CLINICAL STUDY PROTOCOL

SER-109

(Eubacterial Spores, Purified Suspension, Encapsulated)

SERES-012: ECOSPOR III: A Phase 3 Multicenter, RandomizEd, Double Blind, Placebo-COntrolled, Parallel-Group 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)

SPONSOR:

Seres Therapeutics, Inc.
200 Sidney Street, Suite 410
Cambridge, MA 02139
[redacted]

TITLE:

ECOSPOR III: A Phase 3 Multicenter, RandomizEd, Double Blind, Placebo COntrolled, Parallel Group 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)

CLINICAL PHASE: 3

[redacted]

Original Protocol Date: March 06, 2017

Amendment 1 Date: June 5, 2017

Amendment 2 Date: 08 September 2017

Amendment 3 Date: 25 October 2017

Amendment 4 Date: 11 January 2018

Amendment 5 Date: 22 March 2018

Amendment 6 Date: 4 January 2019

Amendment 7 Date: 24 April 2019

Amendment 8 Date: 10 April 2020

CLINICAL RESEARCH ORGANIZATION (CRO):

[redacted]

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

Declaration of Sponsor or Responsible Medical Officer

Title: ECOSPOR III: A Phase 3 Multicenter, RandomizEd, Double-Blind, Placebo-COntrolled, Parallel-Group 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)

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

[redacted]

13 April, 2020

Date

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the SERES-012 Protocol Amendment 8 dated 10 April 2020 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

STUDY CONTACTS

Sponsor Responsible Medical Officer

[redacted]

CRO Medical Monitor

[redacted]

1. PROTOCOL SYNOPSIS

SPONSOR NAME: Seres Therapeutics, Inc.

ACTIVE INGREDIENT: SER-109 (Eubacterial Spores, Purified Suspension, Encapsulated)

PROTOCOL TITLE: ECOSPOR III- A Phase 3 Multicenter, Randomiz**E**d, Double-Blind, Placebo-**CO**ntrolled, Parallel-Group **S**tudy to Evaluate the Safety, Tolerability, and Efficacy of SER-109 vs. **P**lacebo to Reduce Recurrence of *Cl**O**st**R**idium difficile* Infection (CDI) in Adults Who Have Received Antibacterial Drug Treatment for Recurrent CDI (RCDI)

STUDY CENTERS: Approximately 100 study centers in North America

PLANNED STUDY PERIOD:

Estimated date first patient enrolled: 2Q2017

Estimated date last patient completed: 3Q2020

CLINICAL PHASE: 3

DEFINITIONS:

For this study, CDI recurrence during the study is defined by the following criteria:

- Positive *Clostridium difficile* test on a stool sample determined by a toxin assay
- ≥ 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
- Assessment by the investigator (based on clinical assessment) that the patient's condition warrants antibiotic treatment

OBJECTIVES:

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

Secondary Efficacy Objectives

- To demonstrate the superiority of SER-109 versus placebo in the reduction of CDI recurrence rates, determined using 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

Primary Safety Objective

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

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

STUDY DESIGN:

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, 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 (RCDI), based on the proportion of subjects experiencing a CDI recurrence requiring antibiotic treatment up to 8 weeks after initiation of treatment.

The target accrual will be 188 subjects.

Subjects with a history of RCDI, diarrhea and a positive *C. difficile* stool sample tested by a toxin assay preferably performed by a central laboratory (see Laboratory Manual), 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]) 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). Local laboratory toxin testing for the qualifying episode must be from a Clinical Laboratory Improvement Amendments-certified laboratory using a Food and Drug Administration-approved *C. difficile* toxin test. 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.

Potential subjects will be screened from -24 to -2 days prior to initiation of dose administration. Prospective subjects include those who have been diagnosed with their third or subsequent episode of CDI, defined as diarrhea (≥3 unformed stools per day for at least 2 consecutive days), a documented positive *C. difficile* stool sample tested by a toxin assay preferably performed by a central laboratory, and who are currently taking or have completed a 10-21 day course of standard-of-care (SOC) antibiotic (defined as vancomycin [125 mg QID] and/or fidaxomicin [200 mg BID]) to treat their CDI. Alternatively, subjects with a suspected third or subsequent CDI episode (≥3 unformed stools per day for 2 consecutive days), but who have not had a CDI stool test are eligible to be screened. To be randomized into the study, all subjects must have a positive *C. difficile* stool sample tested by a toxin assay preferably performed by a central laboratory and an adequate clinical response following SOC antibiotic therapy, defined as < 3 unformed stools in 24 hours for 2 or more consecutive days up to randomization. All subjects must be able to be dosed with study drug within 4 days of SOC antibiotic completion. On Day -1, within 3 days of completing SOC antibiotic treatment for their CDI, subjects will undergo a bowel cleanse by consuming 10 oz. (~300 mL) of oral magnesium citrate followed by overnight fasting. Subjects with impaired kidney function who are unable to take magnesium citrate will take 250 mL of GoLytely (polyethylene glycol electrolyte solution). On the day of randomization (Day 1), subjects will report to the clinic and will receive either 1 dose of SER-109 ([redacted]) or 1 dose of matching placebo for oral administration. Subjects will remain in the clinic until all safety evaluations have been completed. On Day 2 and Day 3, subjects may elect to come to the clinic to receive a single daily dose of study drug or may choose to receive a phone call to confirm administration of a single daily dose of study drug. If subjects elect to receive a phone call, prior to leaving the clinic on Day 1 they will receive a 2-day supply of study drug per treatment assignment, as well as instructions for home administration of single daily doses (4 capsules) in the morning before breakfast on Day 2 and Day 3. Subjects electing phone confirmation of dosing will be contacted by phone on Day 2 and Day 3 to confirm they have taken study drug before breakfast and to inquire about their general health. If subjects have not taken study drug when contacted, they will be reminded to do so as soon as possible. From Day 1 to Week 8, all subjects will be contacted by phone by study site personnel weekly, with the exception of a home or in-clinic visit at Week 2 and an in-clinic visit at Week 8, and queried for adverse events (AEs) and diarrheal symptoms. In addition, subjects will use a patient-reported diary card to capture solicited adverse reactions for 7 days after Day 3 of study drug (Day 4 through Day 10). After Week 8, all subjects will be contacted by phone by study site personnel every 4 weeks (i.e., Weeks 12, 16, 20, and 24) and queried for serious adverse events [SAEs] and adverse events of special interest [AESIs]). Health-related quality of life and health outcomes will be assessed throughout the study via the CDI-specific, Cdiff32 Health Related Quality of Life (HRQoL) and EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaires.

To document episodes of diarrhea, subjects will complete a daily diarrhea log (see Investigator Site File) to include days with diarrhea as well as no diarrhea. If diarrheal symptoms recur (≥ 3 unformed stools per day over 2 consecutive days) between scheduled visits, subjects will be instructed to contact the investigator and return to the clinic for a *C. difficile* stool test and clinical evaluation for recurrence of CDI (Recurrence Visit). Subjects with confirmed CDI recurrence, as defined in the protocol, up to 8 weeks after initiation of SER-109 or placebo treatment, may be eligible to enroll in the open-label SER-109 extension study (SERES-013). Assessments performed during the Recurrence visit may be used for the Screening labs for SERES-013. Subjects who do not choose to enroll in the SERES-013 study or subjects with a confirmed recurrence after Week 8 should continue to be followed for safety assessments through Week 24. Favorable clinical outcome, or sustained clinical response, in this study will be determined by the absence of CDI recurrence up to 8 and 12 weeks after initiation of study drug. CDI recurrence is 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* stool sample tested by a toxin assay and a decision by the investigator (based on clinical assessment), that antibiotic treatment is needed. To inform subject care, a *C. difficile* stool test may be performed locally at the study site. Stool samples collected for suspected CDI recurrence will also be processed and shipped to a central laboratory for *C. difficile* stool testing (see Laboratory Manual for details of central laboratory testing). The subject should not initiate antibiotic treatment for suspected CDI prior to providing a stool sample for the central laboratory stool testing. 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.

An independent data safety and monitoring committee (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 schedule of assessments and procedures is provided in Table 1.

PLANNED NUMBER OF SUBJECTS:

This study will enroll approximately 188 subjects randomized in a 1:1 ratio between SER-109 and placebo.

PRIMARY DIAGNOSIS: Recurrent CDI

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, or their legally authorized representative, must be willing 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] and/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 postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy.
   b. Of childbearing potential and is practicing at least 1 highly effective method of birth control including: the barrier method; oral or parenteral contraceptives; a vasectomized partner; or abstinence from sexual intercourse. The investigator will discuss with the subject the option of practicing more than 1 of the above methods for the duration of the study.
6. If male, and partner is of childbearing potential, subject agrees to practice at least 1 highly effective method of birth control for the duration of the study.
7. If currently taking probiotics, must be willing to stop at time of consent, for the duration of the study.

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 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.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Study drug is for investigational use only. Study drug dispensed at the study site will be stored at the study site or pharmacy. Subjects will be provided instructions for proper storage of study drug dispensed for administration at home. Instructions for storage are provided in the Investigator Site File. SER-109 and placebo will be supplied in size 00 capsules.

The dose, route, and schedule of study drug administration are presented in the following table:

Treatment Group	Treatment	Dose	Dosage Form and Amount	Route	Number of Doses	Number of Subjects
I	SER-109	[redacted]	4 capsules once daily for 3 days	Oral	3	94
II	Placebo	0	4 capsules once daily for 3 days	Oral	3	94

STUDY DURATION:

A total of ~27 weeks, including a ~3-week Screening Period, and 8-week Efficacy Period, and a 16-week Follow-Up Period.

STATISTICAL METHODS:

Analysis Populations:

Intent-to-Treat- Population

The Intent -to-Treat (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.

Modified Intent -to-Treat Population

The Modified ITT (mITT) Population will consist of all subjects who were randomized and received any amount of study drug, whose CDI was clinically controlled by antibiotic treatment before receiving study drug, and who have at least 1 post-baseline evaluation. 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.

Per Protocol- Population

The Per Protocol (PP) Population will consist of subjects from the mITT Population who do not have any major protocol deviations. Forced randomizations are considered to be major protocol deviations and therefore, subjects who are randomized using forced randomization will be excluded from the PP Population. The PP Population will be detailed in the Statistical Analysis Plan (SAP) and defined before un-blinding of the data.

Safety Population

The Safety Population will consist of all randomly assigned subjects who received 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.

Study Endpoints:

Primary Efficacy Endpoint

- Recurrence of CDI as determined by a toxin assay up to 8 weeks after initiation of treatment

Secondary Efficacy Endpoints

- 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

Exploratory Efficacy Endpoints

- 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 8 and 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

Safety Endpoints

- Incidence of AEs
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

Analysis of Primary Efficacy Endpoint:

The primary efficacy outcome measure for this study will be the relative risk (RR) of CDI recurrence of SER-109 to placebo. The primary efficacy endpoint analysis will be based on the Cochran-Mantel-Haenszel (CMH) test, stratified by age and antibiotics for the qualifying episode.

The CMH estimate of the common relative risk, stratified by age and baseline type of antibiotics, will be reported. The confidence interval (CI) for the common RR will be obtained using the Greenland and Robins variance estimate for the natural logarithm of the common RR.

Multiplicity Adjustment for Testing the Primary Efficacy Endpoint for Ho: RR ≥ 1.0 and Ho: RR ≥ 0.833

Adjustments for multiple testing will be made for testing the primary efficacy endpoint.
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:

- H_1: RR ≥ 1.0
- 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.

Table 1: Schedule of Assessments and Procedures

	SCREENING PERIOD			EFFICACY PERIOD							FOLLOW UP PERIOD		Recurrence Visit(s)	ET [o] Visit
	Clinic	*TC*[a]	*TC*[b]	*Clinic*	*Clinic or home*[e]	*Clinic or home*[e]	*TC*	*Clinic or home*[f,p]	*TC Weekly*	*Clinic*[p,q]	*TC*	*TC –Study Completion*	*Clinic*[m,p,q]	*Clinic p,q*
Day/Week	**Screening**	**-4 to -2**[b] *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Day 2**	**Day 3**	**Week 1 (±2 d)**	**Week 2 (±2 d)**	**Week 3-7 (±2 d)**	**Week 8 (±2 d)**	**Weeks 12, 16, 20 (± 3 d)**	**Week 24 (±3 d)**		
Assessments and Procedures														
Informed Consent	X													
Eligibility criteria review	X		X	X										
Endpoint review by medical monitor													X	X
IxRS registration/ randomization	X			X										
Medical History	X													
Physical Exam	X			X										
Focused History and Physical										X			X	X
Height (at Screening only), Weight	X			X						X			X	X
Vital signs[c]	X			X[d]		DAYS 4-DAY 10[c, f]				X			X	X
Chemistry and hematology	X			X						X			X	X
Blood for FBMR				X[g]										
Serum for FBMR				X[g]				X		X			X	X
Routine urine dipstick	X			X[g]									X[a]	
Pregnancy test (WOCBP) Note: Serum at Screen only	X			X[g]						X			X	X
Stool: Study Entry: central lab: *C. Diff* toxin assay	X													

	SCREENING PERIOD			**EFFICACY PERIOD**							**FOLLOW UP PERIOD**		**Recurrence Visit(s)**	ET [o] **Visit**
	Clinic	***TC*[a]**	***TC*[b]**	***Clinic***	***Clinic or home*[e]**	***Clinic or home*[e]**	***TC***	***Clinic or home*[f,p]**	***TC Weekly***	***Clinic*[p,q]**	***TC***	***TC –Study Completion***	***Clinic*[m,p,q]**	***Clinic p,q***
Day/Week	**Screening**	**-4 to -2[b]** *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Day 2**	**Day 3**	**Week 1 (±2 d)**	**Week 2 (±2 d)**	**Week 3-7 (±2 d)**	**Week 8 (±2 d)**	**Weeks 12, 16, 20 (± 3 d)**	**Week 24 (±3 d)**		
Assessments and Procedures														
Stool: On Study Recurrence/ET: central lab: *C. Diff* testing													X	
Stool: microbiome testing[i]			X[i]				X	X[h]		X[i]		X	X	X
Stool: metabolomics testing[i]			X[i]				X	X[h]		X[i]			X	X
Stool: central lab: *C. Diff* isolation and ribotyping[j]	X												X	
Provide stool collection kits	X			X						X				
Stop SOC Abx		X												
Administer bowel cleanse			X											
Confirm subject fasted for ≥8 h prior to study drug dosing				X										
Confirm subject administered bowel cleanse on Day -1				X										
Study drug dosing				X	X	X								
Confirmation of study drug administration[k]					X[k]	X[k]								
Study drug accountability										X			X[n]	
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment				X	X	X	X	X	X	X	X	X	X	X
Solicited AE Diary						DAYS 4-DAY 10[f]								

	SCREENING PERIOD			EFFICACY PERIOD							FOLLOW UP PERIOD		Recurrence Visit(s)	ET [o] Visit
	Clinic	*TC*[a]	*TC*[b]	*Clinic*	*Clinic or home*[e]	*Clinic or home* [e]	*TC*	*Clinic or home* [f,p]	*TC Weekly*	*Clinic* [p,q]	*TC*	*TC –Study Completion*	*Clinic* [m,p,q]	*Clinic p,q*
Day/Week	**Screening**	**-4 to -2**[b] *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Day 2**	**Day 3**	**Week 1 (±2 d)**	**Week 2 (±2 d)**	**Week 3-7 (±2 d)**	**Week 8 (±2 d)**	**Weeks 12, 16, 20 (± 3 d)**	**Week 24 (±3 d)**		
Assessments and Procedures														
Evaluation of diarrheal episodes	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cdiff32 HRQoL Survey				X			X			X			X[l]	X[l]
EuroQol 5 Dimensions 5 Level (EQ-5D-5L)[q]				X						X		X	X	X

Abbreviations: Abx=antibiotics; AE=adverse event; *C.diff=clostridium difficile*; ET=early termination; FBMR=future biomedical research; HRQoL=Health-Related Quality of Life; IxRS=interactive voice and web response system; SOC=standard of care; TC=telephone call; WOCBP=women of childbearing potential

[a] Phone call to remind subjects to stop taking antibiotics and to collect a stool sample on Day -1 before magnesium citrate or GoLytely (polyethylene glycol electrolyte solution) bowel cleanse.

[b] Phone call to confirm termination of antibiotics on day of last scheduled antibiotic dose and review instructions for Day -1 activities including collection of a stool sample before beginning the magnesium citrate or GoLytely (polyethylene glycol electrolyte solution) bowel cleanse. Stool sample collected at Day -1 will be returned to the clinic on Day 1.

[c] Blood pressure, pulse, respiratory rate, and body temperature. Oral Temperature will be measured at home and recorded on the Solicited AE diary page for Days 4-10.

[c] To be assessed immediately before and approximately 30 minutes after study drug dosing

[e] Day 2 and Day 3 dosing may be in clinic or self-administered at home. If self-administered at home, site personnel will call subject to confirm study drug was taken.

[f] At the Week 2 clinic visit or in-home visit, Solicited AEs diary should be collected from the subject.

[g] All samples to be collected prior to study drug dosing. Urine pregnancy testing results to be assessed prior to study drug dosing.

[h] Stool samples may be collected in the clinic or at home. If the subject elects to have an in-clinic visit, the sample may be collected at home prior to the visit and brought to the study site. If the subject is unable to bring the stool sample to the study site, arrangements may be made to pick up the sample at the subject's home and bring it to the study site or may ship directly to the central laboratory (i.e., home visit by nurse or courier).

[i] The stool sample collected on Day -1 should be collected prior to the bowel cleanse and may be brought to the study site for the Day 1 visit. The stool samples collected on Week 8 (in clinic visit) may be collected at home prior to the visit and brought to the study site. If the subject is unable to bring the sample to the study site at any other visit, a courier may be arranged to pick up the sample at the subject's home and bring it to the study site.

[j] For subjects screened during or after completion of SOC antibiotics, efforts should be made to obtain the stool sample used to diagnose the qualifying episode of CDI for ribotyping. If sample is unavailable, a portion of the stool sample collected prior to the bowel cleanse on Day -1 should be used for ribotype analysis.

[k] May include in-clinic visit or home visit.

[l] Administer if prior to Week 8 visit

[m] Subjects with a confirmed CDI recurrence prior to Week 8 after initiation of treatment may enroll in the SERES-013 open-label extension study, if eligible, after completion of the Recurrence visit and documentation of clinical response to protocol-directed antibiotic therapy (10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]). Assessments performed during the Recurrence visit may be used for the Screening labs for SERES-013. Subjects who do not enroll in the SERES-013 study or subjects with a confirmed recurrence after Week 8 should continue to be followed for safety assessments through Week 24.

[n] These assessments should be added to the Recurrence Visit for subjects who anticipate enrollment in the SERES-013 prior to a Week 8 Visit in SERES-012, to complete the full set of Screening assessments required for enrollment in SERES-013. These procedures are not required for subjects not being Screened for entry into SERES-013 (such as those subjects having a Recurrence Visit evaluation after study week 8).

[o] ET visit to be conducted on subjects withdrawing from study only. Any subject suspected of having an episode of CDI per protocol definition (≥ 3 unformed stools per day over 2 consecutive days) will be asked to contact the investigator and return to the clinic for a Recurrence Visit to include C. difficile stool test and evaluation for recurrence of CDI.

[p] As necessary for safety of subject, study visits including *Week 2, Week 8, Unscheduled, and Early Termination,* may be conducted remotely at subject's home, with qualified nurse or site personnel who will be appropriately documented on the site's delegation log to perform these Remote Study Visits and associated procedures (Modification due to COVID-19 pandemic). If a nurse or site personnel cannot perform the visits, a telephone call or a video conference (Zoom, Skype, FaceTime, etc.) should be conducted in place of the Week 2, Week 8, Unscheduled, and Recurrence / Early Termination visits and must be documented in the source. Any required procedures not performed during a remote visit at the subject's home will be documented as a protocol deviation by site staff.

[q] when visits are conducted over the phone, transcription of the EQ-5D-5L may be performed over the phone by site staff. The discussion with the subject must be documented in source files. (Modification due to COVID-19 pandemic).

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CCNA	Cell Cytotoxicity Neutralization Assay
CDI	*Clostridioides difficile* infection
Cdiff32 HRQoL	*Clostridium difficile* (CDiff32) Health-Related Quality of Life Survey
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendment
CMH	Cochran-Mantel-Haenszel
DRG	Diagnosis-related group
DSMC	Data Safety Monitoring Committee
eCRF	electronic Case Report Form
EAIR	exposure-adjusted incidence rates
EIA	Enzyme immunoassay
ET	Early Termination
EQ-5D-5L	EuroQol 5 Dimensions 5 Level
FDA	Food and Drug Administration
FMT	Fecal microbiota transplantation
GCP	Good Clinical Practice
GDH	Glutamate dehydrogenase
GI	Gastrointestinal
HRQoL	Health-Related Quality of Life
IBS	Irritable Bowel Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISC	Independent Statistical Center
ITT	Intent-to-Treat
IxRS	Interactive voice and web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
OTU	Operational taxonomic unit
PCR	Polymerase Chain Reaction
PP	Per-Protocol
RCDI	Recurrent *Clostridioides difficile* infection
RR	Relative risk
SAE	Serious adverse event
SAER	Serious adverse event report
SAP	Statistical Analysis Plan
[redacted]	[redacted]

SOC	Standard of care
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

4. INTRODUCTION

Clostridium difficile is a spore forming -Gram positive- anaerobe present throughout the environment and, in low amounts, can be a component of the gut flora of a healthy individual. *Clostridium difficile* infection (CDI) usually develops in patients with a history of antibiotic use that depletes the normal gut flora, enabling *C. difficile* to colonize and proliferate within the colon, elaborating virulent toxins A and B. These toxins invade epithelial cells disrupting their cytoskeleton, resulting in damage to the epithelial barrier and promoting mucosal inflammation. The clinical manifestations of CDI vary broadly, ranging from nuisance diarrhea lasting a few days, to more pronounced disease with severe colonic inflammation that can develop into pseudomembraneous colitis with associated systemic toxicity requiring lifesaving colectomy.

With ever increasing- use of antibiotics, particularly in the aging populations in hospitals and in nursing homes, the incidence of *C. difficile*-associated disease has been increasing such that *C. difficile* is the leading cause of nosocomial infection in the United States (US). The Centers for Disease Control and Prevention estimate that *C. difficile* causes diarrhea linked to approximately 29,000 American deaths each year (Lessa et al, 2015). In Canada, there are approximately 37,900 CDI episodes each year (2012); 7980 (21%) of these are relapses (Levy, 2015). In the European Union (EU), the number of reported cases of CDI has also increased in recent years, and is estimated to affect 172,000 patients per year.

Clostridium difficile spores can survive for months in hospitals and longterm- care facilities where they can cause repeated CDI episodes. Virtually all antibiotics have been implicated in association with CDI. The mechanistic link to antibiotic use is based on the finding that a healthy microbial ecology resists pathogen colonization by competing for nutrients and resources in the gut (Theriot et al, 2014; Weingarden et al, 2014). Antibiotic use disrupts the microbiota and liberates nutrients that enable colonization by *C. difficile* (Ng et al, 2013).

The incidence of recurrent CDI has paralleled the increased incidence of primary infection. CDI recurs in approximately 25% of patients after antibiotic treatment for first time disease (Bakken et al, 2011; Depestel and Aronoff, 2013; Surawicz- et al, 2013). After the first recurrent episode, patients are at an even higher risk for subsequent CDI, estimated to be > 60% after the second or subsequent episode (Higa and Kelly, 2013). There are few proven, approved therapeutic options for significantly reducing CDI recurrence in patients with recurrent CDI. Some patients are treated with antibiotics indefinitely to avoid persistent diarrhea and other sequelae of CDI.

SER109 is an Ecobiotic® drug being developed for the treatment of adults with recurrent CDI. SER-109 is an ecology of bacteria in spore form, enriched from stool donations obtained from healthy, screened donors. The bacterial spores are enriched by thorough killing of the vegetative microorganisms, then fractionating the resulting spore population away from inactive components and formulating and encapsulating the spores for oral delivery. SER-109 is administered to subjects after completion of a course of antibiotic therapy for recurrent CDI.

SER-109 has been shown to prevent CDI and to treat *C. difficile* relapse in nonclinical studies in mice and hamsters (see Investigator's Brochure for more information). Clinical experience with SER-109 includes three studies: 1) a completed open-label, two-part study in 30 subjects with a history of 3 or more occurrences of CDI (SERES-001); 2) a completed double-blind, placebo-controlled, parallel-group study in adults with recurrent CDI (SERES-004) and 3) an expanded access for intermediate-size patient populations and open-label extension of study

SERES-004 (SERES-005). To date, a total of 142 subjects have received 1 or 2 doses of SER-109 ([redacted]) in the completed and ongoing clinical studies with SER-109. The available safety data collected to date suggests that SER-109 is well-tolerated with an acceptable safety profile, although it is associated with a slight increase in gastrointestinal adverse effects, particularly diarrhea, compared to placebo (25% vs 14%). There have been 2 deaths (one in Study SERES-004 and one in the ongoing, open-label Study SERES-005), both of which were deemed by the investigators not related to SER-109. There have been no concerning trends in laboratory values, vital sign values, or physical examination findings in the completed SERES-001 or SERES-004 studies or in the SERES-005 preliminary safety datasets. A summary of clinical efficacy and safety is presented below.

4.1.1. Summary of Clinical Efficacy and Safety

Study SERES-001 was a 2-part study exploring the safety and efficacy of SER-109 in adult subjects (22 to 88 years of age) with recurrent CDI. The primary efficacy measure was response to SER-109 treatment up to 8 weeks after initiation of therapy. Response was defined as the absence of CDI during the efficacy evaluation period (Day 1 to Week 8). Fifteen subjects in Part 1 of the study received oral SER-109 ([redacted]) administered over 2 days. Fifteen subjects in Part 2 of the study received oral SER-109 ([redacted]) administered over 1 day.

In the open label study, SERES-001, SER109 resulted in -per protocol- efficacy of 86.7% (26/30 subjects) and an 8-week clinical cure rate of 96.7% (29/30 subjects). One subject had a recurrence at Day 5 and declined re-treatment. Three subjects reported diarrhea with a concomitant positive test result for *C. difficile* between 5 and 9 days after receiving SER-109. All 3 subjects were negative for *C. difficile* carriage and clinically CDI free- at 8 weeks, and were judged to be clinically cured without treatment with a course of antibiotics. One subject had a recurrence at 26 days after dosing, was re-treated per protocol, and was CDI free- 8 weeks after their second dose.

Most subjects (27/30) experienced ≥ 1 AE in Study SERES-001, all of which were treatment emergent- AEs (TEAEs). Fourteen TEAEs were considered related to study drug and all were mild or moderate. The most common system organ class (SOC) was GI disorders, and the most common preferred term was diarrhea. Four subjects experienced a total of 7 serious AEs (SAEs), none of which were considered by the investigators to be drug related.

SERES-004 was a randomized, double-blind, placebo-controlled Phase 2 study conducted in the U.S. Eighty-nine (89) subjects were randomized 2:1 to receive either [redacted] of SER-109 or placebo, respectively, following antibiotic treatment for recurrent CDI, and stratified by age (< 65 years; ≥ 65 years). The primary objective was to demonstrate the superiority of SER-109 versus placebo based on the proportion of subjects experiencing a CDI recurrence up to 8 weeks after treatment. The primary safety objective was to evaluate the safety of SER-109 in adults with recurrent CDI up to 12 weeks after treatment as determined by clinical and laboratory safety assessments.

The study did not meet the primary objective of reducing the relative risk of CDI recurrence up to 8 weeks following dosing. Overall, recurrence of *C. difficile* positive diarrhea requiring antibiotic treatment during the 8 weeks post-treatment occurred in 42 (47.2%) subjects (16 [53.3%] subjects randomized to receive placebo vs. 26 [44.1%] subjects randomized to receive SER-109. The

relative risk of recurrence in subjects receiving placebo vs. SER-109, adjusted for age stratum, was 1.22, with a corresponding 95% CI of (0.79, 1.88). Of the 43 subjects stratified to the <65 years of age strata, recurrence was observed in 12/28 (42.9%) subjects randomized to receive SER-109 and 4/15 (26.7%) subjects randomized to receive placebo. Of the 46 subjects stratified to the ≥65 years of age strata, recurrence was observed in 14/31 (45.2%) subjects randomized to receive SER-109 and 12/15 (80.0%) subjects randomized to receive placebo. Overall, of the 42 subjects who met the primary endpoint of CDI recurrence by Week 8, 35 subjects discontinued the study due to their CDI recurrence prior to Week 8. Of the 35 subjects who discontinued the study due to a CDI recurrence prior to Week 8, 34 enrolled in the open-label extension study SERES-005.

In Study SERES-004, a total of 66 of the 89 subjects randomized (74.2%), 46 of the 60 (76.7%) subjects who received SER-109 and 20 of the 29 (69.0%) subjects who received placebo, experienced at least 1 TEAE. Fifteen of the 89 (16.9%) subjects, 11 of the 60 (18.3%) subjects who received SER-109 and 4 of the 29 (13.8%) subjects who received placebo, experienced at least 1 TEAE that was considered by the investigators to be drug-related. Like Study SERES-001, the most commonly reported SOC was GI disorders (55% in the SER-109 group and 44.8% in the Placebo group). The most commonly reported (incidence ≥5%) preferred terms in the GI SOC reported in subjects who received SER-109 were diarrhea, abdominal pain, flatulence, nausea, and constipation. The majority of TEAEs were mild or moderate in severity. Six of the 60 (10%) subjects who received SER-109 experienced an event that has been reported as severe. Twelve of the 89 (10.1%) subjects enrolled (9 subjects who received SER-109 [15%] and 3 subjects who received placebo [10.3%] have experienced a total of 43 treatment-emergent SAEs, none of which were considered to be drug-related by the investigator. One subject had an SAE (metastatic non-small cell lung cancer) that was fatal and led to study withdrawal.

SERES-005 began as an open-label extension study of SERES-004 conducted in the U.S, offered to subjects who received an investigational product in SERES-004, but recurred prior to 8-weeks post-treatment. In April 2016, the study was amended to include expanded access to an intermediate-size patient population of adults, 18 years of age or older with recurrent CDI, for whom there is no comparable or alternative therapy. Seventy-three patients, 34 who enrolled from Study SERES-004 and 39 who enrolled under an expanded access met the eligibility criteria for the study. SERES-005 subjects who enrolled from study SERES-004 have completed the study; the subjects enrolled under expanded access are continuing in the study. The primary efficacy objective is to evaluate CDI recurrence rates in adults up to 8 weeks post-treatment with SER-109. The primary safety objective is to evaluate the safety and tolerability of SER-109 in adults with recurrent CDI. Among the 34 subjects who enrolled from Study SERES-004 and who have completed the study, recurrence of CDI up to 8 weeks post-treatment with SER-109 was observed in 11 (32.4%) subjects.

Preliminary results from the ongoing SERES-005 study indicate that, overall, 3 out of the 44 (6.8%) subjects, for whom safety data is available, experienced at least 1 treatment-emergent SAE. None of these SAEs are considered to be related to study treatment. One subject enrolled under the extension study experienced a total of 8 treatment-emergent SAEs. Five of these treatment-emergent SAEs resulted in death. Cerebrovascular accident, congestive cardiac failure, myocardial infarction, aspiration pneumonia, and type 2 diabetes mellitus were reported as the cause of death. The most commonly reported SOCs have been GI disorders in the extension study population and Infections and Infestations in the expanded access population. The most commonly

reported (incidence ≥5%) preferred terms overall have been diarrhea, abdominal pain, nasopharyngitis, constipation, flatulence, nausea, and urinary tract infection. The majority of TEAEs have been mild or moderate in severity.

Thus, clinical experience to date suggests that SER-109 is well-tolerated with an acceptable safety profile. Overall, there have been no drug-related treatment-emergent SAEs and the majority of related TEAEs have been mild or moderate in severity and most commonly associated with the gastrointestinal tract. Additional information regarding clinical experience with SER-109 can be found in the Investigator's Brochure.

Although safety data with SER-109 has been relatively consistent across studies, efficacy data in the placebo-controlled Study SERES-004 was inconsistent with results from the open-label Study SERES-001. Hypotheses to explain why the primary endpoint of reducing the relative risk of CDI recurrence at up to 8-weeks was not achieved in Study SERES-004 include that the diagnostic test for entry may not have differentiated subjects with active CDI disease from those with *C. difficile* carriage. This would have led to enrolling subjects who may have been experiencing post-CDI irritable bowel syndrome (IBS)-like symptoms but, were only colonized by *C. difficile* and not an active infection, the diagnostic test for recurrences which primarily used PCR overestimated recurrences, and although analysis of the microbiome identified that SER-109 in SERES-004 was biologically active, the dose administered in Phase 2 may need to be increased for optimal efficacy (see rationale below).

4.2. Rationale

There are few proven, approved therapeutic options for significantly reducing CDI recurrence in patients with recurrent CDI. The aim of this study is to further evaluate the safety and efficacy of SER-109 in the treatment of adult subjects 18 years of age or older with recurrent CDI, as defined by a history of ≥ 3 CDI episode within 12 months, inclusive of the current episode.

4.2.1. Rationale for Dose and Treatment Regimen

In this study, subjects will receive a dose of SER-109 ( ) or a dose of matching placebo per day for 3 consecutive days. The dose and treatment regimen were chosen based on several factors.

In Study SERES-001, subjects received doses of SER-109 ranging from given over one or two days. Analysis of changes in the subject microbiome demonstrates that spore forming species richness in the subjects' GI tract at 1 week was positively correlated with SER-109 dose. Importantly, of subjects who recurred in SERES-004, about 50% of recurrences in both placebo and SER-109 arms happened by Day 10 and 75% by Day 20, starting as early as Day 3. In SERES-004, the engraftment of SER-109 spore-forming bacteria in treated subjects' gastrointestinal tracts was less robust and less rapid as compared to that observed in SERES-001, although it was significantly greater than the changes in placebo-treated subjects. Engraftment improved at later time points, but due to early recurrences, the SER-109-induced microbiome change in SERES-004 may have been too late from a therapeutic perspective. In addition, it was generally observed that commensal spore-forming species richness at 1-week post dosing is correlated with better clinical outcome. In aggregate, these observations are central to the design of the proposed regimen that provides a higher daily dose ( ) repeated daily over 3 days following the completion of antibiotics as compared to dosing in SERES-004. Due to

the fact that recurrence happens early, the slower SER-109-induced microbiome changes in SERES-004 suggest that the [redacted] was likely below the required amount to achieve a therapeutic response. To account for variations in antibiotic washout, and to provide dosing prior to the earliest observed recurrences, three (3) doses will be administered on Days 1 - 3 following antibiotic cessation. We have chosen a three-fold higher dose level based on the [redacted], as an amount commensurate with engraftment richness to the degree correlating with protection against recurrence.

4.2.2. Rationale for Endpoints and *C. difficile* Diagnostic Criteria

The introduction of molecular tests, which are more sensitive and detect microbial DNA instead of toxin, has led to greater detection of *C. difficile* but detect *C. difficile* bacteria regardless of toxin production. This phenomenon has called into question whether a positive PCR result reflects clinical disease or represents *C. difficile* colonization (Polange et al, 2015).

Thus, in SERES-004, the diagnostic test for entry may not have differentiated subjects with active CDI disease from those with *C. difficile* carriage. This would lead to enrolling subjects who may be experiencing a post-CDI irritable bowel syndrome (IBS) if colonized by *C. difficile.* IBS following CDI is reported to occur in up to 25% of CDI patients (Wadhwa et al, 2016). This would have decreased the power of the study to differentiate the treatment arms as those subjects without a true diagnosis of RCDI are less likely to recur.

Since PCR diagnostics in SERES-004 may have led to misclassification of subjects with diarrhea and *C. difficile* colonization as recurrence, the primary efficacy endpoint in this study is the recurrence of CDI in subjects who receive SER-109 or placebo using a *C. difficile* toxin positive diagnostic (not toxin gene-based) up to 8 weeks after initiation of treatment. Unlike the PCR diagnostic for *C.* difficile, the toxin based tests, such as enzyme immunoassay (EIA) for toxin A and B or the cell cytotoxicity neutralization assay (CCNA) detects the presence of *C. difficile* toxin in fecal samples. Thus, recurrence is defined as ≥ 3 unformed stools per day for 2 consecutive days with a positive *C. difficile* test on a stool sample determined by a toxin assay, and assessment by the investigator that the clinical condition of the subject warrants antibiotic treatment.

5. STUDY OVERVIEW

This 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.

The target accrual will be 188 subjects.

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 performed 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]) 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). Local laboratory toxin testing for the qualifying episode must be from a Clinical Laboratory Improvement Amendments-certified laboratory using a Food and Drug Administration-approved *C. difficile* toxin test.

Subjects will receive an oral dose of SER-109 ([redacted]) 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.

Favorable clinical outcome in this study will be determined by the absence of CDI recurrence up to 8 and 12 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. Sustained clinical response is defined as a favorable clinical outcome.

An independent data safety and monitoring committee (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.

5.1. Trial Conduct

Subjects with a history of RCDI, diarrhea and a positive *C. difficile* stool sample tested by a toxin assay preferably obtained from a central laboratory (see Laboratory Manual, who have responded to 10 to 21 days of standard -of-care (SOC) antibiotic treatment will be enrolled. Potential subjects will be screened from -24 to -2 days prior to initiation of dose administration. Prospective subjects include those who have been diagnosed with their third or subsequent episode of CDI, defined as diarrhea (≥ 3 unformed stools per day for at least 2 consecutive days), a documented positive *C. difficile* stool sample tested by a toxin assay preferably performed by a central laboratory (see Laboratory Manual), and who are currently taking or have completed a 10-21 day course of standard-of-care (SOC) antibiotic (defined as vancomycin [125 mg QID] and/or fidaxomicin [200 mg BID]) to treat their CDI. Alternatively, subjects with a suspected third or subsequent CDI episode (≥ 3 unformed stools per day for 2 consecutive days), but who have not had a CDI stool test are eligible to be screened. To be randomized into the study, all subjects must have a positive *C. difficile* stool sample tested by a toxin assay preferably performed by the central laboratory and an adequate clinical response following SOC antibiotic therapy, defined as <3 unformed stools in 24 hours for 2 or more consecutive days up to randomization. Local laboratory toxin testing for the qualifying episode must be from a Clinical Laboratory Improvement Amendments-certified laboratory using a Food and Drug Administration-approved *C. difficile* toxin test. All subjects must be able to be dosed with study drug within 4 days of SOC antibiotic completion. On Day -1, within

3 days of completing SOC antibiotic treatment for their CDI, subjects will undergo a bowel cleanse by consuming 10 oz. (~300 mL) of oral magnesium citrate followed by overnight fasting. Subjects with impaired kidney function who are unable to take magnesium citrate will take 250 mL of GoLytely (polyethylene glycol electrolyte solution). On the day of randomization (Day 1), subjects will report to the clinic and will receive either 1 dose of SER-109 ([redacted]) or 1 dose of matching placebo for oral administration. Subjects will remain in the clinic until all safety evaluations have been completed. On Day 2 and Day 3, subjects may elect to come to the clinic to receive a single daily dose of study drug, or may choose to receive a phone call from study staff to confirm subject has taken a single daily dose of study drug. If subjects elect to take the study drug at home on Day 2 and Day 3, they will receive a phone call to confirm dosing on Days 2 and 3. For those subjects taking Days 2 and 3 study drug at home, prior to leaving the clinic on Day 1 they will receive a 2-day supply of study drug per treatment assignment, as well as instructions for home administration of single daily doses (4 capsules) in the morning before breakfast on Day 2 and Day 3. Subjects electing phone confirmation of dosing will be contacted by phone on Day 2 and Day 3 to confirm they have taken study drug before breakfast and to inquire about their general health. If subjects have not taken study drug when contacted, they will be reminded to do so as soon as possible. From Day 1 to Week 8, all subjects will be contacted by phone by study site personnel weekly, with the exception of a home or in--clinic visit at Week 2, and an in-clinic visit at Week 8, and queried for adverse events (AEs) and diarrheal symptoms. In addition, subjects will use a patient-reported diary card to capture solicited adverse events for 7 days after Day 3 of study drug (Day 4 through Day 10). After Week 8, all subjects will be contacted by phone by study site personnel every 4 weeks (i.e., Weeks 12, 16, 20, and 24) and queried for serious adverse events [SAEs] and adverse events of special interest [AESIs]). Health-related quality of life and health outcomes will be assessed throughout the study via the CDI-specific, Cdiff32 Health Related Quality of Life (HRQoL) and EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaires.

All AEs, SAEs/AESIs, and concomitant medications will be collected from the time of randomization up to Week 8. From Week 8 up to Week 24, all SAEs/AESIs and SAE/AESI-related data, and any antibiotic medication and its corresponding indication will be collected.

To document episodes of diarrhea, subjects will complete a daily diarrhea log (see Investigator Site File) to include days with diarrhea as well as no diarrhea. If diarrheal symptoms recur (≥ 3 unformed stools per day over 2 consecutive days) between scheduled visits, subjects will be instructed to contact the investigator and return to the clinic for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI (Recurrence Visit). Subjects with a confirmed CDI recurrence, as defined in the protocol, prior to Week 8, may be eligible to enroll in the open-label SER-109 extension study (SERES-013), and if eligible, offered an opportunity to enroll. Subjects who do not enroll in the SERES-013 study or subjects with a confirmed recurrence after Week 8 should continue to be followed for safety assessments through Week 24.

Favorable clinical outcome or sustained clinical response in this study will be determined by the absence of CDI recurrence up to 8 and 12 weeks after initiation of treatment. CDI recurrence is 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, a positive *C. difficile* stool toxin assay and a decision by the investigator (based on clinical assessment), that antibiotic treatment is needed. To inform subject care, a *C. difficile* stool test may be performed locally at the study site. Stool samples collected for suspected CDI recurrence will also be processed and shipped to a central laboratory for *C. difficile* stool testing (see Laboratory Manual for details of

central laboratory testing). The subject should not initiate antibiotic treatment for suspected CDI prior to providing a stool sample for the central laboratory stool testing. Data from the *C. difficile* toxin assay performed at the central laboratory (either enzyme immunoassay [EIA] or cell cytotoxicity neutralization assay [CCNA]) 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.

An independent data safety and monitoring committee (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 schedule of assessments and procedures is provided in Table 1.

6. STUDY OBJECTIVES

6.1. Primary Efficacy Objective

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

6.2. 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

6.3. Primary Safety Objective

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

6.4. 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

7. STUDY ENROLLMENT AND WITHDRAWAL

7.1. 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, or their legally authorized representative, must be willing 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 agrees to discontinue probiotics at time of consent and will not take probiotics for the duration of the study.

7.2. 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 past 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.

7.3. Subject Monitoring and Withdrawal

7.3.1. Reasons for Withdrawal

Subjects should continue to be followed for safety assessments up to 24 weeks after treatment, even after a CDI recurrence. However, a subject may withdraw from the study at any time for any

reason, without any consequence. In addition, a subject may be withdrawn from the study for reasons including the following:

- AE (typically an SAE)
- Subject choice (withdrawal of consent by subject or their legally authorized representative; investigator will attempt to ascertain reason)
- Protocol violation/noncompliance

7.3.2. Handling of Withdrawals and Discontinuations of Treatment

The primary reason for withdrawal from the study will be recorded in an electronic case report form (eCRF). Subjects who voluntarily withdraw, or who are withdrawn from the study will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 10.3.3. Although subjects are free to withdraw at any time, subjects will be encouraged to remain in the study for follow-up safety evaluation.

Those subjects who withdraw from the study will be referred to a physician for follow-up care.

7.3.3. Lost to Follow-up

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

7.3.4. Termination of Study

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

8. INVESTIGATIONAL PRODUCT

8.1. SER-109

SER-109 is an ecology of bacterial spores enriched from stool donations obtained from healthy, screened donors. SER-109 is formulated as an oral capsule for administration to patients following cessation of antibiotic therapy.

8.1.1. Donor Screening

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

8.1.2. Manufacturing

SER-109 is manufactured using current Good Manufacturing Practice (GMP). Stool raw material is sourced from donors who are screened for health history, physical status, and a panel of pathogen tests; materials from a single donor are pooled to make a manufacturing lot. The manufacturing process inactivates non-spore forms of live bacteria and fungi, and potential parasites and viruses, and substantially reduces the amount of undigested food and inactivated non-spore components via successive separation steps. The purified material is then concentrated to enable oral capsule formulation, stored frozen, and quality control tested until formulation.

8.2. Placebo

Placebo will be identical to the investigational product but will not contain product spores or non-spore solids. [redacted]

8.3. SER-109 and Placebo Kits Storage and Handling

The investigational product (SER-109) and placebo will be provided as a per subject kit to include 3 bottles, each containing four size 00 capsules ([redacted]) in an opaque, 40 mL high density polyethylene container sealed with foil.

The SER-109 and placebo are odorless and tasteless as prescribed. If chewed or if capsule integrity is compromised, SER-109 and placebo have a sweet taste.

Instructions for shipment, storage, accountability, reconciliation, and destruction of study drug are provided in the Investigator Site File.

8.4. Compliance

Subjects will be instructed to return all unused medication and all used packaging materials to the clinic at the Week 8 visit. Subject compliance to study drug will be checked by the investigator or their designee(s) and documented in the CRFs (e.g., tablet count). Subjects will be instructed to take all study drug doses in the morning after an overnight fast (nothing by mouth except for small amounts of water) of ≥ 8 hours. Subjects will be asked to remain fasting for 60 minutes following dosing. Subjects must come to the clinic or self-administer drug at home on Day 2 and Day 3.

8.5. 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 on Day 1 to receive either a single dose of [redacted] of SER-109 in 4 capsules daily for 3 days or a single dose of matching placebo in 4 capsules 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 each age group and type of antibiotic used to treat the qualifying CDI episode 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 of double-blinded study medication that will be available at the study site for that subject and visit. 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 is returned unopened.

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

8.6. 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. This data will be used for the 8-week efficacy and safety data analysis. The 12-week cut-off is used to preserve blinding of all efficacy and safety data up to Week 12, which is the primary efficacy timepoint for the EMA. Only a small team at Seres Therapeutics, specifically the Chief Medical Officer or designee, the Senior Vice President of Regulatory Affairs, and Statistical Consultant IMD will have access to the unblinded tables, listings and figures (TLFs) at this time.

8.7. Concomitant Medications

8.7.1. Prohibited Concomitant Medications/Procedures

The following therapies are prohibited for the duration of the study:

- Probiotics
- Loperamide
- Diphenoxylate/atropine
- Cholestyramine
- Opiate treatment unless on a stable dose. Note: Short term opiate use is permitted (e.g., for a dental extraction).
- Oral Fidaxomicin, oral metronidazole, oral vancomycin, used to treat for anything else other than suspected or confirmed CDI recurrences
- Fecal Microbiota Transplantation (FMT) prior to recurrence in the study

8.8. Criteria for Confirmed *Clostridium difficile* Recurrence Post-Randomization

Subjects suspected of having CDI will be asked to contact the investigator and return to the clinic for a *C. difficile* stool toxin test and evaluation for recurrence of CDI (Recurrence Visit) (see Section 10.3.3).

Subjects must fulfill the following criteria:

1. ≥ 3 unformed stools per day over 2 consecutive days
   - Diarrhea should continue up until the day antibiotics to treat CDI are initiated.
2. A positive *C. difficile* test on a stool sample determine by a toxin assay
   - A *C. difficile* stool test may be performed at the local laboratory to inform subject care; the central laboratory result will be used for the primary endpoint analysis. The central laboratory results will be communicated to the investigator.
3. Assessment by the investigator that the clinical condition of the subject warrants treatment

9. STUDY PROCEDURES

The schedule of assessments and procedures is presented in Table 1.

9.1. Duration of Participation

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

9.2. Medical History

At the time of Screening, subjects will be evaluated for inclusion and exclusion criteria, and medical history will be obtained with particular attention to prior CDI history (≥ 3 episodes of CDI within the previous 12 months is required). Documented history must be obtained for 2 episodes of CDI within the previous 12 months, inclusive of the current episode. Documentation must include 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.

9.3. Physical Examination

A physical examination will be conducted by a physician at the timepoints indicated in Table 1. A focused history and physical will be conducted at Week 8 and at the Early Termination Visit or any Recurrence Visit to the study site, if applicable.

9.4. Body Weight and Height

Body weight will be obtained at all in-clinic visits according to the schedule in Table 1. Height will be obtained at the in--clinic Screening Visit only.

9.5. Vital Signs

Vital sign assessments including systolic and diastolic blood pressure, pulse, respiratory rate, and oral body temperature measurements will be obtained at the visits indicated in Table 1. Vital sign assessments on Day 1 should be obtained immediately before and approximately 30 minutes after dosing. In addition, oral body temperature measurements will be obtained by the subject on Days 4-10 and documented on the Solicited AE diary.

9.6. Laboratory Assessments

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

9.6.1. Hematology and blood chemistry

Blood samples for hematology and blood chemistry will be obtained according to the schedule in Table 1. Blood samples for hematology and blood chemistry obtained on Day 1 (pre-dose) will be used to determine baseline data, but will not be used to confirm eligibility criteria.

The central laboratory will flag subjects if they have all of the following abnormal laboratory results:

- Alanine aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) ≥ 3 x ULN
- Total bilirubin > 2 x ULN

- Alkaline phosphatase < 2 x ULN

These subjects meet the conditions of a Hy's Law case, and should be reported in the same manner as an SAE (see Section 11.1).

9.6.2. Urinalysis

Urine dipstick testing will be performed at the study site according to the schedule in Table 1. If results for nitrates or leukocytes are positive, the urine sample may be sent to the central laboratory for analysis at the discretion of the investigator.

9.6.3. Pregnancy Testing

Women of childbearing potential (WOCBP) will have serum pregnancy tests at Screening, and a urine pregnancy test before dosing on Day 1, at Week 8, and at the ET visit or any recurrence visit, if applicable.

9.7. Stool Sample Collection and Analysis

Subjects will be asked to collect stool at home or in the clinic according to the schedule in Table 1. The sample collected on Day -1 may be brought to the study site for the Day 1 Visit. If the subject is unable to bring the stool sample to the study site for any visit, arrangements may be made to pick up the sample at the subject's home and bring it to the study site or may ship directly to the central laboratory (i.e., home visit by nurse or courier). Samples brought to the study site will be processed and then shipped to a central laboratory according to procedures defined in the Laboratory Manual. Stool collection kits will be provided to the subjects by the study sites.

C. difficile isolation and ribotype analysis will be performed on stool samples obtained at Screening and at a Recurrence (if applicable). If the sample obtained at Screening is not available for ribotyping, a portion of the stool sample collected prior to the bowel cleanse on Day -1 should be used for ribotype analysis. Microbiome and metabolomics testing may be performed on some or all stool samples collected on Day -1 (prior to administering the bowel cleanse), at Week 1, Week 2, Week 8, Week 24 (for microbiome testing only), and at the Early Termination Visit or any Recurrence Visit to the study site, if applicable.

If recurrent CDI is suspected, to inform subject care, a *C. difficile* test can be performed by a CLIA -certified local laboratory using an FDA-approved test in order to inform subject treatment. Stool samples collected for suspected CDI recurrence must also be processed and shipped to a central laboratory for *C. difficile* stool testing and *C. difficile* isolation and ribotyping (see Laboratory Manual for details of *C. difficile* testing performed at the central laboratory). The subject should not initiate antibiotic treatment for suspected CDI prior to providing a stool sample for the central laboratory stool testing. 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 their assessment.

9.8. Biological Specimen Collection for Future Biomedical Research

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

9.9. Monitoring of Diarrheal Symptoms and General Health

Subjects will be instructed to complete a daily diarrhea log (see Investigator Site File) to include days with diarrhea as well as no diarrhea. At all scheduled telephone calls and study site visits, subjects will be queried regarding general well-being; AEs; diarrheal symptoms, including the day, frequency, and quality of bowel movements described as diarrhea; and concomitant medications according to a standardized questionnaire. Any subject suspected of having an episode of CDI per protocol definition (≥ 3 unformed stools per day lasting ≥ 2 consecutive days) will be asked to come in for an in-clinic visit, where possible, for a *C. difficile* stool toxin test and evaluation for recurrence of CDI (see Section 10.3.3). In addition, subjects will use a patient-reported diary card to capture solicited adverse events for 7 days after Day 3 of study drug (Day 4 through Day 10).

9.10. Health Outcome Assessment

Information such as mortality from any cause, hospitalizations, and hospital length of stay (in days), including days in the intensive care unit, will be collected as part of the health outcomes assessment throughout this study.

9.11. Quality of Life Assessment

The EQ-5D-5L is a standardized measure of health status. The CDiff32 HRQoL is a newly developed and validated health-related quality of life questionnaire specific to patients with CDI (Garey et al, 2016). Subjects will complete the EQ-5D-5L and Cdiff32 HRQoL at the time points indicated in the Schedule of Assessments (Table 1).

9.12. Clinical Response Evaluation

Recurrence of CDI will be determined by the investigator based on the following definition:

- A CDI episode is defined as ≥ 3 unformed stools per day over 2 consecutive days with a positive *C. difficile* stool 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.

If subjects experience diarrhea symptoms (≥ 3 unformed stools per day for 2 consecutive days) or suspect a CDI episode, they should contact the investigator immediately (including on weekends) to arrange a Recurrence Visit for clinical evaluation and a *C. difficile* stool toxin test. The subject should not initiate antibiotic treatment for suspected CDI until instructed to do so by the investigator, after providing a stool sample for the central laboratory stool testing.

10. STUDY SCHEDULE

The Schedule of Assessments and Procedures is presented in Table 1. Study days are relative to the oral administration of the first dose of study drug on Day 1. Assessments will be performed and noted in each subject's chart or record. As necessary for safety of subject, study visits including *Week 2, Week 8, Unscheduled, and Early Termination,* may be conducted remotely at subject's home, with qualified nurse or site personnel who will be appropriately documented on the site's delegation log to perform these Remote Study Visits and associated procedures. If a nurse or site personnel cannot perform the visits, a telephone call or a video conference (Zoom, Skype, FaceTime, etc.) should be conducted in place of the Week 2, Week 8, Unscheduled, and Recurrence / Early Termination visits and must be documented in the source. Any required procedures not performed during a remote visit at the subject's home will be documented as a protocol deviation by site staff. The option of additional home visits was added to maintain follow-up when subjects were not able to be seen in the clinic for planned study visits due to COVID-19.

10.1. Screening Period

10.1.1. Clinic Visit (Day -24 to Day -2)

- After a full explanation of the study protocol, have each subject (or their legally authorized representative) sign an informed consent form (ICF) before performance of any study related activity (including Screening activities).
- Register subject in the IxRS.
- Assess each subject to ensure all inclusion criteria are met and no exclusion criteria are met.
- Perform diarrhea assessment:
  - a) If subject is suspected of having active CDI (≥ 3 unformed stools per day for 2 consecutive days), a *C. difficile* test on unformed stool should be sent to the central lab for *C. difficile* testing by a toxin assay.
  - b) If subject is already taking antibiotics for an active CDI, ensure that the regimen is consistent with the protocol (i.e., 10 to 21 days of standard of care antibiotics, defined as treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID], but excluding pulse tapered antibiotic regimens). Arrange to have stool sample from the local laboratory that performed the *C. difficile* diagnostic testing shipped to the central laboratory for *C. difficile* stool testing (see Laboratory Manual). If a stool sample is no longer available and the subject had a positive *C. difficile* test on a stool sample determined by a toxin assay by the local laboratory, then the subject may be included. Verify that subject can be dosed with study drug within 4 days of standard-of-care antibiotic completion.
  - Ship stool sample to central laboratory for *C. difficile* isolation and ribotyping.

  - As necessary, prescribe a 10- to 21-day standard of care antibiotic regimen (defined as treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID], but excluding pulse tapered antibiotic regimens) to control CDI.

- Obtain prior and concomitant medication use within the 8 weeks before anticipated randomization, including prior antibiotic or immunosuppressive medication use that may affect eligibility.
- Obtain medical history, including baseline conditions. Documented history of 2 or more episodes of CDI within the previous 12 months, inclusive of the current (qualifying) episode, including dates, test results, and antibiotic treatments received must be obtained. 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. In addition, the following information should be obtained:
  - Use of antibiotics before the study and the duration of their use
  - Use of proton pump inhibitors or antacids before the study
  - Information about the strain(s) of *C. difficile* responsible for the previous infections, if available
- Perform a physical examination, including vital sign measurements (i.e., blood pressure, pulse, respiratory rate, and body temperature), height, and weight.
- Collect blood and urine samples and ship to the central laboratory for evaluation of:
  - Blood chemistry
  - Hematology
  - Urine dipstick performed at the study site; if positive for nitrates and/or leukocytes, sample may be sent to central laboratory for analysis at the investigator's discretion
  - Serum pregnancy test, if applicable
- Instruct subjects that, should they enroll in the study, they will need to meet the following requirements:
  - If subject is currently taking a probiotic, subject must stop taking it for the duration of the study.
  - On any day from Day -4 to Day -2, subject is to take their last dose of standard of care antibiotic treatment for their CDI.
  - On Day -1, before beginning the magnesium citrate or GoLytely (polyethylene glycol electrolyte solution) bowel cleanse, subject is to collect a stool sample.
  - On the evening of Day -1, subject must take 1 bottle (10 oz/~300 mL) of magnesium citrate (or, for subjects with impaired kidney function, 250 mL of GoLytely [polyethylene glycol electrolyte solution]) followed by a fast (no food or drink other than small amounts of water) for ≥ 8 hours before receipt of study drug until at least 1 hour after receipt of the study drug the next day.

- On Day 1, subject must take 4 oral capsules of study drug and continue their fast for 1 hour after dosing.
- Subjects who do not arrange in-clinic visits on Days 2 and 3, will receive a 2-day supply of study drug with instructions for home administration of single daily doses in the morning before breakfast on Day 2 and Day 3.
- Stool samples will be collected by the subject at home and brought to the clinic at Screening, Day-1, Week 1, Week 2, Week 8, Week 24, and at the Early Termination Visit or any Recurrence Visit (if applicable). If the subject is unable to bring the stool sample to the study site for any visit, arrangements may be made to pick up the sample at the subject's home and bring it to the study site or may ship directly to the central laboratory (i.e., home visit by nurse or courier). Samples brought to the study site will be processed and then shipped to a central laboratory according to procedures defined in the Laboratory Manual. Stool collection kits will be provided for these at home collections.
- Subjects are to contact the investigator immediately (including on weekends) if they experience diarrheal symptoms or suspect a CDI episode to arrange a Recurrence Visit (see Section 10.3.3) for clinical evaluation and a *C. difficile* stool toxin test. Advise subjects that antibiotic treatment should be initiated only after a positive *C. difficile* test, and clinical assessment by the investigator.
- Provide paper diarrhea log at the screening visit (Day-24 to Day -2) and instruct subject to complete the log daily

10.1.2. Pre-treatment Preparation Phone Call Visit (Day -4 to -2)

Contact subject by phone to:

- Perform diarrhea assessment to ensure that subject's diarrhea has been controlled (< 3 unformed stools per day for 2 consecutive days).
- Review concomitant medications.
- Remind subject to not take antibiotics beyond Day -2.
- Remind subject to collect a stool sample before beginning the magnesium citrate or GoLytely (polyethylene glycol electrolyte solution) bowel cleanse on Day -1.

10.1.3. Pre-treatment Preparation Phone Call Visit (Day -1)

Contact subject by phone to:

- Ensure all inclusion criteria continue to be met and no exclusion criteria are met, including that subject's CDI has responded to antibiotics without diarrhea over the previous 2 days (< 3 unformed stools per day).
- Ensure subject has discontinued antibiotics to control CDI symptoms, and has had their last dose of antibiotic on any day from Day- 4 to Day -2.
- Remind subject to collect a stool sample before beginning the magnesium citrate or GoLytely bowel cleanse.

- Ensure subject consumes a 10 oz (~300 mL) bottle of magnesium citrate (or, for subjects with impaired renal function, 250 mL of GoLytely and is prepared to fast overnight (no food or drink other than small amounts of water for ≥8 hours) before anticipated receipt of study drug.
- Review concomitant medications.
- Remind subject to bring their Day -1 stool sample collected at home to the study site to be processed for shipment to the central laboratory.

10.2. Efficacy Period

10.2.1. Clinic Visit (Day 1)

10.2.1.1. Before Administering Study Drug (Pre-dose)

- Assess subject to ensure all inclusion criteria are met and no exclusion criteria are met, including that subject's CDI has responded to antibiotics without diarrhea for the previous 2 days (< 3 unformed stools per day).
- Review concomitant medications and update information regarding prior medication use. Confirm that subject took their last dose of standard of care antibiotic treatment for their CDI on any day from Day -4 to Day -2.
- Ensure subject consumed a 10 oz (~300 mL) bottle of magnesium citrate or 250 mL of GoLytely on Day -1.
- Ensure subject is undergoing a fast (no food or drink other than small amounts of water) for ≥ 8 hours before anticipated receipt of study drug.
- Obtain stool sample from subject's Day -1 at home collection and process, store, and ship per Laboratory Manual.
- Perform a physical examination, including vital sign measurements (i.e., blood pressure, pulse, respiratory rate, and body temperature) and weight.
- Collect blood and urine samples for the following laboratory tests:
  - Blood chemistry
  - Hematology
  - Blood for future biomedical research
  - Serum for future biomedical research
  - Urine dipstick performed at the study site; if positive for nitrates and/or leukocytes, the sample may be sent to central laboratory for analysis at the discretion of the investigator
  - Urine pregnancy test, if applicable
- Assess AEs.
- Administer the EQ-5D-5L and CDiff32 questionnaires.

- Randomly assign subject to treatment by using the IxRS and obtain dose of study drug.
- Collect screening diary

10.2.1.2. Administering Study Drug

On Day 1, administer 4 study drug capsules orally with at least 8 oz of water (capsules are to be swallowed, not chewed).

10.2.1.3. After Administering Study Drug (Post-dose)

- Observe subject in the clinic for ≥ 60 minutes.
- Assess vital sign measurements (i.e., blood pressure, pulse, respiratory rate, and oral body temperature) approximately 30 minutes after dosing.
- Assess AEs.
- Provide subject with stool collection kits.
- Provide specific instructions on making entries into the diarrhea log/device daily
- Provide diary, thermometer and specific instructions on completing the Solicited Adverse Event Diary on Days 4-10
- Ensure subject continues to fast for a total of 60 minutes after dosing (post-dose).
- For subjects who do not arrange in-clinic visits on Days 2 and 3, dispense a 2-day supply of study drug according to treatment assignment at randomization to subjects with instructions for proper storage and home administration on Day 2 and Day 3. Release subject from the clinic upon authorization by the investigator.
- Investigators should manage subjects' expectations, they may have diarrhea early-on after receiving drug in the study.

10.2.2. Clinic Visit or Phone Call (Day 2)

Arrange an in-clinic visit or phone call to:

- Confirm administration of 2nd dose of study drug before breakfast
- Inquire about general health
- Perform diarrhea assessment:
  - Remind subjects they may have diarrhea early-on after receiving drug in the study
  - Remind subjects to complete the diarrhea log/device daily (see Investigator Site File)
- Assess AEs
- Review concomitant medications

10.2.3. Clinic Visit or Phone Call (Day 3)

Arrange an in-clinic visit or phone call to:

- Confirm administration of 3rd dose of study drug before breakfast.
- Inquire about general health
- Perform diarrhea assessment:
  - Remind subjects they may have diarrhea early-on after receiving drug in the study.
  - Remind subjects to complete the diarrhea log (see Investigator Site File)
  - Remind subjects to complete the Solicited Adverse Event Diary for Days 4-10
  - Remind subject to measure oral body temperature on Days 4-10 at the same time each day and record on the Solicited Adverse Event Diary
- Assess AEs
- Review concomitant medications
- Remind subject to bring their Week 1 stool sample collected at home to the study site to be processed for shipment to the central laboratory or make arrangements for a courier for delivery to the study site.

10.2.4. Phone Call Visit (Week 1)

Contact subject by phone at Week 1 (± 2 days).

- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.
  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, obtain stool sample. Complete Recurrence Visit assessments (see Section 10.3.3).
- Assess AEs.
- Review concomitant medications.
- Administer the CDiff32 questionnaire.
- Remind subject to bring their Week 1 stool sample collected at home to the study site to be processed for shipment to the central laboratory or make arrangements for a courier for delivery to the study site. Remind subject to complete the Solicited AE Diary for Day 4 - Day 10 and bring to their Week 2 Visit (if in-clinic) or provide to health care provider attending the home visit.

10.2.5. Clinic or Home Visit & Phone call (Week 2)

Arrange for a home visit or an in-clinic visit at Week 2 (± 2 days) to:

- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.

  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, obtain stool sample. Complete Recurrence Visit assessments (see Section 10.3.3).
- Assess AEs.
- Review concomitant medications.
- Collect a blood sample and a stool sample.
- Collect the Solicited Adverse Event Diary

10.2.6. Phone Call Visits (Weeks 3-7)

Contact subject by phone at Weeks 3-7 (± 2 days).

- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.
  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, arrange a Recurrence Visit (see Section 10.3.3).
  - Advise subject to continue diarrhea log, and collect stool sample for the Recurrence Visit.
  - Advise subject to not initiate antibiotic treatment for CDI until advised to do so by the study investigator.
- Assess AEs.
- Review concomitant medications.
- Remind subject to bring their Week 8 stool sample collected at home to the study site to be processed for shipment to the central laboratory.

10.2.7. End of Efficacy Period Clinic Visit (Week 8)

Subjects will be seen in the clinic at the study site or in a home visit at Week 8 (± 2 days). Subjects with a confirmed CDI recurrence prior to Week 8 may enroll in the SERES-013 open-label extension study, if eligible, and are not required to have completed their Week 8 visit. Subjects who do not choose to enroll in the SERES-013 study or subjects with a confirmed recurrence after Week 8 should continue to be followed for safety assessments through Week 24.

- Obtain stool sample from subject's Week 8 at home collection and process, store, and ship per Laboratory Manual.
- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.

  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, obtain stool sample. Complete Recurrence Visit assessments (see Section 10.3.3).
- Assess AEs.
- Review concomitant medications.
- Perform a focused history and physical exam.
- Collect blood and urine samples for the following laboratory tests:
  - Blood chemistry
  - Hematology
  - Serum for future biomedical research
  - Urine pregnancy test, if applicable
- Administer subject to complete the EQ-5D-5L and CDiff32 questionnaires.
- Provide subject with stool collection kits as necessary.
- If subject has had a confirmed recurrence and has agreed to enroll in SERES-013, instruct subject to continue completing diarrhea log daily on SERES-012 device until they randomize on Day 1 of SERES-013

10.3. Follow-up Period

10.3.1. Phone Call Visits (Every 4 Weeks)

Contact subject by phone at Weeks 12, 16 and 20 (± 3 days) to:

- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.
  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, arrange a Recurrence Visit (see Section 10.3.3)
  - Advise subject to continue diarrhea log, and collect stool sample for the Recurrence Visit
  - Advise subject not to initiate antibiotic treatment for CDI until advised to do so by the study investigator.
- Assess AEs.
- Review concomitant medications.
- Remind subject to bring their Week 24 stool sample collected at home to the study site to be processed for shipment to the central laboratory or make arrangements for a courier for delivery to the study site.

10.3.2. Phone Call Visit - Study Completion (Week 24)

Contact subject by phone at Week 24 (± 3 days) to:

- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI, obtain information regarding the day, frequency, and quality of bowel movements during diarrheal episodes.
  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, obtain stool sample. Complete Recurrence Visit assessments (see Section 10.3.3).
- Assess AEs.
- Review concomitant medications.
- Instruct subject to complete the EQ-5D-5L questionnaire
- Remind subject to bring their Week 24 stool sample collected at home to the study site to be processed for shipment to the central laboratory or make arrangements for a courier for delivery to the study site.

10.3.3. Recurrence and Early Termination (ET) Visits

Any subject suspected of having an episode of CDI per protocol definition (≥ 3 unformed stools per day over 2 consecutive days) will be asked to contact the investigator and return to the clinic or have a home visit for a *C. difficile* stool test and evaluation for recurrence of CDI. Additionally, all subjects will be seen in the clinic or have a home visit if the subject withdraws early from the study, whenever possible.

Subjects with a confirmed CDI recurrence prior to Week 8 may enroll in the SERES-013 open-label extension study, if eligible. Assessments performed during the Recurrence visit may be used for the Screening labs for SERES-013.

Perform the following assessments and procedures:

- Obtain stool sample from subject's at-home collection and process, store, and ship sample per Laboratory Manual.
- Perform diarrhea assessment:
  - If subject has a suspected episode of CDI that has not already been reported, obtain information regarding the day, frequency, and quality of bowel movements during diarrhea episodes.
  - If subject reports episode(s) of diarrhea (≥ 3 unformed stools per day) lasting 2 or more consecutive days, obtain stool sample. Ship stool to the central laboratory for *C. difficile* stool testing (see Laboratory Manual). The subject should not initiate antibiotic treatment for suspected CDI prior to providing a stool sample for the central laboratory stool testing. To inform subject care, a *C. difficile* test on unformed stool may be performed locally at the study site (see Laboratory Manual);

  - If the *C. difficile* test on a stool sample determined by a toxin assay performed by the Central Laboratory is positive and the investigator determines that antibiotic treatment is appropriate per protocol guidelines (see Section 8.8), prescribe standard of care antibiotic regimen to control CDI.
  - For this study, and to qualify for entry into SERES-013, CDI SOC antibiotic therapy are defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID].
  - Send stool sample to central laboratory *C. difficile* isolation and ribotyping
  - Advise subject to continue diarrhea log up until the day of initiation of antibiotic treatment for their CDI.
- Assess AEs.
- Review concomitant medications.
- Perform a focused history and physical exam.
- Collect blood and urine samples for the following laboratory tests:
  - Blood chemistry
  - Hematology
  - Serum for future biomedical research
  - Urine pregnancy test, if applicable
- Administer subject to complete the EQ-5D-5L and CDiff32 questionnaires (*Note: the CDiff32 questionnaire should only be completed for an ET or Recurrence Visit prior to Week 8).
- If subject did not have a recurrence prior to week 8 or if subject has had a recurrence and has chosen not to enroll in SERES-013, the subject should continue to complete the diarrhea log.
- If subject did have a recurrence prior to Week 8 and has chosen to enroll in SERES-013, this visit will be used as Screening Visit for SERES-013. Additionally, perform the following assessments:
  - Routine urine dipstick
  - Study drug accountability

    Note: Study drug may be returned to the study site by courier if the subject is unable to be assessed in the clinic.

11. ASSESSMENT OF SAFETY AND ADVERSE EVENT REPORTING

All AEs, SAEs/AESIs, and concomitant medications will be collected from the time of randomization up to Week 8. From Week 8 up to Week 24, all SAEs/AESIs and

SAE/AESI -related data, and any antibiotic medication and its corresponding indication will be collected.

The investigator is responsible for:

- Informing the sponsor in the event that a subject or a subject's partner becomes pregnant during the study. A "Pregnancy Report Form" will be generated and the pregnancy will be captured in the safety database and will be followed through to the outcome.
- Instructing subjects in the self-reporting of selected AEs including diarrhea and abdominal discomfort.
- Evaluating subject safety including assessment of AEs for seriousness, severity, and causality.
- Informing the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of AEs as required and SAEs as per IRB/IEC guidelines.

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

- Solicited Adverse Events will be captured on a diary card for Days 4 through Day 10 and entered into the CRF. For this study solicited Adverse Events include: Gas or flatulence, Abdominal distention or bloating, Abdominal pain or cramping, Nausea, Anorexia (Loss of appetite), Vomiting, Fatigue, Chills or Shivering, and Constipation. Additionally, diarrhea will be collected using a daily diarrhea log. For solicited AEs on Days 4-10, criteria for diarrhea severity will be as follows:
    - mild: 3-4 unformed bowel movements per day
    - moderate: 5-6 unformed bowel movements per day
    - severe: ≥7 unformed bowel movements per day
- Subjects will also be asked to measure body temperature on Days 4-10.

An SAE is any AE regardless of causality that:

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

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

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

In this protocol, 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.

All AEs, including SAEs and AESIs, will be graded for severity by using the common terminology criteria for adverse events' (Common Terminology Criteria for Adverse Events v4.0 (CTCAE) Publish Date: May 28, 2009, with the exception of diarrhea. Criteria for diarrhea severity is provided above. In general, the severity of AEs can be assessed using following guidelines:

Severity Description

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL)**

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

episode.

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

- Is associated with accompanying symptoms

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

Laboratory results that fall outside the reference range and do not meet one of the criteria above will not be reported as AEs. Repeating a test because of an abnormal result, in the absence of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error will not be reported as an AE.

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

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

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

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

Diarrhea

With regards to events of diarrhea, diarrhea that meets the protocol definition of CDI recurrence (≥ 3 unformed stools per day over 2 or more consecutive days, a positive *C. difficile* test on a stool sample determined by a toxin assay, and assessment by the investigator that treatment is required) should NOT be entered as an AE. Events of diarrhea that are not associated with CDI recurrence (e.g., due to food poisoning or flu), should be reported as an AE (e.g., Diarrhea [Not CDI related]). Other symptoms associated with CDI recurrence, e.g. abdominal pain, abdominal distension, should be reported as adverse events.

When CDI recurrence is deemed serious due to hospitalization, CDI recurrence should be included as an SAE term and recorded as the reason for hospitalization in the Health Care Utilization CRF page.

Additionally, diarrhea will be collected using a daily diarrhea log. For solicited AEs on Days 4-10, criteria for diarrhea severity will be as follows:

- mild: 3-4 unformed bowel movements per day

- moderate: 5-6 unformed bowel movements per day
- severe: ≥7 unformed bowel movements per day.

11.1. Serious Adverse Event Reporting

The sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the sponsor (or sponsor's designee) must be notified immediately regarding any SAE that occurs after administration of the study drug.

All SAEs must be reported to the sponsor or sponsor's designee ([redacted]) within 24 hours of knowledge of the event at the study site. Refer to the Investigator Site File for detailed instructions.

The study site will transmit an SAE report (SAER) to the sponsor or sponsor's designee by facsimile or email. The study site will be provided with SAER forms wherein the following information is requested:

- Subject identification, investigator name, and study site number
- SAE information: event term, onset date, severity, and causal relationship to study drug
- The outcomes attributable to the event (i.e. serious criteria) (e.g., death, life threatening, inpatient hospitalization, prolongation of existing hospitalization, a congenital anomaly, a persistent or significant disability or incapacity, or other important medical event)
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The date of study drug administration
- Whether or not the study drug was discontinued
- Supplemental information, which may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

In addition, relevant eCRF pages should be appended to communicate relevant study drug and subject outcome information.

The SAER should be faxed or emailed within 24 hours with as much of the above information as available at the time. The following minimum information is required for an initial SAE report: subject identification, reporting source (i.e., Site Name and Site Number), and an event or outcome. Supplemental information may be transmitted by using a follow-up report and should not delay the initial report. The sponsor may contact the study site to solicit additional information or follow-up on the event.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded in the appropriate pages of the subject's eCRF.

12. STATISTICAL METHODS

12.1. Study Endpoints

12.1.1. Primary Efficacy Endpoint

- 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. A recurrence is defined as ≥ 3 unformed stools per day for 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 assessment by the investigator that the clinical condition of the subject warrants antibiotic treatment.

12.1.2. Secondary Efficacy Endpoints

- Recurrence of CDI as determined by a PCR algorithm up to 8 weeks 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

12.1.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are the following:

- 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

12.1.4. Safety Endpoints

Safety endpoints are the following:

- Incidence of AEs, including solicited AEs from Days 4-10
- Laboratory evaluation results
- Vital sign measurements
- Physical examination findings

12.2. Analysis Population

There are four analysis populations:

- Intent to Treat (ITT) Analysis Population: All subjects who were randomly assigned, including those who were not exposed to any study drug, and will be analyzed based on the treatment to which they were randomly assigned. 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.
- Modified Intent to Treat Analysis Population: All subjects who were randomly assigned and received any amount of study drug, whose CDI was clinically controlled by antibiotic treatment before receiving study drug, and who have at least 1 post-baseline evaluation. 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.
- Per Protocol (PP) Population: Subjects from the mITT Population who do not have any major protocol deviations. Forced randomizations are considered to be major protocol deviations and therefore, subjects who are randomized using forced randomization will be excluded from PP Population. The PP Population will be detailed in the SAP and defined before unblinding of the data.
- Safety Population: The Safety Population will consist of all randomly assigned subjects who received 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.

12.3. Determination of Sample Size

The original planned sample size for this study was 160 subjects per treatment group for a total sample size of 320 subjects. However, due to the competition for subjects because of the increasing acceptance of fecal microbiota transplants (FMT) by physicians as a treatment option

for recurrent CDI and its provision without the need for an IND under the FDA's guidance of Enforcement Discretion, the 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.

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:

- 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.

12.3.1. 8-Week Efficacy and Safety Data Analysis

SER-109 is a Breakthrough Therapy Designated product that has the potential to address the significant unmet medical need of recurrent CDI. SERES-012 is a Phase 3 study which, as discussed with the FDA, has the potential to provide the basis for BLA approval. In order to expedite the clinical development plan for SER-109, FDA agreement was obtained to conduct an unblinded analysis of the 8-week efficacy and safety endpoints when all planned subjects in the study are enrolled, have been evaluated for the primary efficacy endpoint and have completed their 8-week visit. Key efficacy and safety summary tables will be generated. Only a small team at Seres, specifically the Chief Medical Officer, the Senior Vice President of Regulatory Affairs and a Statistical Consultant, IMD will have access to the unblinded tables, listings and figures (TLFs) at this time.

While the primary efficacy timepoint for the FDA is 8 weeks, the primary efficacy timepoint for the EMA is 12 weeks. Therefore, all clinical data up to the 12-week visit for all subjects enrolled

in the study will be entered in the database, cleaned and locked prior to the unblinding. No changes to any locked data in the database will be permitted, unless deemed to be highly warranted. Therefore, all efficacy results evaluated up to the Week 12 timepoint will be considered final. A comparison of the data at the time of the 12-week unblinding and at the end of the study will be performed. An audit trail of any changes made to the locked data will be available.

Before the 12-week efficacy data is declared complete and final, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. The 12-week cut-off is used in order to preserve blinding of all efficacy and safety data up to Week 12.

Any deviations from the planned analyses will be described and justified in the final clinical study report.

12.4. General Statistical Considerations

Inferential statistical analyses of the primary and secondary endpoints will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for dichotomous or categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for SER-109 versus placebo. Inferential tests and confidence intervals for efficacy results will be based on methods for stratified analysis, where the stratification variables are age (<65 years; ≥65 years) and type of antibiotic treatment for the qualifying episode (vancomycin vs. fidaxomicin). Exploratory analyses may also be performed. Listings of individual subject data will be produced.

Additional details of the statistical analysis will be addressed in a comprehensive SAP, finalized prior to database lock and data unblinding.

12.5. Subject Populations and Baseline Characteristics

Enrollment, protocol deviations, and discontinuations from the study will be summarized by treatment group and stratum for the ITT Population. Demographics (age, race, ethnicity, sex) and baseline characteristics (weight, height, body mass index (BMI)), and number of previous CDI episodes will be summarized by treatment group in the ITT, mITT, Safety and PP Populations. Additionally, the demography and baseline characteristics will also be presented by stratum for the ITT and Safety populations.

12.6. Study Drug Exposure

The number and percentage of subjects by treatment group and stratum will be summarized for the total number of capsules taken by a subject. The summary will be presented for the Safety, ITT, and mITT Populations.

12.7. Efficacy Analysis

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomly assigned.

12.7.1. Multiplicity Adjustments

Adjustments for multiple testing will be made for testing the primary efficacy endpoint for Ho: RR ≥ 1.0 and Ho: 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:

- H_1: RR ≥ 1.0
- 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.

12.7.2. Primary Efficacy Analysis

The primary measure of efficacy will be the relative risk (RR) of CDI recurrence as determined by a toxin assay 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), as well as antibiotic regimen for the qualifying episode (vancomycin; fidaxomicin). Rules for imputing CDI recurrence status for subjects with missing data are in the SAP, which includes a complete list of imputed recurrence status for subjects who have at least one component of the CDI recurrence endpoint criteria missing.

The CMH estimate of the common relative risk, stratified by age and baseline type of antibiotics, will be reported. The confidence interval (CI) for the common RR will be obtained using the Greenland and Robins variance estimate for the natural logarithm of the common RR.

12.7.2.1. Additional Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy outcome in the ITT Population will also be conducted using similar methods described in the preceding section as follows:

- All subjects who are lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence before Week 8 will be considered to have a favorable outcome in both treatment groups. Subjects who miss any contact with the study site before Week 8 (phone calls or Week 2 visit) but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the Week 8 visit will be defined as having a favorable outcome for this analysis.

- Subjects who are lost-to-follow-up, terminated the study prematurely, or died without having a CDI recurrence before Week 8, or who have missing data 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. Subjects who miss any contact with the study site before Week 8 (phone calls or Week 2 visit) but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the Week 8 visit will be defined as having a favorable outcome for all subjects this analysis.
- The primary efficacy analysis will also be performed without adjustment for stratification by age and type of antibiotic for the qualifying episode.

Analysis of the primary efficacy outcome will also be conducted in the mITT and PP Populations as additional sensitivity analyses.

Differences in the proportions of subjects with CDI recurrence between treatment groups will be tested by using the CMH test, stratified by age (<65 years, ≥65 years) and type of baseline antibiotics (vancomycin vs. fidaxomicin). Ninety-five percent (95%) CIs will also be provided for the difference between the treatment groups in the proportion of subjects with a CDI recurrence, adjusted for the age and type of baseline antibiotics stratification factors using CMH weights with methods as described in Kim and Won (2013).

Sustained clinical response rate (%), the proportion of subjects who have not had a recurrence by 8 and 12 weeks of SER-109 group (1-P1) and the placebo group (1-P2) and its 95% CI, as well as the p value 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 - recurrence rate, the test for the sustained clinical response is the same test as the one for the recurrence rate difference.

12.7.3. Secondary Efficacy Analyses

12.7.4. Analyses of Secondary Endpoints

Time to recurrence of CDI will be summarized by treatment group, and age and type of baseline antibiotics stratum for the ITT and mITT Populations by using the median and 25th and 75th percentiles from a Kaplan-Meier analysis. 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 type of baseline antibiotics (vancomycin, fidaxomicin). Kaplan-Meier estimates for the separate age and baseline antibiotics 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 type of baseline antibiotics stratum.

The RR of CDI recurrence of SER-109 to placebo and 95% CIs for the RR at 4, 12 and 24 weeks after treatment will be analyzed using the same method described for the primary efficacy endpoint analysis. The number and percentage of subjects who have recurrence of CDI up to 4, 12 and 24 weeks after treatment will be presented by treatment group for the ITT and mITT Populations.

The RR of CDI recurrence of each SER-109 donor lot to placebo up to 8 weeks after treatment will also be assessed in the ITT population. The same analysis as described for the primary efficacy analysis will be conducted for each SER-109 donor lot comparison to placebo.

12.8. Exploratory Analysis

Planned analyses of the exploratory efficacy endpoints will be detailed in the SAP.

12.9. Safety Analysis

All safety analyses will be conducted in the Safety Population, unless specified otherwise. Subjects will be analyzed according to the treatment they actually receive, rather than that to which they are randomly assigned. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Safety summaries will be presented by treatment group on Day 10, Week 2, Week 8 and Week 24 (End of Study), with selected safety summaries also presented by age and type of baseline antibiotics stratum. A listing of all AEs, including those occurring before the start of study drug, will be provided.

A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity after initiation of study drug. The number and percentage of subjects with TEAEs will be tabulated by system organ class and preferred term (PT) for each treatment group and stratum. Serious TEAEs and TEAEs leading to study discontinuation will be similarly tabulated. Summaries of TEAEs by maximum severity and by maximum relationship to study drug will also be summarized by system organ class and PT.

In addition to summaries of all TEAEs, the incidence of TEAEs and TEAEs related to treatment occurring before the subject received antibiotics for recurrence of CDI will be tabulated by system organ class and PT for each treatment group and stratum, and by severity and relationship to study drug.

All preceding AE summaries will be presented by treatment group, and selected safety summaries also presented by age and type of baseline antibiotics stratum, on Day 10, Week 2, Week 8 and Week 24 (End of Study).

A summary of solicited AEs from Days 4 to 10 by treatment group will be provided. A similar summary will also be provided by treatment group and stratum.

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 8 (up to Week 24 for SAEs or AESIs), including TEAEs for subjects who did not receive antibiotics for treatment of CDI

before Week 8 (up to Week 24 for SAEs or AESIs). Incidence rates per 100 person years will be presented for the following: 1) subjects with at least one SAE; 2) subjects with at least one 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 8 (or Week 24 for SAEs or AESIs) 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 8 (or Week 24 for SAEs or AESIs) 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 8 (or Week 24, if SAEs or AESIs). 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.

Descriptive statistics of the laboratory parameters and vital sign measurements will be presented by treatment group for all study visits at which they were collected. The change from Baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarized by treatment group. Laboratory parameters will be defined as within or outside normal limits, and shift tables from Baseline to each post-baseline visit will be provided by treatment group.

12.10. Handling of Missing Data

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

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 are defined as having an unfavorable outcome for the primary analysis. Subjects who miss any contact with the site before Week 8 (phone calls or Week 2 visit) but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent telephone contact or by Week 8 will be defined as having a favorable outcome for the primary analysis. If the Week 8 visit is missed, a subject will be considered as having an unfavorable outcome for the primary analysis if he reports 2 or more consecutive days with ≥ 3 unformed stools at the next unmissed telephone contact or visit. If any of the 3 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 3 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. The imputed recurrence status for subjects who have at least one component of the CDI recurrence endpoint criteria missing will be detailed in the SAP.

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. Sensitivity analyses of the time to recurrence endpoint will be provided in the SAP.

No other imputations for missing data will be made (except as detailed in the SAP for missing dates and times).

13. ADMINISTRATIVE REQUIREMENTS

13.1. Good Clinical Practice

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

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

13.2. Trial Governance and Oversight

This study was developed in collaboration with a Clinical Advisory Committee, which comprises both sponsor employed and independent scientific experts who provide input on study design, interpretation of study results, and subsequent peer reviewed scientific publications.

13.3. Ethical Considerations

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

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

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

13.4. Subject Information and Informed Consent

Before any testing under this protocol, including screening tests and assessments, written informed consent with the IRB/IEC approved ICF must be obtained from the subject or their legally authorized representative (LAR), in accordance with local practice and regulations.

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

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

13.5. Subject Confidentiality

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

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

13.6. Protocol Compliance

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

13.7. Future Use of Stored Specimens

The sponsor may, where permitted by local regulations, conduct future biomedical research on specimens (including blood, serum, and stool) routinely and specifically collected during this clinical study for potential commercial use by Seres Therapeutics, Inc., and specimens may be stored for up to 10 years. This research may include genetic analyses of DNA/RNA and/or the measurement of other analytes.

13.8. Study Monitoring

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

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

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

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

13.9. Case Report Forms and Study Records

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

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

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

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

13.10. Study Completion

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

- Laboratory findings, clinical data, and all special test results from the time of informed consent through the End of Study Visit at Week 24
- Electronic CRFs properly completed by appropriate study personnel and signed and dated by the investigator
- Complete study drug accountability records
- Copies of IRB/IEC approval and notification of the original protocol and of any protocol amendments, if appropriate
- A summary of the study prepared by the investigator (an IRB/IEC summary letter is acceptable)

14. LIST OF REFERENCES

Anderson MJ, Walsh DCI. PERMANOVA, ANOSIM, and the Mantel test in the face of heterogeneous dispersions: what null hypothesis are you testing? Ecol Monogr. 2013;83(4):557 74.

Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, et al; Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011 Dec;9(12):1044 9.

Centers for Disease Control and Prevention. Clostridium difficile infection. Available from: http://www.cdc.gov/hai/organisms/cdiff/Cdiff_infect.html. Accessed 2015 Mar 01.

Chao A. Nonparametric estimation of the number of classes in a population. Scand J Statist. 1984;11(4):265 70.

Colwell RK, Coddington JA. Estimating terrestrial biodiversity through extrapolation. Philos Trans R Soc Lond B Biol Sci. 1994 Jul 29;345(1311):101 18.

Cui L, Hung HMJ and Wang, SJ. Modification of Sample Size in Group Sequential Trials. Biometrics. 1999 Sep; 55:853 57.

Depestel DD, Aronoff DM. Epidemiology of Clostridium difficile infection. J Pharm Pract. 2013 Oct;26(5):464 75.

Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Statistics In Medicine. 1990 May;1447-1454.

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.

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

Garey KW, Aitken SL, Gschwind L, Goddu S, Xie Y, Duff C, et al. Development and validation of a Clostridium difficile health-related quality-of-life questionnaire. J Clin Gastroenterol. 2016 Sep;50(8):631-7.

Higa JT, Kelly CP. New drugs and strategies for management of Clostridium difficile colitis. J Intensive Care Med. 2013 Feb 7;29(4):190 9.

Hughes JB, Hellmann JJ, Ricketts TH, Bohannan BJ. Counting the uncountable: statistical approaches to estimating microbial diversity. Appl Environ Microbiol. 2001 Oct;67(10):4399 406.

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

Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015 Feb 26;372(9):825 34.

Levy A. et. al. (2015) Incidence and Costs of Clostridium difficile Infections in Canada, OFID, 1-10.

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 29, 2009, NIH publication # 09-7473

Ng KM, Ferreyra JA, Higginbottom SK, Lynch JB, Kashyap PC, Gopinath S, et al. Microbiota liberated host sugars facilitate post antibiotic expansion of enteric pathogens. Nature. 2013 Oct 3:502(7469):96 9.

Polange, CM, Gyorke CE, Kennedy MA, Leslie JL, Chin DL, Wang S, et al. Overdiagnosis of Clostridium difficile infection in the molecular test era. JAMA Intern Med. 2015 Nov;175(11):1792-801.

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.

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013 Apr;108(4):478 98.

Theriot CM, Koenigsknecht MJ, Carlson PE Jr, Hatton GE, Nelson AM, Li B, et al. Antibiotic induced shifts in the mouse gut microbiome and metabolome increase susceptibility to Clostridium difficile infection. Nat Commun. 2014;5:3114.

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

Wadhwa A, Al Nahhas MF, Dierkhising RA, Patel R, et al. High risk of post-infectious irritable bowel syndrome in patients with Clostridium difficile infection. Aliment Pharmacol Ther. 2016 Jul 22. doi: 10.1111/apt.13737.

Weingarden AR, Chen C, Bobr A, Yao D, Lu Y, Nelson VM, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent Clostridium difficile infection. Am J Physiol Gastrointest Liver Physiol. 2014 Feb 15;306(4):G310 9.