discussed below.

For the primary endpoint, subjects who are lost-to-follow-up, terminated from the study prematurely, or died without a CDI recurrence before 8 weeks after treatment (Day 58) are defined as having an unfavorable outcome for the primary analysis. Reasons for withdrawal from the study will be recorded on the eCRF.

If the number of unformed bowel movements (UBM) is missing on any day from the date of randomization to the end of the study, then the missing UBM counts will be assumed to be ≥ 3.

If a subject missed entry into the diarrhea log on any day, the site will call the subject to inquire how many UBMs they had on the day entry into the device was missed and remind them to enter their UBM count every day until the end of the study. Subject's response to how many UBMs they had on the day entry was missed will be entered in the EDC database, but not used to assess the primary endpoint, i.e. criteria (i) above will be evaluated based solely on the data entered in the diarrhea log by the subject.

If entry into the device is missed for 1 day and the subject reports ≥3 UBMs for either of the adjacent days, the subject will be contacted by the site. If the subject reports ≥3 UBMs for the missed entry, the subject will be asked to return to the clinic for a *C. difficile* stool toxin test and

clinical evaluation for recurrence of CDI. If the subject reports having <3 UBMs on the missed day, then the site will complete the Suspected CDI Recurrence page in the eCRF, without requiring the subject to come to the site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.

If entry into the device is missed for ≥2 consecutive days and the subject reports 2 consecutive days of ≥3 UBMs the next time the site is able to make contact, the subject will be asked to return to the clinic for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI. If entry into the device is missed for ≥2 consecutive days, but the subject reports not experiencing 2 consecutive days of ≥3 UBMs the entire time entry into the diarrhea log was missed at the next contact, then the site will complete the Suspected CDI Recurrence page in the eCRF, without requiring the subject to come to the site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.

Data from the *C. difficile* toxin assay (either enzyme immunoassay [EIA] or cell cytotoxicity neutralization assay [CCNA]), performed at the central laboratory, will be used for the primary endpoint analysis. If the results of the *C. difficile* toxin assay from the central laboratory are missing, then the results of the *C. difficile* toxin test performed by a CLIA-certified local laboratory using an FDA-approved toxin test will be used, if available.

If any of the components of the CDI recurrence criteria is missing, and the non-missing components meet the CDI recurrence criteria, then an unfavorable outcome for the primary analysis is imputed. However, if some of the components of the CDI recurrence criteria are missing, and at least 1 of the non-missing components does not meet the CDI recurrence criteria, then a favorable outcome for the primary analysis is imputed.

Sensitivity analyses of the primary endpoint will be conducted using various methods for handling missing data as detailed in Section 6.3.

For the secondary endpoints of recurrence of CDI by Weeks 4, 12, and 24, subjects will be considered as having had a recurrence using similar rules.

Missing data for the time to CDI recurrence analyses will be handled with censoring by the Kaplan-Meier method. Subjects who complete the study and do not experience a CDI recurrence by the end of the follow-up period will be censored on the date of last contact. Subjects who are lost to follow-up or who terminate the trial prematurely before experiencing a CDI recurrence will be censored on the date of last contact. Subjects who die before experiencing a CDI recurrence will be censored on their date of death. Subjects who were assessed to have a CDI recurrence due to missing or incomplete data for one or more of the 3 components of CDI recurrence will not be counted as an event, but censored on their last date of contact. A sensitivity analysis of the time to CDI recurrence will be conducted as detailed in Section 8.2.2.3.

6.4. VISIT WINDOWS

For the primary endpoint of CDI recurrence up to 8 weeks after the start of treatment, and secondary endpoints of CDI recurrence up to 4 weeks, 12 weeks, and 24 weeks after last treatment regimen received, CDI recurrences will be included in the analyses for the specified endpoints as follows:

Endpoint	Recurrences Included in Analysis
CDI recurrence up to 4 weeks after treatment	Up to Day 30
CDI recurrence up to 8 weeks after treatment	Up to Day 58
CDI recurrence up to 12 weeks after treatment	Up to Day 87
CDI recurrence up to 24 weeks after treatment	Up to Day 171

The incidence of hospitalization will also be summarized by timepoint (Week 8 and 24) using the same cut-off days specified for the primary endpoint. Observed study visits will be used for other efficacy analyses, including responses to the questionnaire data. For analyses of vital signs and laboratory data, data collected at an early termination visit will be presented separately.

A summary describing adherence to visit schedules by treatment group will be provided for the ITT Population. The summary will include the count and percentage of subjects who have discontinued on or prior to the end of the previous clinic visit/phone contact window; and those who are still ongoing at the current visit/phone contact. Ongoing subjects are those who have not discontinued on or prior to the end of the previous clinic visit/phone contact window and are further classified into: (i) those with data collected within the window for the respective visit/phone contact, (ii) those with data collected outside the window for the respective visit/phone contact, (iii) those who experienced a CDI recurrence since the end of the previous clinic visit/phone contact window through the end of the current clinic visit/phone contact window, and (iv) those with missing data, which includes subjects who discontinued for an AE, withdrew consent, were lost to follow-up, had a protocol deviation, died, or other reason (excluding CDI recurrence) after the end of the previous clinic visit/phone contact window and on or prior to the end of the current clinic visit/phone contact window, and subjects that are ongoing but missed the clinic visit/phone contact. The percentages of subjects who have discontinued and are ongoing will be based on the ITT Population, while the percentages of subjects with data collected in and out of window, CDI recurrence and missing data at each visit/phone contact will be based on the number of ongoing subjects at the respective visit/phone contact.

6.5. POOLING OF CENTERS

There is no planned pooling of centers.

6.6. MULTIPLICITY ADJUSTMENTS

Adjustments for multiple testing will be made for testing the primary efficacy endpoint for H_1: RR ≥ 1.0 and H_2: RR ≥ 0.833.

To maintain an overall 1-sided 0.025 type I error rate, the fixed sequence testing method will be used. Testing of the 2 hypotheses in the ITT population will be ordered in the following manner:

1. H_1: RR ≥ 1.0
2. H_2: RR ≥ 0.833

The testing procedure will proceed as follows:

- H_1: RR ≥ 1.0 will be tested at the 1-sided 0.025 α-level. If found to be statistically significant at this α-level, then H_2: RR ≥ 0.833 will be tested at the 1-sided 0.025 α-level.

  However, if the primary efficacy endpoint fails to establish superiority, i.e. H_1: RR ≥ 1.0 is not significant at the 1-sided 0.025 α-level, then testing of the next hypothesis in this sequence, H_2, will not proceed and statistical conclusions about this hypothesis will not be made.

No other adjustments will be made for testing of all other endpoints in the study.

6.7. ANALYSES BY AGE GROUP AND PRIOR CDI ANTIBIOTIC REGIMEN STRATA

Several analyses are planned to investigate the efficacy and safety results by the randomization stratification factors: age group (<65 vs ≥65 years) and prior antibiotic regimen (vancomycin vs fidaxomicin). The following summary tables will be provided by age and prior antibiotic regimen group:

- demographics and baseline characteristics for the ITT and Safety Populations,
- descriptive statistics of CDI recurrence at each time point, along with associated estimates of risk ratios and CIs,
- estimates of CDI recurrence differences and CIs,
- time to CDI recurrence,
- incidence of all-cause mortality,
- incidence of hospitalization,
- incidence of solicited adverse events by severity from Days 4-10,
- overall summary of solicited adverse events,
- overall summary of treatment-emergent adverse events (TEAEs),
- TEAEs by SOC and PT,
- Treatment-emergent SAEs,
- Treatment-emergent AESIs,
- TEAEs by SOC and PT by maximum severity,
- TEAEs by SOC and PT by maximum relationship to study drug,
- TEAEs leading to study withdrawal.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Summary tables for demographics and baseline characteristics will include columns for both treatment groups and overall.

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Summary statistics will tabulate the number and percentage of subjects who are screened, screen failures, randomized, who completed the study, and who prematurely discontinued the study together with reasons for discontinuation by treatment group. The number and percentage of subjects included in each of the analysis populations will be presented. No statistical testing will be performed on these data. The number of subjects in the ITT Population (randomized) of each treatment group will be used as the denominator for percentages.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics (age, race, ethnicity, sex) and baseline characteristics (weight, height, body mass index (BMI)), number of previous CDI episodes, including the BI/NAP1/027 status when available, and previous history of fecal microbiota transplantation (FMT) will be summarized by treatment group for the ITT, mITT, Safety and Per Protocol Populations. Demographics and baseline characteristics summaries by age stratum (<65 years, ≥65 years) and prior antibiotic regimen (vancomycin, fidaxomicin) will also be provided for the ITT and Safety populations.

BMI will be calculated as:

$$\text{BMI } (kg/m^2) = \text{Weight}(kg)/[\text{Height}(m)]^2$$

7.3. MEDICAL HISTORY

A by-treatment summary table of the number and percentage of subjects with medical history by system organ class (SOC) and preferred term (PT) will be produced for subjects in the Safety Population. Medical history will be sorted by highest occurrence in the active treatment group in decreasing order of SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, v20.0 (March 2017). For the summary tables, a subject may appear more than once if he has more than one medical history finding coded under different SOC terms or more than one medical 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 term will also be provided.

7.4. QUALIFYING CDI EPISODE CHARACTERISTICS AND SEVERITY

Severity characteristics of the qualifying CDI episode will be summarized by treatment group in the ITT population. All information collected on the qualifying CDI episode will be included in separate listings for the ITT Population.

The Bowel Prep data on the Screening Day will also be listed.

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.

Partial start dates in prior and concomitant medications will be imputed to the first day of the month (if missing day) or the first month of the year (if missing month). Partial end dates in prior and concomitant medications will be imputed to the last day of the month (if missing day) or the last month of the year (if missing month).

A subject listing of prior and concomitant medications use will be provided, coded by using the ATC classification codes and preferred drug name according to the World Health Organization (WHO) Drug Dictionary Enhanced, (Sept. 1, 2016). Separate summary tables will be provided for prior and concomitant medications in the Safety Population, presenting the number and percentage of subjects by treatment group, and will be sorted by descending frequency of ATC Level 2 and then PT in the overall column. 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.

7.5.1. Antibiotic Medication

Summary tables for prior and concomitant antibiotic medication use by treatment group will be provided separately in the Safety Population. A combined subject listing of prior and concomitant antibiotic use will also be generated.

8. EFFICACY

Efficacy is based on CDI recurrence. CDI recurrence will be determined based on the definition below:

- ≥ 3 unformed bowel movements per day over 2 consecutive days and the requirement that patients must continue to have diarrhea until antibiotic treatment is initiated
- Positive *Clostridium difficile* test on a stool sample determined by a toxin assay from the central laboratory
- Assessment by the investigator (based on clinical assessment) that the patient's condition warrants antibiotic treatment.

The investigator will use the data collected from stool sample analysis (*C. difficile* stool test as described in protocol).

All inferential analyses, point estimates, and CIs will be adjusted for stratification by age (<65 years, ≥65 years) and prior antibiotic regimen (fidaxomicin vs oral vancomycin).

Separate tables will be produced for the age and prior antibiotic regimen strata, separately and combined in the ITT Population. Inferential analyses, point estimates, and CIs will be based on methods for unstratified data, as described in each endpoint's section.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1. Primary Analysis of the Primary Endpoint

The primary efficacy endpoint is the recurrence of CDI as determined by a toxin assay up to 8 weeks after initiation of treatment (up to Day 58) in the ITT population. The primary measure of efficacy will be the relative risk (RR) of CDI recurrence up to 8 Weeks after initiation of treatment, defined as P1/P2, where P1 is the proportion of subjects with CDI recurrence in the SER-109 group and P2 is the proportion of subjects with CDI recurrence in the Placebo group. The primary efficacy analysis will be performed using the Cochran-Mantel-Haenszel (CMH) test of the RR of SER-109 to Placebo, stratified by age (<65 years; ≥65 years), and prior antibiotic regimen for the qualifying episode (vancomycin; fidaxomicin).

The logarithm of the CMH estimate of the common relative risk, RR_{CMH}, stratified by age and prior antibiotic regimen is approximately normal with mean $\log(\rho)$ and variance estimate $\hat{\sigma}$, using the Greenland and Robins (1985) variance estimate for the logarithm of RR_{CMH}. Therefore, the Z-statistic for the Cochran-Mantel-Haenszel estimate for testing the risk ratio of ρ can generally be defined as

$$Z = \frac{\mathrm{Log}(RR_{CMH}) - Log(\rho_0)}{\hat{\sigma}} \quad (1)$$

The Z-statistic has an approximately normal distribution with mean 0 and standard error 1 under the null hypothesis $\rho = \rho_0$. For the primary efficacy endpoint, the null hypothesis will be tested at both ρ_0 = 1 and ρ_0 = 0.833.

The number and percentage of subjects in each treatment group defined as having favorable (no CDI recurrence) and unfavorable (had CDI recurrence) outcomes will be reported. The CMH estimate of the common relative risk, RR_{CMH}, stratified by age and prior antibiotic regimen, and 2-sided CIs will be provided. The α-level used for the 2-sided CIs will correspond to the α-level used for testing the primary endpoint, specified by the multiple testing algorithm for this study in Section 6.6.

Additionally, the following will also be provided

- Mean absolute difference (SER-109-Placebo) of the rate (%), including 95% CI, between the treatment groups will also be provided.
- Mean sustained clinical response rate (%), the proportion of subjects who have not had a recurrence by 8 weeks of SER-109 group (1-P1) and the placebo group (1-P2) and its 95% CI, Aas well as the pvalue and the 95% confidence interval adjusted for the age and type of baseline antibiotics stratification for the difference between these two rates will be provided. Note that the sustained clinical response rate = 1 - recurrent rate, the test for the sustained clinical response is the same test as the one for the recurrent rate difference.
    - Sustaind clinical response rate(%) will also be evaluated for 12 weeks.

Missing data will be handled as described in Section 6.3

8.1.2. Assessment of Homogeneity Between Age Group and Prior Antibiotic Regimen Strata for the Primary Endpoint Analysis

The homogeneity of treatment effect between the age group and CDI antibiotics strata with regards to the primary efficacy endpoint at 8 weeks will be assessed in the following manner:

1. The homogeneity of the RR in the age and prior antibiotic regimen strata will be examined using Cochran's Test of Homogeneity as discussed in Lachin (2011). Cochran's test is algebraically equivalent to the GSK (Grizzle, Starmer, and Koch, 1969) test for the stratum by treatment interaction in SAS PROC CATMOD (Lachin, 2011). Heterogeneity of treatment effect across age and prior antibiotic regimen strata will be concluded if the interaction test is significant at the 2-sided 0.05 level.

2. The summary will be done for:

a. By age (<65, >=65)

b. By prior antibiotics treatment

c. By Age and by prior antibiotics treatment

3. Side by side plots of the RR and 2-sided 95% CI for each age and prior antibiotic regimen stratum will also be presented.

8.1.3. Sensitivity Analyses

Sensitivity analyses of the primary efficacy outcome (as described in Section 8.1.1) in the ITT Population will also be conducted as follows:

- The primary analysis will be repeated with the modification that subjects who are lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence on or before Day 58 will be considered to have a favorable outcome in both treatment groups.

- The primary analysis will be repeated with the modification that subjects who are lost-to-follow-up, terminated the study prematurely, or died without having a CDI recurrence on or before Day 58 in the SER-109 group will be considered to have an unfavorable outcome, whereas placebo subjects under these conditions will be considered to have a favorable outcome.

- The primary efficacy analysis will be performed without adjustment for stratification by age and prior antibiotic regimen.

The confidence interval for the relative risk without stratification by age and prior antibiotic regimen will be calculated using a 2-step process. First, 2-sided CIs will be found for the natural logarithm of the RR. These bounds will then be exponentiated to obtain the desired CI for the RR.

The variance of the natural logarithm of RR will be calculated as:

$$var(\ln \mathrm{RR}) = \frac{(n_1 - x_1)}{n_1 x_1} + \frac{(n_2 - x_2)}{n_2 x_2}$$

where n_1 is the sample size for the SER-109, x_1 is the number of SER-109 subjects with CDI recurrence, and n_2 and x_2 are likewise for the placebo subjects.

The 2-sided CIs for the natural logarithm of RR are then calculated as:

$$\ln RR \ \pm Z\alpha/2 \times \sqrt{var(\ln RR)}$$

The α-level used for the 2-sided CIs will correspond to the α-level used for testing the primary endpoint, specified by the multiple testing algorithm for this study in Section 6.6.

- The primary efficacy outcome will also be analyzed as described in Section 8.1.1 for the mITT and Per Protocol Populations.

All preceding sensitivity analyses will only be conducted for CDI recurrences determined by a toxin assay. Furthermore, all sensitivity analyses will be tested at the α-level used for the primary efficacy analysis, as specified in the multiple endpoints testing strategy in Section 6.6. All 2-sided CIs will be provided using the corresponding α-level used for testing the primary endpoint.

8.1.4. Additional Analyses of the Primary Efficacy Outcome

8.1.4.1. Differences in CDI Recurrence Proportions

Differences in the proportions of subjects with CDI recurrence determined by a toxin assay between treatment groups (SER-109 minus placebo) will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by age (<65 years, ≥65 years) and prior antibiotic regimen (vancomycin, fidaxomicin) in the ITT population. 2- sided 95% CIs for the difference between the treatment groups in the proportions of subjects with a CDI recurrence will be adjusted for the age and prior antibiotic regimen stratification using CMH weights with methods described in Kim and Won (2013). This will be implemented using SAS 9.4 (or later) procedure FREQ with the Riskdiff option as described in the SAS 9.4 documentation section ““Common Risk Difference”.

An unstratified analysis for the differences between treatment groups will also be provided using the chi-square test. 2-sided 95% CIs will also be provided for the difference between the treatment groups in the proportion of subjects with a CDI recurrence using the Newcombe-Wilson method in the ITT population.

This analysis will only be conducted for CDI recurrences determined by a toxin assay.

8.1.4.2. SER-109 Donor Lot

The primary efficacy outcome, RR of CDI recurrence up to 8 Weeks after initiation of treatment, will be assessed in subgroups defined by the SER-109 donor lots. The lot number for SER-109 will be obtained from the IXRS. The number and percentage of subjects defined as having favorable and unfavorable outcomes in each SER-109 donor lot and placebo will be reported. The analyses of the primary efficacy outcome for each SER-109 donor lot compared to placebo will be conducted as described in Section 8.1.1, however testing at a 1-sided α-level of 0.025. Data will be presented on a plot showing the RR of CDI recurrence for each SER-109 donor lot to placebo and the corresponding 2-sided 95% CI. The ITT and mITT Population will be used.

8.1.4.3. Subjects Receiving Antibiotics During 8-Week Treatment Period

An additional subgroup analysis of the primary efficacy outcome will be conducted in those subjects in the ITT Population who did and did not receive antibiotics other than those given for CDI recurrence during the 8-week treatment period (Day 1 to Day 58). The analysis will be conducted as described in Section 8.1.1, however testing at a 1-sided α-level of 0.025, with corresponding 2-sided 95% CI provided. The prior and concomitant medications eCRF form will

identify whether a medication is considered an antibiotic. Subjects not receiving antibiotics during the study other than those given for CDI recurrence, or the interval between the SER-109 dose start date and first dose of antibiotics is greater than 58 days, i.e.

First antibiotic dose date – SER-109 dose start date + 1 > 58,

will be included in the subgroup of subjects who did not receive antibiotics.

This analysis will only be conducted for CDI recurrences determined by a toxin assay.

8.2. SECONDARY EFFICACY ANALYSES

8.2.1. Analyses of Secondary Efficacy Endpoints

8.2.1.1. Recurrence of CDI up to Week 8 as determined by a PCR Algorithm

The number and percentage of subjects with recurrence of CDI determined by a PCR algorithm up to 8 weeks (Day 58) will be presented by treatment group in the ITT and mITT Populations. Summary tables by age and prior antibiotic stratum will also be provided for the ITT population. RRs and differences in proportions will be estimated and tested using the same methods as for the primary efficacy assessment at Week 8 (Day 58) in Section 8.1.1, however testing at a 1-sided α-level of 0.025, with corresponding 2-sided 95% CIs provided. Additionally, absolute difference (SER-109-Placebo) of the rate (%), including 95% CI, between the treatment groups will also be provided.

8.2.1.2. Time to Recurrence of CDI Determined by a Toxin Assay

Time to first recurrence of CDI determined by a toxin assay will be summarized by treatment group for the ITT and the mITT Populations and also by age and prior antibiotic regimen stratum for the ITT Population only using the median and 25^{th} and 75^{th} percentiles from Kaplan-Meier (K-M) analyses. The 95% CIs for the median will also be provided. Subjects who complete the study and do not experience a CDI recurrence by the end of the follow-up period will be censored on the date of last contact. Subjects who are lost to follow-up or who terminated the study prematurely before experiencing a CDI recurrence will be censored on the date of last contact. Subjects who die before having a CDI recurrence will be censored on the date of death. Subjects who were assessed to have a CDI recurrence due to missing or incomplete data for one or more of the 3 components of CDI recurrence will not be counted as an event, but censored on their last date of contact. Subjects who were not dosed will have their time to recurrence measured from their randomization date.

Differences between treatment groups will be tested for significance using the log-rank test, stratified by age (<65 years, ≥65 years) and prior antibiotic regimen (vancomycin, fidaxomicin). Kaplan-Meier estimates for the separate age and prior antibiotic regimen strata will also be presented with unstratified log-rank tests for the difference in survival distributions between

treatment groups.

Plots of the K-M survival function estimates will be provided by treatment and by treatment within age and prior antibiotic regimen stratum for the ITT and mITT populations.

8.2.1.3. Sensitivity Analysis of Time to Recurrence of CDI Determined by a Toxin Assay

A sensitivity analysis of the time to first recurrence of CDI determined by a toxin assay endpoint will also be conducted using a different censoring rule for missing data in the ITT population. In this analysis, subjects who do not experience a CDI recurrence by the end of the study follow-up period will continue to be censored on the date of last contact. However, subjects who are lost to follow-up or who terminate the trial prematurely prior to experiencing a CDI recurrence will be counted as having a CDI recurrence on the date of last contact. Subjects who die prior to experiencing a CDI recurrence will be counted as having a CDI recurrence on their date of death. Subjects who were assessed to have a CDI recurrence due to missing or incomplete data for one or more of the 3 components of CDI recurrence will be counted as having a CDI recurrence on the date of the earliest diarrhea, *C. difficile* stool test, assessment of investigator that the subject's condition warrants antibiotics or the date of last contact, whichever is the earliest, in the analysis.

Analyses will be conducted as described in Section 8.2.1.2 above.

Note that the preceding sensitivity analyses will only be conducted for CDI recurrences determined by a toxin assay.

8.2.1.4. Time to Recurrence of CDI Determined by a PCR Algorithm

The same analyses described in Section 8.2.1.2 for time to first CDI recurrence determined by a toxin assay will be conducted for the analysis of time to first CDI recurrence determined by a PCR algorithm.

8.2.1.5. Recurrence of CDI up to 4, 12, and 24 Weeks Post-Treatment Determined by a Toxin Assay

The number and percentage of subjects with recurrence of CDI determined by a toxin assay up to 4 (Day 30), 12 (Day 87), and 24 weeks after treatment (Day 171) will be presented by treatment group in the ITT and mITT Populations. Summary tables by age and prior antibiotic stratum will also be provided for the ITT population. RRs and differences in proportions will be estimated and tested using the same methods as for the primary efficacy assessment at Week 8 (Day 58), however testing at a 1-sided α-level of 0.025, with corresponding P-values and 2-sided 95% CI provided. Additionally, absolute difference (SER-109-Placebo) of the rate (%), including 95% CI, between the treatment groups will also be provided.

8.2.1.6. Recurrence of CDI up to 4, 12, and 24 Weeks Post-Treatment Determined by a PCR Algorithm

The same analyses described in Section 8.2.1.5 will be conducted for the recurrence of CDI determined by a PCR algorithm up to 4, 12, and 24 weeks post-treatment.

8.3. EXPLORATORY EFFICACY ANALYSES

8.3.1. Microbiome Outcome Analysis

A separate Microbiome Statistical Analysis Plan will be provided by Seres Therapeutics.

8.3.2. Incidence of All-Cause Mortality

The numbers and percentages of subjects who experience death from any cause through Weeks 8, 12, and 24 will be summarized for the ITT Population. The denominator will be the number of subjects in the ITT Population within each respective treatment group. No statistical tests will be conducted. In addition, a separate summary will be provided by age and prior antibiotic regimen stratum for each treatment group for the ITT Population.

8.3.3. Incidence of Hospitalizations

The numbers and percentages of subjects who are hospitalized for recurrent CDI through Weeks 8, 12, and 24 will be summarized for the ITT Population. Subjects with more than one hospitalization within a time period will be counted only once. The denominator will be the number of subjects in the ITT Population within each respective treatment group. No statistical tests will be conducted.

A similar summary will also be produced for the incidence of all hospitalizations, regardless of reason.

The number of hospitalizations per subject for recurrent CDI and for any reason will be summarized with frequencies and percentages.

Descriptive statistics for the total length of stay (in days) of all hospitalizations through 24 weeks for recurrent CDI and for any reason will be provided. No adjustments for time on study will be made.

Analyses for hospitalizations will also be provided by age and prior antibiotic regimen stratum for each treatment group for the ITT Population.

8.3.4. EQ-5D-5L Questionnaire

The EQ-5D-5L was developed by the EuroQol Group. The questionnaire measures health outcomes in 5 dimensions, using 5 levels of responses indicating severity. A visual analog scale (VAS) is also included. The dimensions are: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the respondent's overall self-rated health on a scale of 0 to 100.

A unique health state is obtained by combining the levels from each of the 5 dimensions into a 5-digit number – a maximum of 3125 possible health states is possible. For example, 11111 indicates no problems on any dimensions. 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain

or discomfort, and extreme anxiety or depression. Missing values for a dimension are coded as 9.

The EQ VAS is scored as 0 to 100, where 0 is the worst health you can imagine, and 100 is the best health you can imagine.

An index value for the EQ-5D-5L can be obtained by using the Crosswalk Index Value Calculator, downloadable from the EuroQol website.

Responses on each dimension will be summarized with frequencies and percentages at each visit, including the early termination visit. Shift tables from baseline to each visit, including the early termination visit, will also be constructed.

Summary statistics will be supplied for the Crosswalk Index Value and EQ VAS at each visit, including the early termination visit, and also for the changes from baseline.

8.3.5. Cdiff32 Health-care Quality of Life (HRQOL) Questionnaire

The Cdiff32 HRQOL questionnaire is a validated CDI-specific instrument (Garey et al, 2016) developed to assess HRQOL changes related to CDI with a focus on recurrent disease.

The questionnaire comprises 32 questions with 5 possible levels of response for each question. It measures health outcomes in 3 domains (physical, mental and social), and 5 sub-domains (general physical complaints, specific physical complaints, anxiety future, anxiety current, and relationship).

The responses are scored from 0 to 100 for each question, with the most positive response scored as 0 and incrementing by 25 points as the response becomes more negative. For example, for Question 1 'Have you had any difficulties and/or disruption carrying out your daily activities?', the possible responses are scored as follows: Not at all = 0, A little bit = 25, Moderately = 50, Quite a bit = 75, and Extremely = 100.

The overall score for each subject is derived using the average score of the subject's responses to all 32 questions. Each domain and sub-domain score for each subject is similarly derived by taking the average of all of the subject's responses to all questions within the domain and sub-domain, respectively. The following items are included in the specified domains and sub-domains:

Domain	Sub-domain	Item Number
Physical	General physical complaints	1–4, 9-10
	Specific physical complaints	11-18
Mental	Anxiety future	5-8, 27
	Anxiety current	19-26, 28

Social	Relationship	29-32

Descriptive statistics of the overall score, as well as the domain and sub-domain scores will be presented by treatment group for all study visits, including the early termination visit, at which they were collected for the ITT population. The change from baseline to each post-baseline visit, including the early termination visit, will also be summarized by treatment group.

All responses to the Cdiff32 HRQOL questionnaire will be listed.

9. SUBGROUP ANALYSES

A summary table of the RR of SER-109 to placebo recurrence of CDI up to 8 weeks after treatment (Day 58), together with the corresponding 95% CIs calculated using the variance of the natural logarithm of the RR, will be presented for the following baseline characteristics in the ITT Population:

- Age (<65 years old, ≥65 years old)
- Prior Antibiotic Regimen (Vancomyin, Fidaxomicin)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other)
- Hospitalization status at baseline (Inpatient, Outpatient).
- Domicile at baseline for Outpatients (Home Residence-Assisted Living, Home Residence-Self-Care, Rehabilitation Center, Nursing Home, Other)
- Region (USA, Canada)
- *C. difficile* result at Screening (Positive, Negative, Missing)
- *C. difficile* BI/NAP1/027 strain at baseline (Yes, No)
- Number of Prior CDI Episodes (3, >3)
- History of fecal microbiota transplantation (FMT) (Yes, No)
- PPI use at baseline (Yes, No)
- H2-Blocker use at baseline (Yes, No)
- PPI and/or H2-Blocker use at baseline (Yes, No)
- Creatinine Clearance at baseline (<30 ml/min, >=30 ml/min to <=50 ml/min, >50 ml/min to <=80 ml/min, >80 ml/min

  Creatinine clearance (mL/min) at baseline will be approximated by the estimated GFR (ml/min), using the Cockcroft-Gault equation,

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

  This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female.

Note: When serum creatinine is measured in µmol/L,

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

where Constant is 1.23 for men and 1.04 for women.

A forest plot of the RR with the corresponding 95% CI for the different subgroups will be presented.

In addition, a multiple logistic regression analysis with incidence of CDI recurrence as the dependent variable, and treatment group (SER-109 vs placebo), age group (<65 years vs ≥ 65 years), prior antibiotic regimen (vancomycin vs fidaxomicin) and history of FMT (yes vs no) as independent variables will be conducted to further assess the impact of FMT history on CDI recurrence after adjusting for the other variables in the model.

10. SAFETY

All safety analyses will be conducted in the Safety Population, unless specified otherwise. Subjects will be analyzed according to the treatment they actually received, rather than that to which they are randomized. Safety summaries will also be presented by age and prior antibiotic regimen stratum.

10.1. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Exposure and compliance will be assessed by the number of capsules taken on each of the 3 dosing days and overall, as well as the percentage of subjects who took each number in the Safety, ITT, mITT, and Per Protocol Populations.

10.2. ADVERSE EVENTS

10.2.1. Solicited Adverse Events

For this study, solicited AEs include:

- Gas or flatulence
- Abdominal distention or bloating
- Abdominal pain or cramping
- Nausea
- Anorexia (Loss of appetite)
- Vomiting
- Fatigue
- Chills or Shivering
- Constipation
- Diarrhea
- Fever

Solicited adverse events (AEs) including the severity of the solicited AEs will be captured on a diary card completed by the subjects on Days 4 through 10, with the exception of diarrhea. Diarrhea is being collected daily for the entire duration of the study using the diarrhea device. For the analysis of diarrhea as one of the solicited AEs, diarrhea collected from the diarrhea device on Days 4-10 will be used. Criteria for mild, moderate and severe diarrhea will be as follows:

- **Mild**: 3 - 4 UBMs per day
- **Moderate**: 5 - 6 UBMs per day
- **Severe**: >=7 UBMs per day

Subjects will also be asked to measure body temperature on Days 4-10. Criteria for mild, moderate and severe fever will be based on the CTCAE v4.0, May 2009, specifically,

- **Mild**: 38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)
- **Moderate**: >39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)

- **Severe**: >40.0 degrees C (>104.0 degrees F) for <=24 hours

The number and percentage of subjects with the specified solicited AE will be presented by severity and treatment group on Days 4 -10 in the Safety Population. Furthermore, for each solicited AE, a summary of the number of subjects with any reported AE, any Moderate AE, any Severe AE and any Moderate/Severe AE reported from Days 4-10 will also be tabulated. The summary tables will also be presented for each age group and prior antibiotic regimen stratum in the Safety Population.

10.2.2. Adverse Events (Excluding Solicited AEs)

AEs will be coded using MedDRA v20.0 (March 2017). A listing of all AEs from the time of randomization up to Week 8 will be summarized; from Week 8 up to Week 24, only serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected and summarized.

An AESI (serious or non-serious) is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate. In this protocol, an invasive infection (e.g., bacteremia, abscess, meningitis) is designated as an AESI, and as such, will be reported and followed in the same manner as an SAE during the course of the study.

Only treatment-emergent adverse events (TEAE) will be collected and summarized in this study. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

All TEAE summary tables described in this section will include solicited AEs on Days 4-10 which are considered TEAEs. Furthermore, additional analyses for the solicited AEs will be conducted and are described in Section 10.2.1.

The following TEAE summaries will be presented by treatment group on Day 10, Week 2, Week 8 and Week 24 (End of Study):

- An overall summary, including the number and percentage of
  - TEAEs
  - Subjects with At Least One TEAE
  - Subjects with No TEAEs
  - Study Drug Related or Possibly Related TEAEs
  - Subjects with Study Drug Related or Possibly Related TEAEs
  - Serious TEAEs
  - Subjects with Serious TEAEs
  - Treatment-Emergent AESIs
  - Subjects with Treatment-Emergent AESIs
  - Serious TEAEs Related or Possibly Related to Study Drug
  - Subjects with Serious TEAEs Related or Possibly Related to Study Drug
  - Treatment-emergent AESIs Related or Possibly Related to Study Drug

  - Subjects with Treatment-emergent AESIs Related or Possibly Related to Study Drug
  - Severe TEAEs
  - Subjects with Severe TEAEs
  - TEAEs Leading to Study Withdrawal
  - Subjects with TEAE Leading to Study Withdrawal
  - Related or Possibly Related TEAEs Leading to Study Withdrawal
  - Subjects with Related or Possibly Related TEAEs Leading to Study Withdrawal
  - Serious TEAEs Leading to Study Withdrawal
  - Subjects with Serious TEAEs Leading to Study Withdrawal
  - Serious and Related or Possibly Related TEAEs Leading to Study Withdrawal
  - Subjects with Serious and Related or Possibly Related TEAEs Leading to Study Withdrawal
  - Treatment-emergent AESIs Leading to Study Withdrawal
  - Subjects with Treatment-emergent AESIs Leading to Study Withdrawal
  - Related or Possibly Related Treatment-emergent AESIs Leading to Study Withdrawal
  - Subjects with Related or Possibly Related Treatment-emergent AESIs Leading to Study Withdrawal
  - TEAEs Leading to Death
  - Subjects with TEAEs Leading to Death

- Overall Summary by Age and Prior Antibiotic Regimen Stratum
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by System Organ Class (SOC) and Preferred Term (PT) by Age and Prior Antibiotic Regimen Stratum
- TEAEs by PT, sorted by descending incidence in the SER-109 group
- TEAEs by PT, sorted by descending incidence in the SER-109 group by Age and Prior Antibiotic Regimen Stratum
- Related or Possibly Related TEAEs by PT, sorted by descending incidence in the SER-109 group
- Serious TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Serious TEAEs by System Organ Class (SOC) and Preferred Term (PT) by Age and Prior Antibiotic Regimen Stratum
- TEAEs Leading to Study Withdrawal by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs Leading to Study Withdrawal by System Organ Class (SOC) and Preferred Term (PT) by Age and Prior Antibiotic Regimen Stratum
- TEAEs by System Organ Class (SOC), Preferred Term (PT) and Maximum Severity
- TEAEs by System Organ Class (SOC), Preferred Term (PT) and Maximum Severity by Age and Prior Antibiotic Regimen Stratum
- TEAEs by System Organ Class (SOC), Preferred Term (PT) and Maximum Relationship to Study Drug

- TEAEs by System Organ Class (SOC), Preferred Term (PT) and Maximum Relationship to Study Drug by Age and Prior Antibiotic Regimen Stratum
- TEAEs Occurring Before Antibiotic Use by System Organ Class (SOC), Preferred Term (PT) and Maximum Severity
- TEAEs Occurring Before Antibiotic Use by System Organ Class (SOC), Preferred Term (PT) and Maximum Severity by Age and Prior Antibiotic Regimen Stratum

The following subject listings will be provided:

- Deaths,
- Serious TEAEs,
- AESIs, and
- TEAEs leading to study withdrawal.

For all TEAE tables summarized by SOC and PT, a subject contributes only once to the count for a given TEAE on the SOC level and on the PT level within SOC.

In the summary by maximum severity, subjects reporting AEs at different severities will be counted only once at the greatest severity reported within an AE level (SOC or PT). Severity categories will include mild, moderate, and severe. Any missing severity will be imputed as severe prior to selecting the report that will contribute to the summary; as a result, a subject would be counted as severe due to a missing severity, even if the subject reported similar events at a lesser degree of severity.

In the summary by maximum relationship, subjects reporting AEs at different relationships will be counted only once at the strongest relationship reported within an AE level (SOC or PT). Relationship categories will include related, possibly related and unrelated. Any missing relationship will be imputed as related prior to selecting the report that will contribute to the summary; as a result, a subject would be counted as having a related AE due to a missing relationship, even if the subject reported similar events at a lesser relationship.

In all summary tables, TEAEs will be sorted in decreasing incidence, first by SOC and then by PT within the SOC, according to the incidence in the SER-109 treatment group. SOCs and PTs occurring at the same incidence will be sorted alphabetically, unless specified otherwise.

No statistical tests will be performed.

Additional analyses will determine the exposure-adjusted incidence rates (EAIR) per 100 person years of specific TEAEs occurring before subjects received antibiotics for recurrence of CDI, based on the number of days the subjects were followed up to Week 24/End of Study, including TEAEs for subjects who did not receive antibiotics for treatment of CDI before Week 24/End of Study. Incidence rates per 100 person years will be presented for the following:

1) subjects with at least one treatment-emergent SAE,

2) subjects with at least one treatment-emergent AESI, and

3) subjects with at least one TEAE leading to study withdrawal.

The EAIR per 100 person years will be calculated as (100*number of subjects with events)/total person years, where total person years equals the sum of the following: 1) [(earliest of the date of first antibiotic treatment before Week 24/End of Study or the date of the event of interest) – date of dose + 1]/365.25, summed across subjects who received antibiotics for treatment of CDI; and 2) [(earliest of the date of last contact up to Week 24/End of Study or the date of the event of interest) – date of dose + 1]/365.25, summed across subjects who did not receive antibiotics for treatment of CDI before Week 24/End of Study. The treatment difference between rates will be accompanied by a 95% CI obtained using the normal approximation to the Poisson distribution, without accounting for stratification.

10.3. LABORATORY EVALUATIONS

All hematology, chemistry, blood screening, and pregnancy laboratory tests will be performed by a central laboratory. Descriptive statistics of the laboratory parameters will be presented by treatment group for all study visits at which they were collected. The change from baseline to each post-baseline visit, including the early termination visit, and to the minimum and maximum post-baseline value will also be summarized by treatment group.

Laboratory parameters will be defined as within or outside normal range limits and shift tables from baseline to each post-baseline visit will also be provided by treatment group.

All laboratory evaluations will be included in the data listings.

10.4. VITAL SIGNS

Vital signs data include measurements of weight (kg), height (cm), blood pressure (mmHg), respiratory rate (breaths/minute), body temperature (Celsius), and Body Mass Index (kg/m^2). Descriptive statistics of the vital signs will be presented by treatment group for all study visits, including the early termination visit, at which they were collected. The change from baseline to each post-baseline visit, including the early termination visit and to the minimum and maximum post-baseline value, will also be summarized by treatment group.

All vital signs data will be listed.

10.5. PHYSICAL EXAMINATION

A listing with physical examination findings will be provided.

10.6. OTHER SAFETY

All data in the Diarrheal Assessment Log will be listed.

11. DATA AND SAFETY MONITORING COMMITTEE

An independent DSMC will review unblinded safety data through review of suspected, unexpected serious adverse reactions (SUSARs) as they occur, as well as monthly review of blinded SAE and AESI listings.

The roles and responsibilities of the DSMC, including its membership, scope, timing of meetings, and communication plan are defined in the DSMC charter. The DSMC will monitor the study for subject safety throughout the trial. The DSMC may recommend changes to study conduct based on emerging safety information to protect the safety and welfare of clinical study subjects.

12. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

There are no planned changes from the analyses specified in the protocol (SERES-012 Protocol Amendment 7 dated 24 April 2019).

13. REFERENCE LIST

Food and Drug Administration, *Multiple Endpoints in Clinical Trials. FDA Guidance for Industry.* January 2017.

Fekety R, et al. CID 1997; 24:324. Recurrent *Clostridium difficile* diarrhea: Characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial.

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Kim Y, Won S. Adjusted proportion difference and confidence interval in stratified randomized trials. PharmaSUG 2013; Paper SP04.

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

McFarland LV, et al. JAMA 1994; 271:1913. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease.

National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0, NCI, NIH, DHHS. May 28, 2009, NIH publication # 09-7473.

Surawicz CM, et al. CID 2000; 31:1012. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*.

van Nood E, et al. NEJM 2013; 368:407. Duodenal infusion of donor feces for recurrent *Clostridium difficile*.

14. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or later (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will follow [redacted] templates and output specifications.

15. INDEX OF TABLES

Table Number	Table Title	Population
14.1.1.1	[redacted]	Screened
14.1.2.1		Randomized
14.1.2.2		Randomized
14.1.3.1.1		Safety
14.1.3.1.2		ITT
14.1.3.1.3		mITT
14.1.3.1.4		PP8
14.1.3.1.5		PP24
14.1.3.1.6.1		Safety
14.1.3.1.6.2		Safety
14.1.3.1.7		ITT
14.1.3.2		ITT
14.1.3.3		Safety
14.1.4.1		Safety
14.1.4.2		Safety
14.1.4.3		Safety
14.1.4.4		Safety
14.1.4.5		ITT
14.1.5.1		By Pop.
14.2.1.1.1		ITT
14.2.1.1.2		mITT
14.2.1.1.3		PP8
14.2.1.1.4		PP24
14.2.1.1.5		ITT
14.2.1.1.6		ITT
14.2.1.1.7		ITT

Table Number	Table Title	Population
14.2.1.2.1	[redacted]	ITT
14.2.1.2.2	[redacted]	mITT
14.2.1.2.3	[redacted]	ITT
14.2.1.3.1	[redacted]	ITT
14.2.1.3.2	[redacted]	ITT
14.2.1.3.3	[redacted]	ITT
14.2.1.3.4	[redacted]	ITT
14.2.1.4.1	[redacted]	ITT
14.2.1.4.2	[redacted]	ITT
14.2.1.5.1	[redacted]	ITT
14.2.1.6.1	[redacted]	ITT
14.2.1.6.2	[redacted]	mITT
14.2.2.1.1	[redacted]	ITT

Table Number	Table Title	Population
14.2.2.1.2	[redacted]	mITT
14.2.2.1.3	[redacted]	ITT
14.2.2.2.1	[redacted]	ITT
14.2.2.2.2	[redacted]	mITT
14.2.2.2.3	[redacted]	ITT
14.2.2.2.4	[redacted]	ITT
14.2.2.3.1	[redacted]	ITT
14.2.2.3.2	[redacted]	ITT
14.2.3.1.1	[redacted]	ITT
14.2.3.1.2	[redacted]	ITT
14.2.3.2.1.1	[redacted]	ITT
14.2.3.2.1.2	[redacted]	ITT
14.2.3.2.2.1	[redacted]	ITT
14.2.3.2.2.2	[redacted]	ITT
14.2.3.3.1	[redacted]	ITT
14.2.3.3.2	[redacted]	ITT
14.2.3.4	[redacted]	ITT
14.3.1.1	[redacted]	Safety
14.3.1.2	[redacted]	Safety

Table Number	Table Title	Population
14.3.1.3	[redacted]	Safety
14.3.1.4	[redacted]	Safety
14.3.1.5	[redacted]	Safety
14.3.1.6	[redacted]	Safety
14.3.1.7	[redacted]	Safety
14.3.1.8	[redacted]	Safety
14.3.1.9	[redacted]	Safety
14.3.1.10	[redacted]	Safety
14.3.1.11	[redacted]	Safety
14.3.1.12	[redacted]	Safety
14.3.1.13	[redacted]	Safety
14.3.1.14	[redacted]	Safety
14.3.1.15	[redacted]	Safety
14.3.1.16	[redacted]	Safety
14.3.1.17	[redacted]	Safety
14.3.1.18	[redacted]	Safety

Table Number	Table Title	Population
14.3.1.19	[redacted]	Safety
14.3.1.20		Safety
14.3.2.1		Safety
14.3.2.2		Safety
14.3.2.3		Safety
14.3.2.4		Safety
14.3.3.1		Safety
14.3.3.2		Safety
14.3.3.3		Safety
14.3.3.4		Safety
14.3.4.1.1.1		Safety
14.3.4.1.1.2		Safety
14.3.4.1.1.3		Safety
14.3.4.1.2.1		Safety
14.3.4.1.2.2		Safety
14.3.4.1.2.3		Safety
14.3.4.2.1		Safety

16. INDEX OF FIGURES

Figure Number	Figure Title	Population
14.2.1.1	[redacted]	ITT
14.2.1.2		mITT
14.2.2.1		ITT
14.2.2.2		ITT
14.2.2.3		ITT
14.2.2.4		mITT
14.2.2.5		mITT
14.2.2.6		mITT
14.2.3.1		ITT
14.2.3.2		mITT
14.2.4		ITT
14.2.5		ITT
14.2.6		ITT
14.2.7		ITT

17. INDEX OF LISTINGS

Listing Number	Listing Title
16.2.1.1	
16.2.1.2	
16.2.1.3	
16.2.2.1	
16.2.4.1	
16.2.4.2.1	
16.2.4.2.2	
16.2.4.2.3	
16.2.4.3	
16.2.4.4	
16.2.4.5	
16.2.4.6	
16.2.5.1	
16.2.5.2	
16.2.6.1	
16.2.6.2	
16.2.6.3	
16.2.6.4	
16.2.6.5	
16.2.6.6	
16.2.6.7	
16.2.6.8	
16.2.6.9	
16.2.6.10	
16.2.6.11	
16.2.7.1	
16.2.7.2	
16.2.8.1.1	
16.2.8.1.2	
16.2.8.1.3	
16.2.8.1.4	
16.2.8.1.5	
16.2.8.1.6	
16.2.8.2.1	
16.2.8.2.2	
16.2.8.2.3	

SERES 012_ Final_SAP_Version 4.0 SW LS

Final Audit Report 2020-04-14

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"SERES 012_ Final_SAP_Version 4.0 SW LS" History

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