CLINICAL STUDY PROTOCOL

SER-109

(Eubacterial Spores, Purified Suspension, Encapsulated)

SERES-013: ECOSPOR IV: AN OPEN-LABEL EXTENSION OF STUDY SERES-012 AND OPEN-LABEL PROGRAM FOR EVALUATING SER-109 IN ADULT SUBJECTS WITH RECURRENT *CLOSTRIDIOIDES DIFFICILE* INFECTION (RCDI)

SPONSOR:

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TITLE:

ECOSPOR IV: An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Adult Subjects with Recurrent *Clostridioides difficile* Infection (RCDI)

CLINICAL PHASE: 3

IND NUMBER: 16262

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Amendment 7 date: 31 July 2020

CLINICAL RESEARCH ORGANIZATION (CRO):

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Declaration of Sponsor or Responsible Medical Officer

Title: ECOSPOR IV: An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Adult Subjects with Recurrent *Clostridioides difficile* Infection (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.

Lisa von Moltke Electronically signed by: Lisa von Moltke Reason: I have reviewed the document and approve. Date: Jul 31, 2020 16:27 EDT 31 July 2020

Lisa von Moltke, MD Date

Executive Vice President and Chief Medical Officer

Seres Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

I have read the SERES-013 Protocol Amendment -7, dated 31 July 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

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1. PROTOCOL SYNOPSIS

SPONSOR NAME: Seres Therapeutics, Inc.

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

PROTOCOL TITLE: ECOSPOR IV: An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Adult Subjects with Recurrent *Clostridioides difficile* Infection (RCDI)

STUDY CENTERS: Approximately 80 study centers in the North America

PLANNED STUDY PERIOD:	**CLINICAL PHASE:** 3
Estimated date first patient enrolled: 4Q2017 Estimated date last patient completed: 2Q2022	

DEFINITIONS:

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

- Positive *Clostridioides 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:

Subjects who are participating in the open-label extension of Study SERES-012 (Cohort 1) have the following objectives.

Primary Efficacy Objective

- To evaluate SER-109 in the reduction of CDI recurrence rate and increase in sustained clinical response rate determined by a toxin assay, up to 8 weeks after initiation of treatment

Secondary Efficacy Objectives

- To evaluate SER-109 in the reduction of CDI recurrence rates, determined using a PCR algorithm (see Laboratory Manual) up to 8 weeks after initiation of treatment
- To evaluate the time to CDI recurrence, determined by a toxin assay, after initiation of a treatment regimen of SER-109
- To evaluate the time to CDI recurrence, determined using a PCR algorithm, after initiation of a treatment regimen of SER-109
- To evaluate the proportion of subjects experiencing CDI recurrence, determined by a toxin assay, up to 4, 12, and 24 weeks after initiation of a treatment regimen of SER-109
- To evaluate the proportion of subjects experiencing CDI recurrence, determined using a PCR algorithm, up to 4, 12, and 24 weeks after initiation of a treatment regimen of SER-109

Primary Safety Objective

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

Exploratory Objectives

- To evaluate changes in the composition of the gut microbiome from Baseline up to 1, 2, 8, and 24 weeks after initiation of a treatment regimen of SER-109

- To evaluate changes in the fecal metabolome from Baseline up to 1, 2, and 8 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- 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 a treatment regimen of SER-109
- 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 after initiation of a treatment regimen of SER-109, respectively

After the last subject rolls over from SERES-012 (Cohort 1), SERES-013 will commence enrollment of Cohort 2, the Open-Label population. The objectives for Cohort 2 are the following:

Primary safety objective

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

Efficacy objectives

- To evaluate SER-109 in the reduction of CDI recurrence rates and increase in sustained clinical response rates, determined by a toxin assay, up to 8 and 12 weeks after initiation of treatment

No Secondary efficacy objectives

Exploratory objectives

- To evaluate changes in the composition of the gut microbiome from Baseline to 1 week after initiation of a treatment regimen of SER-109
- To evaluate changes in the fecal metabolome from Baseline to 1 week after initiation of a treatment regimen of SER-109
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- 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 a treatment regimen of SER-109

STUDY DESIGN:

ECOSPOR IV; Cohort 1 is an open-label extension of Study SERES-012. This study is designed to evaluate the safety, tolerability, and efficacy of a SER-109 treatment regimen in adult subjects 18 years of age or older with recurrent *Clostridioides. difficile* infection (RCDI), who received a SER-109 or placebo treatment regimen in Study SERES-012.

Approximately 30 eligible subjects with recurrent CDI disease from Study SERES-012 are expected to enroll in Cohort 1.

Subjects who had a per-protocol recurrence of CDI within 8 weeks of receipt of a SER-109 or placebo treatment regimen in Study SERES-012 and who have responded to CDI SOC antibiotic therapy defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID] will be eligible to enroll in Study SERES-013, and will receive a SER-109 treatment regimen. A SER-109 treatment regimen is 3×10^7 spore colony forming units (SCFUs) administered orally in 4 capsules once daily for 3 consecutive days.

Subjects being considered for SERES-013 will start screening for 013 at the Recurrence Visit of Study SERES-012. Subjects with a confirmed recurrence of CDI will receive 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]. On Day -1, within 3 days of completion of SOC antibiotic treatment for their CDI, subjects will undergo a bowel cleanse followed by overnight fasting prior to scheduled randomization on Day 1.

Laboratory values or procedures obtained during the screening window and from the central laboratory of Study SERES-012 (e.g. Recurrence Visit) do not need to be repeated at the Screening Visit for SERES-013. The SERES-012 Recurrence Visit may be used for the SERES-013 Screening Visit. However, if the SERES-012 Recurrence Visit occurred outside the SERES-013 screening window (Day -24 to Day -2), the required screening procedures for SERES-013 must be repeated within the screening window.

Subjects will come to the clinic after an overnight fast on the morning of Day 1 to receive a single dose of oral SER-109 (3×10^7 SCFUs) in 4 capsules and have all safety evaluations performed. On Day 1, subjects will be dispensed a 2-day supply of SER-109 (3×10^7 SCFUs) in 4 capsules with instructions for home-administration of a single daily dose in the morning before breakfast on Day 2 and Day 3. Subjects 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. 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 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 who have a confirmed CDI recurrence 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 weeks after initiation of the SER-109 treatment regimen. CDI recurrence is defined as ≥3 unformed stools per day over 2 consecutive days and the requirement that subjects must continue to have diarrhea until antibiotic treatment is initiated, with a positive *C. difficile* toxin assay on a stool sample 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). The subject should not initiate antibiotics for suspected CDI prior to providing a stool sample for the central laboratory stool testing. Data from the *C. difficile* toxin test (either EIA or 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.

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

The Open-Label cohort (Cohort 2) will commence after the last subject from SERES-012 rolls over into SERES-013. The primary objective in Cohort 2 is to describe safety and tolerability of SER-109 in subjects 18 years of age or older with at least a first recurrence of CDI. Approximately 195 subjects are expected to be enrolled in Cohort 2

Subjects with symptoms suggestive of RCDI may submit a stool sample for CDI toxin testing at a Clinical Laboratory Improvement Amendment (CLIA)- certified local laboratory or the central laboratory with a prescreening consent. All subjects who are confirmed to have toxin positive CDI will undergo all Screening Visit assessments after providing signed informed consent. .Subjects with one or more recurrences of CDI (including the current episode) who have responded to CDI SOC antibiotic therapy defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID] will be potentially eligible to enroll in Study SERES-013 to receive a SER-109 treatment regimen. A SER-109 treatment regimen is 3×10^7 spore colony forming units (SCFUs) administered orally in 4 capsules once daily for 3 consecutive days. During the screening window (Day -24 to Day -2), after informed consent is obtained, subjects will be assessed for eligibility and undergo physical examination. Vital signs and laboratory specimens will be obtained.
On Day -1, within 3 days of completion of SOC antibiotic treatment for their CDI, subjects will undergo a bowel cleanse with magnesium citrate, or GoLytely if they have renal impairment, prior to scheduled allocation on Day 1

Subjects will come to the clinic on the morning of Day 1 to receive a single dose of oral SER-109 (3×10^7 SCFUs) in 4 capsules. On Day 1, subjects will be dispensed a 2-day supply of SER-109 (3×10^7 SCFUs) in 4 capsules with instructions for home-administration of a single daily dose in the morning on Day 2 and Day 3. Subjects will be contacted by phone on Day 2 and Day 3 to confirm they have taken study drug 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 8, and queried for adverse events (AEs) and diarrheal symptoms. 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]) and diarrheal symptoms. If diarrheal symptoms recur (≥ 3 unformed stools per day over 2 consecutive days), subjects will be instructed to contact the investigator and have an in-home or clinic visit for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI (Recurrence Visit).

Subjects who have a confirmed CDI recurrence 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 the SER-109 treatment regimen. CDI recurrence is defined as ≥3 unformed stools per day over 2 consecutive days and the requirement that subjects must continue to have diarrhea until antibiotic treatment is initiated, with a positive *C. difficile* toxin assay on a stool sample and a decision by the investigator (based on clinical assessment), that antibiotic treatment is needed. Stool samples collected for suspected CDI recurrence will be processed and shipped to a central laboratory for *C. difficile* stool testing (see Laboratory Manual). The subject should not initiate antibiotics for suspected CDI prior to providing a stool sample for the central laboratory stool testing. Data from the *C. difficile* toxin test (either EIA or CCNA), performed at the central laboratory, will be used for the primary efficacy endpoint. 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.

The schedule of assessments and procedures for Cohort 2 is provided in Table 2.

PLANNED NUMBER OF SUBJECTS:

Approximately 30 adults who experienced recurrent *C. difficile* by Week 8 in Study SERES-012 will make up Cohort 1. Approximately 195 subjects will be enrolled in Cohort 2 for a total of 225 subjects across Cohorts 1 and 2.

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:

For Cohort 1:

1. Previously enrolled in Study SERES-012 and experienced a CDI recurrence within 8 weeks after receipt of a treatment regimen of SER-109 or placebo in Study SERES-012
2. 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.
3. The CDI recurrence in Study SERES012 must have met the protocol definition of:
   a. ≥3 unformed stools per day for 2 consecutive days
   b. A positive *C. difficile* stool toxin assay
   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].
   d. An adequate clinical response following SOC antibiotic therapy, defined as (<3 unformed stools in 24 hours) for 2 or more consecutive days before initiation of study drug on Day 1.
4. If female, subject is nonlactating, 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.
5. 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.

For Cohort 2

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. ≥ 2 episodes of CDI within the previous 12 months, inclusive of the current episode, with date, test result 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.
3. The CDI recurrence must have met the protocol definition of:
   a. ≥3 unformed stools per day for 2 consecutive days
   b. A positive *C. difficile* stool toxin assay (either local or central laboratory)
   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]. 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 initiation of study drug on Day 1.
   e. The requirement that the subject can be dosed with study drug within 4 days of antibiotic completion
4. Male or Female Subject ≥ 18 years of age
5. If female, subject is nonlactating, 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:

For Cohort 1:

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/mm^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 past3 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 (One day) 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) in the past 3 months.
17. Known active intravenous drug or alcohol abuse or use of other drugs of abuse.
18. 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).
19. 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.
20. Life expectancy is 24 weeks or less.

For Cohort 2 (all Cohort 1 exclusion criteria plus number 21 below apply)

21. Previously enrolled in a Seres Therapeutics clinical study

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 home-administration at home. Instructions for storage are provided in the Investigator Site File. SER-109 will be supplied in size 00 capsules.

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

Treatment	Dose	Dosage Form and Amount	Route	Number of Subjects
SER-109	3×10^7 spore colony forming units (SCFUs)	4 capsules once daily for 3 consecutive days	Oral	~ 30 subjects Cohort 1 ~195 subjects Cohort 2 Total of 225 subjects

STATISTICAL METHODS:

Analysis Populations:

Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all enrolled subjects.

Modified Intent-to-Treat Population

The Modified ITT (mITT) Population will consist of all enrolled subjects who received any amount of SER-109, whose CDI was clinically controlled by antibiotic treatment before receiving SER-109, and who have at least 1 post-baseline evaluation.

Safety Population

The Safety Population will consist of all enrolled subjects who received any amount of SER-109. All safety analyses will be conducted based on the Safety Population.

Study Endpoints: For Cohort 1,

The terminology for primary, secondary, and exploratory efficacy endpoints are retained for Cohort 1, but have been changed for Cohort 2.

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- Recurrence of CDI as determined by 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
- Recurrence of CDI, as determined by a PCR algorithm, up to 4, 12 and 24 weeks after initiation of treatment

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 up to Week 24, and assessed by the Cdiff32 HRQoL from up to Week 8, or at an 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

Study Endpoints for Cohort 2

Primary Safety Endpoints

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

Efficacy Endpoint

- Recurrence of CDI and sustained clinical response as determined by a toxin assay up to 8 and 12 weeks after initiation of treatment
- There are no secondary endpoints

Exploratory Endpoints

- Change in the composition of the gut microbiome from Baseline up to 1 week after initiation of treatment in a subgroup of up to approximately 50 subjects
- Change in the fecal metabolome from Baseline up to 1 week after initiation of treatment in a subgroup of up to approximately 50 subjects
- 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)

Analysis of Primary Efficacy Endpoint:

In Cohort 1, the primary efficacy outcome is the recurrence of CDI determined by a toxin assay through Week 8 after receipt of a SER-109 treatment regimen in the ITT Population. Subjects will be categorized as having favorable (sustained clinical response) (no CDI recurrence) or unfavorable outcomes (had CDI recurrence). Rules for imputing CDI recurrence status for subjects with missing data will be provided in the Statistical Analysis Plan (SAP).

The number and percentage of subjects defined as having favorable and unfavorable outcomes will be reported with exact 95% confidence intervals (CIs) for subjects who were randomized to SER-109 and placebo in SERES-012 separately, as well as both groups combined. The CIs will be derived using the Clopper-Pearson exact method.

In Cohort 2, the efficacy outcome is the recurrence of CDI determined by a toxin assay through Week 8 and 12 after receipt of a SER-109 treatment regimen in the ITT Population. Subjects will be categorized as having favorable (sustained clinical response) (no CDI recurrence) or unfavorable outcomes (had CDI recurrence). Rules for imputing CDI recurrence status for subjects with missing data will be provided in the Statistical Analysis Plan (SAP).

The number and percentage of subjects defined as having favorable and unfavorable outcomes will be reported with exact 95% confidence intervals (CIs) derived using the Clopper-Pearson exact method.

Table 1: Schedule of Assessments and Procedures for Cohort 1

	SCREENING PERIOD			EFFICACY PERIOD							FOLLOW UP PERIOD		Recurrence Visit(s)[a]	ET Visit
	Clinic	*TC*[b]	*TC*	*Clinic*	*TC*[c]	*TC*	*TC*	*Clinic or home*[j]	*TC Weekly*	*Clinic*[j,k]	*TC*	*TC – Study Completion*	*Clinic*[j,k]	*Clinic*[j]
Day/Week	**Screening (-24 to -2)** *Note: Assessments performed at Recurrence Visit in SERES-012 do not need to be repeated if performed within the SERES-013 screening window*	**-4 to -2** *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										
Confirm clinical response to SOC antibiotic			X	X										
IxRS registration	X			X										
Medical History	X													
Physical Exam	X									X			X	X
Focused History and Physical				X						X			X	X
Weight	X			X						X			X	X
Vital signs[d]	X			X[e]						X			X	X
Chemistry and hematology	X			X[f]						X			X	X

	SCREENING PERIOD			**EFFICACY PERIOD**							**FOLLOW UP PERIOD**		**Recurrence Visit(s)[a]**	**ET Visit**
	Clinic	***TC[b]***	***TC***	***Clinic***	***TC[c]***	***TC***	***TC***	***Clinic or home[j]***	***TC Weekly***	***Clinic[j,k]***	***TC***	***TC – Study Completion***	***Clinic[j,k]***	***Clinic[j]***
Day/Week	**Screening (-24 to -2)** *Note: Assessments performed at Recurrence Visit in SERES-012 do not need to be repeated if performed within the SERES-013 screening window*	**-4 to -2** *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														
Serum for FBMR				X[f]				X					X	X
Routine urine dipstick	X			X[f]										
Urine pregnancy test (WOCBP)	X			X[f]						X			X	X
Stool: Study Entry: central lab: *C. Diff* toxin assay	X													
Stool: On Study Recurrence/ET: central lab: *C. Diff* testing													X	X
Stool: microbiome testing			X[h]				X[h]	X[g]		X[h]		X[h]	X[h]	X[h]
Stool: metabolomics testing			X[h]				X[h]	X[g]		X[h]			X	X
Provide stool collection kits	X			X						X				
Stop SOC Abx		X												
Administer bowel cleanse			X											

	SCREENING PERIOD			**EFFICACY PERIOD**							**FOLLOW UP PERIOD**		**Recurrence Visit(s)[a]**	**ET Visit**
	Clinic	***TC[b]***	***TC***	***Clinic***	***TC[c]***	***TC***	***TC***	***Clinic or home[j]***	***TC Weekly***	***Clinic[j,k]***	***TC***	***TC – Study Completion***	***Clinic[j,k]***	***Clinic[j]***
Day/Week	**Screening (-24 to -2)** *Note: Assessments performed at Recurrence Visit in SERES-012 do not need to be repeated if performed within the SERES-013 screening window*	**-4 to -2** *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														
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					X	X								
Study drug accountability										X				
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	X	X
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[i]	X[i]

	SCREENING PERIOD			EFFICACY PERIOD							FOLLOW UP PERIOD		Recurrence Visit(s)[a]	ET Visit
	Clinic	*TC*[b]	*TC*	*Clinic*	*TC*[c]	*TC*	*TC*	*Clinic or home*[j]	*TC Weekly*	*Clinic*[j,k]	*TC*	*TC – Study Completion*	*Clinic*[j,k]	*Clinic*[j]
Day/Week	**Screening (-24 to -2)** *Note: Assessments performed at Recurrence Visit in SERES-012 do not need to be repeated if performed within the SERES-013 screening window*	**-4 to -2** *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														
EuroQol 5 Dimensions 5 Level (EQ-5D-5L)				X						X		X	X	X

Abbreviations: Abx=antibiotics; AE=adverse event; *C.diff=Clostridioides 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] Subjects with a confirmed CDI recurrence after Week 8 should continue to be followed for safety assessments through Week 24.

[b] Phone call: 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. All subject should be reminded to collect a stool sample at Day -1. It will be returned to the clinic on Day 1.

[c] Subjects should be called to confirm they have taken study drug in the morning and to inquire about their general health

[d] Blood pressure, pulse, respiratory rate, and body temperature

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

[f] To be assessed prior to study drug dosing

[g] 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).

[h] 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.

[i] Administer if prior to Week 8 visit.

[j.] 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.

[k] 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).

Table 2: Schedule of Assessments and Procedures for Cohort 2

	SCREENING PERIOD			EFFICACY PERIOD				FOLLOW UP PERIOD		Recurrence Visit(s)[a]	ET Visit
	Clinic	*TC*[b]	*TC*	*Clinic*	*TC*	*TC*[c] *Weekly*	*Clinic or Home*	*TC*	*TC – Study Completion*	*Clinic or Home*[j]	*Clinic or Home*[j]
Day/Week	**Screening (-24 to -2)**	**-4 to -2** *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Days 2 and 3**[c]	**Weeks 1 to 7**	**Week 8**[j] **(±2 d)**	**Weeks 12, 16, 20 (± 3 d)**	**Week 24 (±3 d)**		
Assessments and Procedures											
Informed Consent	X[k]										
Eligibility criteria review	X		X	X							
Confirm clinical response to SOC antibiotic			X	X							
IxRS registration	X			X							
Medical History	X										
Physical Exam	X										
Focused History and Physical				X			X			X	X
Weight	X										
Vital signs[d]	X			X[e]			X			X	X
Chemistry and hematology	X						X				X[g]
Urine pregnancy test (WOCBP)	X			X[f]			X			X	X
Stool: Study Entry: central or local lab: *C. Diff* toxin assay	X										

	SCREENING PERIOD			EFFICACY PERIOD				FOLLOW UP PERIOD		Recurrence Visit(s)[a]	ET Visit
	Clinic	***TC*[b]**	***TC***	***Clinic***	***TC***	***TC*[c] *Weekly***	***Clinic or Home***	***TC***	***TC – Study Completion***	***Clinic or Home*[j]**	***Clinic or Home*[j]**
Day/Week	**Screening (-24 to -2)**	**-4 to -2** *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Days 2 and 3[c]**	**Weeks 1 to 7**	**Week 8[j] (±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	X
Provide stool collection kits	X			X			X				
Stop SOC Abx	X	X									
Administer bowel cleanse			X								
Confirm subject administered bowel cleanse on Day -1				X							
Study drug dosing				X	X						
Confirmation of study drug administration											
Study drug accountability							X				
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AE assessment		X	[x]	X	X	X	X	X	X	X	X
Evaluation of diarrhea episodes	X	X	X	X	X	X	X	X	X	X	X
Telephone Contact[h]		X	X			X		X	X		

	SCREENING PERIOD			EFFICACY PERIOD				FOLLOW UP PERIOD		Recurrence Visit(s)[a]	ET Visit
	Clinic	***TC*[b]**	***TC***	***Clinic***	***TC***	***TC*[c] *Weekly***	***Clinic or Home***	***TC***	***TC – Study Completion***	***Clinic or Home*[j]**	***Clinic or Home*[j]**
Day/Week	**Screening (-24 to -2)**	**-4 to -2** *Complete SOC Abx*	**Day -1** *(Within 3d of completing SOC Abx)*	**Day 1**	**Days 2 and 3[c]**	**Weeks 1 to 7**	**Week 8[j] (±2 d)**	**Weeks 12, 16, 20 (± 3 d)**	**Week 24 (±3 d)**		
Assessments and Procedures											
Stool for microbiome and metabolomics testing and future biomedical research			X[i]	X[i]		X[i]					

Abbreviations: Abx=antibiotics; AE=adverse event; *C.diff*=*Clostridioides 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] Subjects with a confirmed CDI recurrence after Week 8 should continue to be followed for safety assessments through Week 24.

[b] Phone call: 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. All subject should be reminded to collect a stool sample collected at Day -1 will be returned to the clinic on Day 1

[c] Subjects should be called on Day 2 and Day 3 to confirm they have taken study drug and to inquire about their general health

[d] Blood pressure, pulse, respiratory rate, and body temperature

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

[f] To be assessed prior to study drug dosing

[g] If termination visit precedes 8 weeks, safety laboratory tests will be obtained at this visit

[h] For all visits performed remotely by a telephone contact, a standardized script will be used to ask about the subject's general health, AEs, concomitant medications and to perform a diarrhea assessment

[i] Stool sample will be collected for all subjects at Day -1 and brought to the clinic at the Day 1 visit. In a subgroup of up to fifty subjects, a stool specimen obtained at Week 1 may be couriered or brought in to the study site

[j] 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 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.

[k] Subjects may sign a pre-screening consent to obtain stool specimen for toxin assay at Local or Central Laboratory

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
Abx	Antibiotics
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CCNA	Cell Cytotoxicity Neutralization Assay
CDI	*Clostridioides difficile* infection
C. difficile or C. diff	*Clostridioides difficile*
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
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
GMP	Good Manufacturing 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
SCFU	Spore Colony Forming Units
SOC	Standard of care
SporQs	Spore Equivalents, a dosing unit measured by dipicolinic acid content
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

4. INTRODUCTION

Clostridioides difficile is a sporeforming Gram-positive anaerobe present throughout the environment and, in low amounts, can be a component of the gut flora of a healthy individual. *Clostridioides 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 pseudomembranous 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.

Clostridioides difficile spores can survive for months in hospitals and long term 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.

SER-109 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 four 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); 3) a completed expanded access for intermediate-size patient populations and open-label extension of study

SERES-004 (SERES-005); and 4) a randomized controlled, blinded study of 3 daily doses in subjects with RCDI (SERES- 012). The unblinded 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 5 deaths (one in Study SERES-004 and four in SERES-005), all 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 safety datasets. A summary of clinical efficacy and safety is presented below.

4.1. 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 (a mean dose of $1.7x10^9$ spore equivalents [SporQs], a dosing unit measured by dipicolinic acid content) administered over 2 days. Fifteen subjects in Part 2 of the study received oral SER-109 (mean dose of $1x10^8$ SporQs) administered over 1 day.

In the open label study, SERES-001, SER-109 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 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-two subjects, 34 who enrolled from Study SERES-004 and 38 who enrolled under expanded access met the eligibility criteria for the study. The primary efficacy objective was to evaluate CDI recurrence rates in adults up to 8 weeks post-treatment with SER-109. The primary safety objective was to evaluate the safety and tolerability of SER-109 in adults with recurrent CDI.

Overall, CDI recurrence was observed within 8 weeks post-treatment in 38.9% (28/72) of subjects, including 52.4% (11/21) in the SERES-004 SER-109 group, 15.4% (2/13) in the SERES-004 Placebo group, and 39.5% (15/38) in the Expanded Access group. Among the 58 subjects treated with vancomycin followed by SER-109, CDI recurrence within 8 weeks post-treatment was observed in 41.4% (24/58). Among the 13 subjects treated with fidaxomicin followed by SER-109, CDI recurrence was observed within 8 weeks post-treatment in 30.8% (4/13) of subjects. Among subjects ≥ 65 years old, CDI occurred in 16/44 subjects (36.4%) and in those < 65 years old, CDI occurred 12/28 subjects (42.9%). Hospitalizations overall occurred in 9 (12.5%), 10 (13.9%), and 12 (16.7%) subjects by 8, 12, and 24 weeks, respectively. All four (5.6%) hospitalizations for CDI occurred within the first 8 weeks.

Overall, 55 (76.4%) subjects had 241 TEAEs. Seven (7) subjects had 11 study-drug related or possibly related AEs. Eleven subjects experienced 21 SAEs. There was a tendency for more subjects with SAEs in those ≥ 65 years old than those < 65 years old, 20.5% vs. 7.1%, respectively. None were drug-related or possibly related. Eight subjects, all ≥ 65 years old had 25 severe TEAEs.

Four subjects, all ≥ 65 years old had TEAEs leading to study withdrawal. The most frequently affected system organ class (SOC) was gastrointestinal (GI) accounting for 52.8% of events with preferred terms diarrhea, abdominal pain, constipation, nausea, flatulence, vomiting followed by Infections and infestations (36.1%) with preferred terms urinary tract infection, nasopharyngitis, and cellulitis. Overall, most events were of mild or moderate intensity: 33.3% of subjects had TEAEs that were mild in intensity, 31.9% subjects had at least TEAE of moderate intensity. Related events mainly affected the GI SOC.

Eleven subjects had 21 SAEs leading to three of four deaths and study discontinuation. One subject had 8 SAEs: diastolic congestive heart failure, myocardial infarction, left face zoster shingles, severe sepsis and septic shock, cerebrovascular accident, pneumonia and aspiration pneumonia. Myocardial infarction, cerebrovascular accident and aspiration pneumonia were fatal. One subject had inflammatory diarrhea and sepsis that was fatal. One subject had dehydration and cerebrovascular accident that was fatal. One subject had *C. difficile* colitis that was fatal. All SAEs were not considered related to study drug.

Of the other SAEs, 3 were severe including diarrhea related to *C. difficile*, recurrent syncope, and CDI recurrence, and 4 were moderate in intensity including lumbar compression fracture, diarrhea, hyperkalemia and exacerbation of end-stage renal disease, and pancolitis. These SAEs and fatality rates are consistent with those expected in the study population with multiple comorbidities.

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.

This study is being conducted primarily to gather safety and tolerability data as well as efficacy from subjects exposed to SER-109 at the dose used in SERES-012. In addition to subjects rolling over from SERES-012 (Cohort 1), subjects with first recurrence or more will be eligible for Cohort 2. There are no data to suggest differences in safety profile in subjects with at least one recurrence versus those with at least two recurrences. In a Phase 3b/4 study that described safety in groups

with 0, 1, or 2 recurrences, there were no differences when comparing an extended pulsed course of fidaxomicin with vancomycin (Cornely 2019).

	Extended FID			Vancomycin		
Number randomized	181			181		
Number preceding CDI episodes	0	1	2	0	1	2
N in group	141	26	10	140	29	10
N with AEs (%)	94 (67)	19 (73)	8 (80)	101 (72)	18 (62)	9 (90)
N with SAEs (%)	58 (41)	7 (27)	3 (30)	61 (44)	11 (38)	5 (50)
N with deaths (%)	25 (18)	1 (4)	2 (20)	32 (23)	3 (10)	1 (10)

The majority of subjects enrolled in the trial were having their first occurrence of CDI. Those with first and second recurrence make up a small proportion of subjects. However, there does not appear to be an increased AE, SAE, or death rate going from first occurrence to second and third occurrences. These data support inclusion of first recurrence (second occurrence) subjects in the larger safety population. Enrollment of patients with first CDI recurrence will allow participating centers to present the protocol to a higher number of subjects, who previously did not qualify.

4.2.1. Rationale for Dose and Treatment Regimen

In this study, subjects will receive a dose of SER-109 ($3x10^7$ spore colony forming units [SCFUs]) per day for 3 consecutive days. The dose and treatment regimen was the one used in SERES-012.

In Study SERES-001, subjects received doses of SER-109 ranging from $3x10^7$ to $2x10^{10}$ SporQs ($2x10^5$ to $5x10^9$ SCFU) 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 SER109 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 ($3x10^7$ SCFU) 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 $1x10^8$ dose target (SporQ) 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 SCFU metric, $3x10^7$ SCFU, 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 *Clostridioides 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

ECOSPOR IV – Cohort 1 is an open-label extension of Study SERES-012. This study is designed to evaluate the safety, tolerability, and efficacy of a treatment regimen SER-109 in adult subjects 18 years of age or older with recurrent *Clostridioides difficile* infection (RCDI), who received a treatment regimen of SER-109 or placebo in Study SERES-012. In Cohort 2 of ECOSPOR IV, the primary study objective is to examine safety and tolerability in a cohort of subjects receiving SER-109 at the dose used in SERES-012.

This study will be conducted at approximately 80 study centers in the North America. For Cohort 1, subjects who had a per-protocol recurrence of CDI within 8 weeks of receipt of a treatment regimen of SER 109 or placebo in Study SERES-012, and who have responded to 10 to 21 days of standard-of-care (SOC) antibiotic treatment for CDI (i.e. vancomycin [125 mg QID] and/or fidaxomicin [200 mg BID]) will be eligible to enroll and receive a treatment regimen of SER-109 in Study SERES-013. A treatment regimen of SER-109 is administered orally as 3×10^7 spore colony forming units (SCFUs) in 4 capsules once daily for 3 consecutive days. Approximately 30 eligible subjects with recurrent CDI disease from Study SERES-012 are expected to enroll in Cohort 1. Approximately 195 subjects will be enrolled through the Open-Label program in Cohort 2. For Cohort 2, subjects with one or more recurrences of CDI (including the current episode) who have responded to CDI SOC antibiotic therapy defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID] will be potentially eligible to enroll in Study SERES-013 to receive a SER-109 treatment regimen.

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

In Cohort 1, favorable clinical outcome, or sustained clinical response, will be determined by the absence of CDI recurrence up to 8 weeks after initiation of treatment of study drug, with CDI recurrence defined as ≥ 3 unformed stools per day over 2 consecutive days with a positive *C. difficile* test on a stool sample determined by a toxin assay and a decision by the investigator (based on clinical assessment) that antibiotic treatment is needed. Data from the *C. difficile* toxin assay (either enzyme immunoassay [EIA] or cell cytotoxicity neutralization assay [CCNA]), performed at the central laboratory, will be used for the primary endpoint analysis. The central laboratory results will be communicated to the investigator and the decision to treat with antibiotics will be based upon the investigator's assessment.

In Cohort 2, favorable clinical outcome, or sustained clinical response, will be determined by the absence of CDI recurrence up to 8 or 12 weeks after initiation of treatment of study drug, with CDI recurrence defined in the same manner as for Cohort 1.

5.1. Trial Conduct

For Cohort 1, screening will begin at the Recurrence Visit of Study SERES-012. Eligible subjects, or their legally authorized representative, will provide informed consent and undergo all baseline evaluations at the Screening Visit. Assessments performed at the Recurrence Visit of Study SERES-012 do not need to be repeated, if performed within the SERES-013 screening window (Day -24 to Day -2) and from the central laboratory of study SERES-012.

For Cohort 2, subjects with symptoms suggestive of RCDI may submit a stool sample for CDI toxin testing at a Clinical Laboratory Improvement Amendment (CLIA)- certified local laboratory

or the central laboratory with a prescreening consent. All subjects who are confirmed to have toxin positive CDI will undergo all Screening Visit assessments after providing signed informed consent.

Cohort 1 subjects will receive 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]. On Day 1, within 3 days of completion of 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).

Subjects will come to the clinic after an overnight fast on Day 1 to receive a dose of oral SER-109 (3×10^7 SCFUs) in 4 capsules and have all safety evaluations performed. On Day 1, subjects will be dispensed a 2-day supply of SER-109 (3×10^7 SCFUs) in 4 capsules with instructions for at-home administration of a single daily dose in the morning before breakfast on Day 2 and Day 3. Subjects will be contacted by phone on Day 2 and Day 3 to confirm they have taken study drug in the morning 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. 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 initiation of study drug administration 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 who have a confirmed CDI recurrence should continue to be followed for safety assessments through Week 24. Favorable clinical outcome in this study will be determined by the absence of CDI recurrence up to 8 weeks after initiation of the SER-109 treatment regimen. Sustained clinical response is favorable clinical outcome. CDI recurrence is defined as ≥3 unformed stools per day over 2 consecutive days and the requirement that subjects must continue to have diarrhea until antibiotic treatment is initiated, with a positive *C. difficile* toxin assay on a stool sample 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). The subject should not initiate antibiotics for the suspected CDI prior to providing a stool sample for the central laboratory stool testing. Data from the *C. difficile* toxin test (either EIA or 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.

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

Cohort 2 subjects will receive 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]. On Day 1, within 3 days of completion of 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).

Subjects will come to the clinic on Day 1 to receive a dose of oral SER-109 (3×10^7 SCFUs) in 4 capsules. On Day 1, subjects will be dispensed a 2-day supply of SER-109 (3×10^7 SCFUs) in 4 capsules with instructions for at-home administration of a single daily dose in the morning on Day 2 and Day 3. Subjects will be contacted by phone on Day 2 and Day 3 to confirm they have taken study drug 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 8, and queried for adverse events (AEs) and diarrheal symptoms. 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]) and diarrheal symptoms.

All AEs, SAEs/AESIs, and concomitant medications will be collected from initiation of study drug administration 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.

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 or have a home visit for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI (Recurrence Visit).

Subjects who have a confirmed CDI recurrence should continue to be followed for safety assessments through Week 24. Favorable clinical outcome, or sustained clinical response, will be determined by the absence of CDI recurrence up to 8 or 12 weeks after initiation of the SER109 treatment regimen. CDI recurrence is defined as ≥3 unformed stools per day over 2 consecutive days and the requirement that subjects must continue to have diarrhea until antibiotic treatment is initiated, with a positive *C. difficile* toxin assay on a stool sample and a decision by the investigator (based on clinical assessment), that antibiotic treatment is needed. Stool samples collected for suspected CDI recurrence will be processed and shipped to the central laboratory for *C. difficile* stool testing (see Laboratory Manual). The subject should not initiate antibiotics for the suspected CDI prior to providing a stool sample for the central laboratory stool testing. Data from the *C. difficile* toxin test (either EIA or 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.

The schedule of assessments and procedures is provided in Table 2.

6. STUDY OBJECTIVES

The study objectives remain the same for Cohort 1.

6.1. Primary Efficacy Objective

- To evaluate SER-109 in the reduction of CDI recurrence rates and increased sustained clinical response rate, determined by a toxin assay, up to 8 weeks after initiation of treatment

6.2. Secondary Efficacy Objectives

- To evaluate SER-109 in the reduction of CDI recurrence rates, determined using a PCR algorithm (see Laboratory Manual) up to 8 weeks after initiation of treatment
- To evaluate the time to CDI recurrence, determined by a toxin assay, after initiation of a treatment regimen of SER-109
- To evaluate the time to CDI recurrence, determined using a PCR algorithm, after initiation of a treatment regimen of SER-109
- To evaluate the proportion of subjects experiencing CDI recurrence, determined by a toxin assay, up to 4, 12, and 24 weeks after initiation of a treatment regimen of SER-109
- To evaluate the proportion of subjects experiencing CDI recurrence, determined using a PCR algorithm, up to 4, 12, and 24 weeks after initiation of a treatment regimen of SER-109

6.3. Primary Safety Objective

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

6.4. Exploratory Efficacy Objectives

- To evaluate changes in the composition of the gut microbiome from Baseline up to 1, 2, 8, and 24 weeks after initiation of a treatment regimen of SER-109
- To evaluate changes in the fecal metabolome from Baseline up to 1, 2, and 8 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of a treatment regimen of SER-109

- 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 a treatment regimen of SER-109
- 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 after initiation of a treatment regimen of SER-109, respectively

For Cohort 2, the primary objectives are safety and tolerability.

6.5. Primary Safety Objective

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

6.6. Efficacy Objectives

- To evaluate SER-109 in the reduction of CDI recurrence rates and increase in sustained clinical response rates, determined by a toxin assay, up to 8 and 12 weeks after initiation of treatment

6.7. Exploratory Objectives

- To evaluate changes in the composition of the gut microbiome from Baseline to 1 week after initiation of a treatment regimen of SER-109
- To evaluate changes in the fecal metabolome from Baseline to 1 week after initiation of treatment
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of hospitalizations for recurrent CDI up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of a treatment regimen of SER-109
- 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 a treatment regimen of SER-109

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:

For Cohort 1:

1. Previously enrolled in Study SERES-012 and experienced a CDI recurrence within 8 weeks after receipt of a treatment regimen of SER-109 or placebo in Study SERES-012.
2. 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.
3. The CDI recurrence in Study SERES-012 must have met the protocol definition of:
   a. ≥3 unformed stools per day for 2 consecutive days
   b. A positive *C. difficile* stool toxin assay
   d. 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] mg BID).An adequate clinical response following SOC antibiotic therapy, defined as (<3 unformed stools in 24 hours) for 2 or more consecutive days before initiation of study drug on Day 1.
4. 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.
5. 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.

For Cohort 2:

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. ≥ 2 episodes of CDI within the previous 12 months, inclusive of the current episode, with date, test result, and antibiotic treatment 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.
3. The CDI recurrence must have met the protocol definition of:
   a. ≥ 3 unformed stools per day for 2 consecutive days
   b. A positive *C. difficile* stool toxin assay. (either local or central laboratory) .
   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]. 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 initiation of study drug on Day 1.
e. The requirement that the subject can be dosed with study drug within 4 days of antibiotic completion.

4. Male or female subject ≥ 18 years of age.
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. If currently taking probiotics, must be willing to stop at time of consent, for the duration of the study.

7.2. Exclusion Criteria

Cohort 1

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/mm^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 (1 day) 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 comorbid 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. Known active intravenous drug or alcohol abuse or use of other drugs of abuse.
18. 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).
19. 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
20. Life expectancy is 24 weeks or less

For Cohort 2 , all Cohort 1 exclusion criteria plus number 21, below, apply.

21. Previously enrolled in a Seres Therapeutics clinical study

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/non-compliance

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 and Storage

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. SER-109 Kit Storage and Handling

The investigational product (SER-109) will be provided as a per subject kit to include 3 bottles containing four size 00 capsules (3×10^7 SCFUs) in an opaque, 40 mL high density polyethylene container sealed with foil.

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

Instructions for shipment, storage, accountability, reconciliation, and destruction of study drug are provided in the Pharmacy Manual.

8.3. 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 up to 60 minutes following dosing. In Cohort 2, fasting is not required.

8.4. Method of Assigning Patients to Study Treatment

This is an open-label study. All subjects who qualify for dosing will receive single daily doses of SER-109 (3×10^7 SCFUs) in 4 capsules administered over 3 consecutive days.

The interactive voice and web response system (IxRS) will assign appropriate bottles of SER-109 that will be available at the site for all subjects on their Day 1 study visit. Subjects who discontinue this study or who have previously received SER-109 in this study will not be permitted to re-enter. Similarly, SER-109 dispensed to a subject may not be re-used, even if the bottle(s) are returned unopened.

8.5. Maintaining the Randomization Codes and Breaking the Study Blind

Not applicable. This study is not randomized or blinded.

8.6. Concomitant Medications

8.6.1. Prohibited Concomitant Medications and 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 metronidazole, oral fidaxomicin and oral vancomycin except for treatment of suspected or confirmed CDI recurrence
- Fecal Microbiota Transplant (FMT) prior to recurrence in the study

8.7. Criteria for Confirmed *Clostridioides difficile* Recurrence Post-Randomization

Cohort 1 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**). For both Cohort 1 and Cohort 2 subjects, during the COVID-19 pandemic home visits will be allowed in place of clinic visits. subjects suspected of having CDI will be asked to contact the investigator and return to the clinic or have a home visit for a *C. difficile* stool toxin test to be sent to the central laboratory and evaluation for recurrence of CDI (Recurrence Visit). If the subject is seen in a home visit, the investigator will determine treatment based on the clinical evaluation and stool test result.

The home visit will remain an option for a clinic visit during follow-up visits after enrollment for Cohort 2.

Subjects must fulfill the following criteria:

1. ≥ 3 unformed stools per day over 2 consecutive days
2. Diarrhea as defined here should continue up until the day antibiotics to treat CDI are initiated. A positive *C. difficile* test on a stool sample determined by a toxin assay
   - A *C. difficile* stool test will be performed at the central laboratory. This 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

For Cohort 1, the schedule of assessments and procedures is presented in Table 1. For Cohort 2, the schedule of assessments and procedures is presented in Table 2.

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 initiation of study drug on Day 1.

9.2. Medical History

At the time of Screening, subjects' medical history will be updated with particular attention to the most recent CDI history. The antibiotic regimen, including dose and duration after the most recent CDI recurrence, will be documented. Subjects must demonstrate an adequate clinical response to the antibiotic regimen to treat the most recent CDI recurrence defined as (<3 unformed stools in 24 hours) for 2 or more consecutive days before study drug dosing.

9.3. Physical Examination

For cohort 1, 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.

For Cohort 2 subjects, a physical examination will be performed by the principal investigator or delegated qualified individual at screening. A focused history and physical by delegated qualified individual will be performed at Day 1, Week 8, any recurrence visit, and the Early Termination Visit if it occurs before Week 8.

9.4. Body Weight

For Cohort 1, body weight will be obtained at all in-clinic visits according to the schedule in Table 1.

For Cohort 2, Body Weight will be obtained at the Screening Visit according to the schedule in Table 2.

9.5. Vital Signs

For Cohort 1, 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.

For Cohort 2, Vital Sign assessments including systolic and diastolic blood pressure, pulse, respiratory rate, and oral temperature measurements will be obtained at the clinic or home visits.

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

For Cohort 1, 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.

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).

For Cohort 2, blood samples for hematology and blood chemistry will be obtained on the Screening Visit, which will be used to determine baseline data. A second and final sample will be obtained at the 8 week visit or the Early Termination Visit (if before 8 weeks).

Subjects who do not have an absolute neutrophil count (ANC) result from the Screening visit must have a local or central laboratory result to ensure study eligibility before the first dose of SER-109 is administered.

9.6.2. Urinalysis

For Cohort 1, 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.

For Cohort 2, urine dipstick testing will no longer be performed. (Table 2)

9.6.3. Pregnancy Testing

For Cohort 1, women of childbearing potential (WOCBP) will have urine pregnancy tests according to the schedule in Table 1.

For Cohort 2, Women of childbearing potential (WOCBP) will have urine pregnancy tests at the Screening Visit and at the 8 week visit or the Early Termination Visit (if before 8 weeks) according to the schedule in Table 12.

9.7. Stool Sample Collection and Analysis

Cohort 1, 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.

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 (see Laboratory Manual for details of *C. difficile* testing performed at the central laboratory). The subject should not initiate antibiotics 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.

For Cohort 2, subjects will be asked to collect stool prior to the bowel cleanse on Day -1. The sample collected on Day -1 may be brought to the study site for the Day 1 Visit. A subgroup of up to approximately 50 subjects will collect a stool specimen at Week 1 and will make arrangements to return it to the clinic or ship directly to the central laboratory. Microbiome and metabolomics testing may be performed on some or all stool samples collected on Day -1 (prior to administering the bowel cleanse), and at Week 1.

The subjects will be instructed to call the study site if diarrhea develops. If recurrent CDI is suspected, stool sample must be collected and shipped to central laboratory for *C. difficile* stool testing (see Laboratory Manual for details of *C. difficile* testing performed at the central laboratory). The subject should not initiate antibiotics 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]), will be used for the primary endpoint analysis. The central laboratory result 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 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.

9.9. Monitoring of Diarrheal Symptoms and General Health

Cohort 1 subjects will be instructed to complete a daily diarrhea log (see Investigator Site File) every day whether or not they experience 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).

Cohort 2: at all scheduled telephone calls and clinic or home visits, subjects will be queried regarding general health;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 arrange for an in-clinic or home visit for a *C. difficile* stool toxin test (to be sent to central laboratory) and evaluation for recurrence of CDI.

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). For Cohort 1 only, administer 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 (central laboratory). The subject should not initiate antibiotic treatment for suspected CDI until instructed to do so by the investigator.

10. STUDY SCHEDULE

The Schedule of Assessments and Procedures is presented in Table 1 and Table 2. 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. In Cohort 1, as necessary for safety of subject, study visits including *Week 2, Week 8, Unscheduled, and Early Termination,* may be conducted 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.

In Cohort 2, the Week 8, early termination, and recurrence visits may all be conducted at home or in the clinic. If a nurse or site personnel cannot perform the visits due to COVID-19, a telephone call or a video conference (Zoom, Skype, FaceTime, etc.) should be conducted in place of the 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.

10.1. Screening Period

For Cohort 2, subjects with symptoms suggestive of RCDI may submit a stool sample for CDI toxin testing at a Clinical Laboratory Improvement Amendment (CLIA)- certified local laboratory or the central laboratory with a prescreening consent.

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

For Cohort 1, screening for this study begins at the Recurrence Visit of Study SERES-012. Assessments performed at the Recurrence Visit in Study SERES-012 do not need to be repeated if performed within the SERES-013 screening window (Day -24 to Day -2) and from the central laboratory of study SERES-012. Cohort 2 subjects will undergo all screening procedures and assessments, with the exception of urine dipstick.

- After a full explanation of the study protocol, have each subject or their legally authorized representative sign an informed consent form (ICF) before performing any study-related activity (including Screening activities).
- Subjects will receive 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID]. On Day -1, within 3 days of completion of 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 in Cohort 1 only. Cohort 2 will not require fasting after bowel cleanse. Subjects with impaired kidney function who are unable to take magnesium citrate will take 250 mL of GoLytely (polyethylene glycol electrolyte solution).
- Assess each patient to ensure all inclusion criteria are met and no exclusion criteria are met.
- Update medical history. Ensure documentation of most recent CDI episode to include dates, test results, duration, and antibiotic treatment received.
- Perform a physical examination including vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature), and weight.
- Provide stool collection kits.
- 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 (Cohort 1 only)
  - Urine pregnancy test, if applicable

    Note: Laboratory values obtained during the screening window and from the central laboratory of Study SERES-012 (e.g., SERES-012 Week 8 visit) do not need to be repeated at the Screening Visit. The SERES-012 Recurrence Visit assessments may be used for the SERES-013 Screening Visit. However, if the Recurrence Visit occurred outside the SERES-013 screening window (Day -24 to Day -2), the required screening procedures for 013 must be repeated within the screening window (Refer to Table 1: Schedule of Assessments and Procedures).

- Obtain information regarding prior medication use within the 8 weeks before anticipated enrollment as well as concomitant medications. Note: For Cohort 1, Comprehensive prior medication and concomitant medicine information from SERES-012 study can be used for this purpose.
- Ensure documentation of recent antibiotic or immunosuppressive medication use that may affect eligibility in the study.
- Assess AEs for Cohort 1 only.
- Register subject in IWRS.
- Instruct subjects that, should they enroll in the study, they will need to meet the following requirements:
  - Probiotic use is prohibited during the study.
  - If currently experiencing an active CDI:
    - On Day -4 to Day -2, subject should take their last dose of antibiotic treatment for their CDI.
    - On Day -1, before beginning the magnesium citrate or GoLytely (polyethylene glycol electrolyte solution) bowel preparation, they should collect a stool sample.
  - 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 testing at the Central Laboratory. Advise subjects that antibiotic treatment should be initiated only after a positive *C. difficile* test, and clinical assessment by the investigator.

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).

- Assess AEs for Cohort 1 only.
- Review concomitant medications.
- Remind subject to not take antibiotics beyond Day -2.
- For both cohorts, remind subject to collect a stool sample at Day -1. For those required to administer a bowel cleanse, instruct the subject to collect the 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. Instruct the subject to collect the 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.
- Assess AEs.
- Review concomitant medications.
- Remind subject to bring their Day -1 stool sample collected at home to the study site on Day 1 to be processed for shipment to the central laboratory.
- Remind subjects in Cohort 1 to bring their SERES-012 electronic diary device to the site at their Day 1 visit so it can be collected and a SERES-013 device can be dispensed. An electronic diary will not be used for subjects in Cohort 2.

10.2. Efficacy Period

10.2.1. Clinic Visit (Day 1)

10.2.1.1. Before Administering Study Drug (Pre-dose)

Both Cohort 1 and 2

- Assess subject to ensure all inclusion criteria are met and no exclusion criteria are met. Ensure 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.
- Obtain stool sample from subject's Day -1 at home collection and process, store, and ship per Laboratory Manual.
- Perform a focused history and physical exam. including vital sign measurements (i.e., blood pressure, pulse, respiratory rate, and body temperature
- Urine Pregnancy test, if applicable
- Access the IxRS to obtain the bottle number of SER-109
- Provide stool collection kit

For Cohort 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 drugCollect blood and urine samples for the following laboratory tests:
  - Blood chemistry
  - Hematology
  - 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
- Assess AEs.
- Administer the EQ-5D-5L and CDiff32 questionnaires.
- Collect SERES-012 diarrhea diary device and dispense SERES-013 device with instructions to continue completing the diary daily through week 24.

For Cohort 2 subjects:

- Subjects will not have to undergo a fast prior to study dose
- For subgroup of up to approximately 50 subjects in Cohort 2, remind subjects to courier or bring their Week 1 stool specimen to the clinic. Provide stool collection kit to these subjects.

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 and a reminder card on reporting and follow-up of symptoms including diarrhea and abdominal discomfort, collection of samples, reporting of any concerns, and, in particular, notification of the investigator of the occurrence of diarrhea.
- Ensure subject continues to fast for a total of 1 hour after dosing (post-dose).(Cohort 1 only; no fasting required in Cohort 2)
- Dispense a 2-day supply of study drug 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.
- Review instructions with subject for recording episodes of diarrhea (See Investigator Site Manual).
- Investigators should manage subjects' expectations, they may have diarrhea early-on after receiving drug in the study.

10.2.2. Phone Call Visit (Day 2)

Contact subject by phone to:

- For cohort 1, confirm administration of 2nd dose (4 capsules) of study drug in the morning before breakfast For cohort 2, confirm administration of 2nd dose (4 capsules) of study drug in the morning. If subject has not yet taken study drug, remind subject to take study drug as soon as possible.
- 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 (see Investigator Site File).(Cohort 1 only)
- Assess AEs.
- Review concomitant medications.

10.2.3. Phone Call Visit (Day 3)

Contact subject by phone to:

- Confirm administration of 3rd dose (4 capsules) of study drug in the morning before breakfast (fasting for Cohort 1 only).For Cohort 2, confirm administration of 2nd dose (4 capsules) of study drug in the morning. If subject has not yet taken study drug, remind subject to take study drug as soon as possible.
- 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 (see Investigator Site File).(Cohort 1 only)
- Assess AEs.
- Review concomitant medications.

For Cohort 1,

- 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.

For Cohort 2

- A subgroup of up to approximately 50 subjects will collect a stool specimen at Week 1 and will make arrangements to return it to the clinic or ship directly to the central laboratory.

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.

For Cohort 1,

- The CDiff32 questionnaire will be administered.
- 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.

For subgroup of up to approximately 50 subjects in Cohort 2, remind subjects to courier their Week 1 stool sample collected at home to the study site to be processed for shipment to the central laboratory.

10.2.5. Clinic or Home Visit (Week 2)

For Cohort 1, 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 serum sample and a stool sample (if ICF for FBMR obtained)

10.2.6. Phone Call Visits (Weeks 3-7)

For Cohort 1, 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.

For Cohort 2, Phone call visits will take place from Week 1-7

- For all phone call visits, a standardized script will be used to inquire about general health, AEs, concomitant medications and to perform a diarrhea assessment. There will be no stool collection for Week 8

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

Subjects will be seen in the clinic at the study site or at a home visit at Week 8 (± 2 days). The home visit option for Cohort 1 is only during COVID-19 period, but for Cohort 2 is option throughout study.

- Obtain stool sample from subject's Week 8 at home collection and process, store, and ship per Laboratory Manual (Cohort 1 only).
- 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
  - Urine pregnancy test, if applicable
- TheEQ-5D-5L and CDiff32 questionnaires will be administered. (for Cohort 1 only)
- Provide subject with stool collection kits as necessary.
- Perform Drug Accountability

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 (For Cohort 1) (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 (For Cohort 1).

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.
- The EQ-5D-5L questionnaire will be administered. (to be completed in Cohort 1 only)
- 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 (Cohort 1 only)
- Remind subject to either send their diarrhea device to the study site with the courier or bring it with them when they drop off their Week 24 stool sample. (Cohort 1 only)

10.3.3. Recurrence and Early Termination (ET) Visits

For Cohort 1, 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. These home visits are permitted only during COVID-19.

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. To inform subject care, a *C. difficile* test on unformed stool may be performed locally at the study site (see Laboratory Manual); ship stool to the central laboratory for *C. difficile* stool testing (see Laboratory Manual). The subject should not initiate antibiotics for CDI prior to providing a stool sample for the central laboratory stool testing.
  - If the *C. difficile* test on a stool sample determined by a toxin assay is positive and the investigator determines that antibiotic treatment is appropriate per protocol guidelines (see Section 8.7), prescribe standard of care antibiotic regimen to control CDI.
  - 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
- The EQ-5D-5L and CDiff32 questionnaires will be administered. (*Note: the CDiff32 questionnaire should only be completed for an ET or Recurrence Visit prior to Week 8).

For Cohort 2, 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 at home or in the clinic if the subject withdraws early from the study, whenever possible.

- 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 to ship to the central laboratory for *C.*

difficile stool testing (see Laboratory Manual). The subject should not initiate antibiotics for CDI prior to providing a stool sample for the central laboratory stool testing.

  - If the *C. difficile* test on a stool sample determined by a toxin assay is positive and the investigator determines that antibiotic treatment is appropriate per protocol guidelines (see Section 8.7), prescribe standard of care antibiotic regimen to control CDI.

- Assess AEs
- Review concomitant medications.
- Perform a focused history and physical exam
- Safety laboratory tests will be performed if termination visit precedes 8 weeks

11. ASSESSMENT OF SAFETY AND ADVERSE EVENT REPORTING

All AEs, SAEs/AESIs, and concomitant medications will be collected from the time of initiation of study drug 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.

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 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 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

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*

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.

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 and the requirement that subjects must continue to have diarrhea until antibiotic treatment is initiated, 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 Hospitalization CRF page.

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 medical monitor 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

For Cohort 1, recurrence of CDI or sustained clinical response as determined by a toxin assay up to 8 weeks after initiation of treatment is the primary efficacy endpoint. A recurrence is defined as ≥ 3 unformed stools per day for 2 consecutive days and the requirement that subjects 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.

For Cohort 2, recurrence of CDI or sustained clinical response as determined by a toxin assay up to 8 and 12 weeks after initiation of treatment are the efficacy endpoints.

12.1.2. Secondary Efficacy Endpoints

For Cohort 1, secondary efficacy endpoints are the following:

- Recurrence of CDI as determined by 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
- Recurrence of CDI, as determined by a PCR algorithm, up to 4, 12 and 24 weeks after initiation of treatment

For Cohort 2, secondary efficacy endpoints are not being sought.

12.1.3. Exploratory Efficacy Endpoints

For Cohort 1, exploratory 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 an ET or Recurrence visit prior to Week 8, after initiation of treatment

For Cohort 2, exploratory endpoints are the following:

- Change in the composition of the gut microbiome from Baseline up to 1 week after initiation of treatment in a subgroup of up to approximately 50 subjects
- Change in the fecal metabolome from Baseline up to 1 week after initiation of treatment in a subgroup of up to approximately 50 subjects.
- 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)

12.1.4. Safety Endpoints

Safety endpoints are the following:

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

12.2. Analysis Populations

Three analysis populations will be defined:

- Intent-to-Treat (ITT) Analysis Population. The ITT Population will consist of all enrolled subjects.
- Modified Intent-to-Treat (mITT) Analysis Population. The mITT Population will be composed of all enrolled subjects who received any amount of SER-109, whose CDI was clinically controlled by antibiotic treatment before receiving SER-109, and who have at least 1 post-baseline evaluation.
- Safety Population. The Safety Population will consist of all enrolled subjects who received any amount of SER-109. All safety analyses will be conducted based on the Safety Population.

12.3. Determination of Sample Size

Approximately 30 subjects are anticipated to enroll from SERES-012 (Cohort 1). The recurrence rates prior to 8 weeks after initiation of study drug assumed in SERES-012 are 16% in SER-109 and 36% in placebo. However, it is expected that only a fraction of subjects who recur in SERES-012 prior to 8 weeks will roll-over to this study, since a follow-up of 8 weeks from start of study drug in earlier protocol versions of SERES-012 (up through and including Amendment 5) was required before rolling over to SERES-013, regardless of when the CDI recurrence occurred in SERES-012. Additionally, 195 subjects with RCDI may enroll in the Open-Label program (Cohort 2) into SERES-013. Approximately 225 subjects total will be assessed for safety and tolerability, and efficacy.

12.4. General Statistical Considerations

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. Listings of individual subject data will be produced.

All summary tables will be presented based on the following groups: For Cohort 1, 1) Subjects who were randomized to SER-109 in SERES-012, 2) Subjects who were randomized to placebo in SERES-012, 3) Overall (groups 1 and 2 combined). For Safety and Tolerability and Primary Efficacy, summary tables will include an additional fourth group consisting of Cohort 2 . The safety summary will be presented combining all subjects (pooling cohort 1 and cohort 2).

A comprehensive statistical analysis plan (SAP) will be submitted to regulatory authorities.

12.5. Subject Population and Baseline Characteristics

Enrollment, protocol deviations, and discontinuations from the study will be summarized by group for the ITT Population. Demographics (e.g., age, race, ethnicity, sex), baseline characteristics (e.g., weight,), medical history, and other baseline characteristics will be summarized by group for the Safety, ITT and mITT Populations.

12.6. Study Drug Exposure

SER-109 exposure will be summarized as the total number of capsules taken with counts and percentages of subjects by group. The summary will be presented for the Safety, ITT, and mITT Populations.

12.7. Efficacy Analysis

12.7.1. Primary Efficacy Analysis

For Cohort 1, the primary efficacy endpoint is the recurrence of CDI up to Week 8 in the ITT Population. Subjects will be categorized as having favorable (no CDI recurrence or sustained clinical response) or unfavorable outcomes (had CDI recurrence). The number and percentage of subjects defined as having favorable (sustained clinical response) and unfavorable (had CDI recurrence) outcomes will be reported with exact 95% confidence intervals (CIs) for each group. The CIs will be derived using the Clopper-Pearson exact method (Clopper and Pearson, 1934). Subjects who are lost to follow-up, terminated the trial early, or died without a recorded recurrence

of CDI before Week 8 will be defined as having an unfavorable outcome for the primary analysis. Subjects who miss any contact with the site (phone calls or the Week 2 visit) before Week 8 but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent contact will be defined as having a favorable outcome (or sustained clinical response) for the primary analysis. Additional rules for imputing CDI recurrence status for subjects with at least one component of the CDI recurrence endpoint criteria missing will be provided in the SAP.

For Cohort 2. the efficacy endpoint is the recurrence of CDI up to Week 8 or 12 in the ITT Population. Subjects will be categorized as having favorable (no CDI recurrence or sustained clinical response) or unfavorable outcomes (had CDI recurrence). The number and percentage of subjects defined as having favorable (sustained clinical response) and unfavorable (had CDI recurrence) outcomes will be reported with exact 95% confidence intervals (CIs) for each group. The CIs will be derived using the Clopper-Pearson exact method (Clopper and Pearson, 1934). For the Week 8 analysis, subjects who are lost to follow-up, terminated the trial early, or died without a recorded recurrence of CDI before Week 8 will be defined as having an unfavorable outcome for the efficacy analysis. Subjects who miss any contact with the site (phone calls or the Week 2 visit) before Week 8 but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent contact will be defined as having a favorable outcome (or sustained clinical response) for the analysis. For the Week 12 analysis, subjects who are lost to follow-up, terminated the trial early, or died without a recorded recurrence of CDI before Week 12 will be defined as having an unfavorable outcome for the efficacy analysis. Subjects who miss any contact with the site (phone calls or the Week 2 visit) before Week 12 but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent contact will be defined as having a favorable outcome (or sustained clinical response) for the analysis. Additional rules for imputing CDI recurrence status for subjects with at least one component of the CDI recurrence endpoint criteria missing will be provided in the SAP.

12.7.2. Sensitivity Analysis for the Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint as described in Section 12.7.1 will also be conducted as follows:

- For Cohort 1, all subjects who are lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence by Week 8, will be considered to have a favorable outcome (sustained clinical response). Subjects who missed any contact with the site before Week 8 (phone calls or the Week 2 visit) but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent contact will continue to be defined as having a favorable outcome (sustained clinical response) for this analysis, which will be conducted in the ITT Population
- For Cohort 2, all subjects who are lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence by Week 8 or 12, will be considered to have a favorable outcome (sustained clinical response) in the two analyses.

The primary efficacy outcome will also be analyzed for the mITT Population**.**

12.7.3. Secondary Efficacy Analysis (applies to Cohort 1 only)

Time to recurrence of CDI will be summarized by group for the ITT and mITT Populations using the median, 25th and 75th percentiles from a Kaplan Meier- analysis. The 95% CI for the median will also be provided. Subjects who complete the follow-up period 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 in the analysis 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 enrollment date.

12.8. Exploratory Analysis

The exploratory endpoints will be summarized descriptively for the mITT populations. Mean, median, standard deviation, maximum and minimum will be presented for continuous variable. Count, Percentage and total will be presented for categorical variables. More details of the exploratory efficacy endpoints will be specified in the SAP.

12.9. Safety Analysis

All safety analyses will be conducted in the Safety Population. All safety summary tables will be presented for the following groups: 1) Cohort 1 2) Cohort 2 3) all subjects pooling Cohorts 1 and 2. Any additional analyses will be detailed in the SAP.

Adverse events will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity after initiation of SER-109. A listing of all AEs, including those occurring before the start of study drug, will be provided. The percentage of patients with TEAEs will be tabulated by system organ class and preferred term on Day 10, Week 2, Week 8 and Week 24. The incidence of TEAEs by system organ class and preferred term, by severity, and by relationship to treatment on Day 10, Week 2, Week 8 and Week 24 will also be presented. Tables of any TEAE leading to SER-109 discontinuation and SAEs will also be provided.

An additional analysis will determine the incidence of TEAEs based on the number of days the patients were followed before receiving antibiotics for treatment of recurrent CDI. The incidence of TEAEs per patient for days before receiving antibiotics will be tabulated by system organ class and preferred term, and by severity and relationship to treatment.

Descriptive statistics of the laboratory parameters and vital sign measurements will be presented 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. Laboratory parameters will be defined, as within or outside normal limits, and shift tables from baseline to each postbaseline visit will be provided.

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 in Cohort 1, 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.

For the efficacy endpoints determined at 2 timepoints in Cohort 2, subjects who are lost-to-follow-up, terminated from the study prematurely, or died without a CDI recurrence before 8 (or 12) 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 (or 12) (phone calls) but who do not report 2 or more consecutive days with ≥ 3 unformed stools at the subsequent telephone contact or by Week 8 (or 12) will be defined as having a favorable outcome for the primary analysis. If the Week 8 (or 12) 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.

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.

For Cohort 2, a prescreen consent will be available for testing the stool for *C. difficile* toxin either at the local or central laboratory.

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 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.

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)

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SERES-013 Protocol Amendment 7.0 Clean

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