Application Type	BLA
STN	125757/0
CBER Received Date	August 26, 2022
PDUFA Goal Date	April 26, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Girish Ramachandran, PhD, Christina Houck
Clinical Reviewer(s)	Joohee Lee, MD
Project Manager	Christina Houck, Qun Wang, PhD
Priority Review	Yes
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician Therapeutics Evaluation Branch 2, DB/OBPV
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Chief, Therapeutics Evaluation Branch 2, DB/OBPV
	John Scott, Ph.D. Director, Division of Biostatistics, OBPV
Applicant	Seres Therapeutics, Inc.
Established Name	Purified Microbiome Therapeutic, (b) (4)
(Proposed) Trade Name	VOWST
Pharmacologic Class	
Formulation(s), including Adjuvants, etc.	Purified microbiome therapeutic
Dosage Form(s) and Route(s) of Administration	Capsules: Each capsule contains a minimum of 1×10^6 spore colony-forming units (SCFU). For oral administration
Dosing Regimen	The recommended dose is 4 capsules taken orally once daily on an empty stomach prior to the first meal of the day for 3 consecutive days.
Indication(s) and Intended Population(s)	To prevent the recurrence of *Clostridioides difficile* infection (CDI) in adults with recurrent CDI

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

AE	Adverse event
AESI	Adverse events of special interest
BLA	Biologics License Application
CDI	*Clostridioides difficile* infection
C. difficile	*Clostridioides difficile*, previously known as *Clostridium difficile*
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
DSMC	Data Safety and Monitoring Committee
FDA	Food and Drug Administration
FMT	Fecal microbiota for transplantation
GCP	Good clinical practice
GI	Gastrointestinal
H	Statistical hypothesis
ICF	Informed consent form
ITT	Intent-to-treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-To-Treat
PCR	Polymerase chain reaction
PP	Per-Protocol
PT	Preferred term
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
UTI	Urinary tract infection

1. EXECUTIVE SUMMARY

The applicant (Seres Therapeutics Inc.) submitted an original Biologics License Application (BLA, STN 125757/0) for SER-109, an oral purified microbiome therapeutic. The proposed indication is to prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI).

Efficacy:
Study SERES-012 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of SER-109 vs. placebo to reduce recurrence of Clostridium difficile Infection (CDI) in adults who have received antibacterial drug treatment. The primary efficacy endpoint analysis in the ITT population resulted in CDI recurrence in 11/89 (12.4%) subjects in the SER-109 group and 37/93 (39.8%) subjects in the placebo group at Week 8. The relative risk of recurrence with SER-109 as compared to placebo was 0.32 (95% CI: 0.18, 0.58). The upper bound of the 95% CI of the relative risk was 0.58, which is lower than 0.833, the study success threshold that CBER agreed could be considered substantial evidence of effectiveness from a single study to support licensure.

Safety:
Study SERES-012 showed a similar overall safety profile between the SER-109 and placebo group: 84/90 (93.3%) subjects in the SER-109 group and 84/92 (91.3%) subjects in the placebo group experienced a total of 529 and 598 TEAEs, respectively. The most commonly observed TEAEs by MedDRA System Organ Class (SOC) and Preferred Terms (PT) were similar in nature and event rates between the SER-109 group and placebo. There were more UTI events in the SER-109 group—8/90 (8.9%) subjects (9 events) versus 1/92 (1.1%) subject (2 events) in the placebo group. Nevertheless, none of the events were considered to be related to study drug treatment by the investigators.

Overall, the primary efficacy results of the Phase 3 study SERES-012 met the success threshold that CBER had agreed could be considered statistically highly persuasive evidence of effectiveness from a single adequate and well-controlled trial. SER-109 showed a similar safety profile to placebo in study SERES-12. No major safety concern was identified from the other studies.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Recurrent *Clostridioides difficile* infection (rCDI)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

ZINPLAVA, a human monoclonal antibody that binds to Clostridioides difficile toxin B, is currently approved in U.S. and indicated to reduce CDI recurrence of in individuals 18

years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence.

REBYOTA (fecal microbiota, live) is currently approved in U.S. and indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

On 11 Jun 2015, SER-109 received breakthrough designation (BTD) for the prevention of rCDI in adults.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

The submission presented no data integrity issues.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

N/A

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on two Phase 3 studies: Phase 3 randomized, double-blind, placebo-controlled study SERES-012; Phase 3, extension and single-arm, open-label study SERES-013. Both studies evaluated the target dose of SER-109.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

• STN 125757/0.1 Module 2.5. Clinical Overview
• STN 125757/0.1 Module 2.7.3. Summary of Clinical Efficacy
• STN 125757/0.1 Module 2.7.4. Summary of Clinical Safety
• STN 125757/0.1 Module 5.3.5.1. Study SERES-012

• STN 125739/0.4 Module 5.3.5.2. Study SERES-013
• STN 125739/0.4 Module 5.3.5.3. Integrated Summary of Safety

5.3 Table of Studies/Clinical Trials

The applicant conducted three non-target dose Phase 1 and 2 studies (SERES-001, SERES-004, and SERES-005) and two target dose Phase 3 studies (SERES-012 and SERES-013). Table 1 summarizes Studies SERES-012 and SERES-013.

Table 1 Summary of SER-109 Clinical Studies (Target Dose Studies)

	Study SERES-012 (NCT03183128)	Study SERES-013 (NCT03183141)
Location	USA and Canada	USA and Canada
Design Objective(s)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of SER-109 vs placebo to reduce recurrence of CDI in adults who have received antibacterial drug treatment for rCDI Primary Efficacy Objective: Demonstrate superiority of SER-109 vs placebo in the reduction of CDI recurrence rates, determined by a toxin assay, up to 8 weeks after initiation of treatment	Phase 3, single arm, open-label extension of study SERES-012 and open-label program evaluating efficacy and safety of SER-109 in adult subjects with rCDI Primary Efficacy Obj: Cohort 1: evaluate SER 109 in reduction of CDI recurrence rates, and increased sustained clinical response rate, determined by toxin assay, up to 8 weeks after initiation of treatment Cohort 2: evaluate SER-109 in the reduction of CDI recurrence rates, and increased sustained clinical response rate, determined by toxin assay, up to 8 and 12 weeks after initiation of treatment
Key Entry Criteria	Adults ≥18 years with: - rCDI, defined as ≥3 prior CDI episodes within 12 months, inclusive of the qualifying episode. - Diarrhea - Positive C. difficile stool sample by toxin assay -Therapeutic response to SOC CDI antibiotics, defined as <3 unformed bowel movements in 24 hrs, for ≥2 consecutive days after commencement of antibiotics	- Adults ≥ 18 years Cohort 1: Previously enrolled in SERES-012 and experienced CDI recurrence within 8 weeks after receipt of a treatment regimen of SER-109 or placebo in SERES-012 -Responded to antibiotics for CDI Cohort 2: ≥2 episodes of CDI, inclusive of the qualifying episode -Responded to SOC antibiotics for CDI (taper regimen acceptable) - Positive C. difficile stool sample by toxin assay or PCR
Route and Regimen	Capsules administered orally 3×10^7 SCFU or matching placebo (1:1 randomization) administered once daily (4 capsules) for 3 consecutive days	Capsules administered orally 3×10^7 SCFU administered once daily (4 capsules), for 3 consecutive days
Duration	Efficacy evaluated at Weeks 4, 8; 12, and 24 Follow-up for all AEs through Week 8 and for all SAEs and AESIs through Week 24	Efficacy evaluated at Weeks 4, 8, 12, and 24 Follow-up for all AEs through Week 8 and for all SAEs and AESIs through Week 24
Number of Subjects by Treatment in ITT population (Entered/ Completed)	SER-109: 89/77 Placebo: 93/56	Overall: 263/249 Cohort 1 (Subjects from SERES-012): SER-109: 4/4 Placebo: 25/23 Cohort 2: 234/222
Sex (M/F) Mean Age (Range) Race	SER-109: 29M/60F; 65.6 (21-100); 92.1% White, 4.5% Black Placebo: 44M/49F; 65.5 (18-96); 94.6% White, 4.3% Black	Overall: 83M/180F; 65 (22-96) years; 92.4% White, 5.3% Black

Source: Adapted from Appendix 1 in Clinical Overview

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

N/A

5.4.2 External Consults/Collaborations (if applicable)

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study SERES-012

Title: A Phase 3 Multicenter, Randomized, Double Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of SER-109 vs. Placebo to Reduce Recurrence of Clostridium difficile Infection (CDI) in Adults Who Have Received Antibacterial Drug Treatment for Recurrent CDI (RCDI)

6.1.1 Objectives (Primary, Secondary, etc)

- Primary Efficacy Objective

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

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

- Primary Safety Objective

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

6.1.2 Design Overview

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the safety, tolerability, and efficacy of SER-109 versus placebo in adult subjects 18 years of age or older with RCDI. The study was designed to evaluate the treatment effect of SER-109 versus placebo to reduce recurrence of CDI up to 8 weeks in adults with a history of recurrent infection. Subjects were stratified by age (<65 years, ≥65 years) and antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin), and randomly assigned in a 1:1 ratio to one of two treatment groups (Treatment Group I [SER-109] or Treatment Group II [placebo]).

6.1.3 Population

Subjects 18 years of age or older with a history of RCDI (≥3 CDI episodes within 12 months, inclusive of the qualifying episode), diarrhea (≥3 unformed stools per day for at least 2 consecutive days), a positive C. difficile stool sample tested by a toxin assay preferably performed by a central laboratory, and who had responded to 10–21 days of standard-of-care antibiotic treatment (i.e., vancomycin or fidaxomicin) were included in the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received oral doses of SER-109 (3×10^7 spore colony forming units [SCFU] in 4 capsules) once daily for 3 consecutive days in Treatment Group I or matching placebo once daily for 3 consecutive days in Treatment Group II.

6.1.6 Sites and Centers

The study was conducted at 56 study centers in North America.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints and Criteria for Study Success

- Primary efficacy endpoint: the recurrence of CDI as determined by a toxin assay up to 8 weeks (or Day 58) after initiation of treatment in the Intent-to-Treat (ITT) Population. The following criteria had to be fulfilled to qualify as on-study recurrence event:
  - ≥3 unformed stools per day over 2 consecutive days
  - A positive C. difficile test on a stool sample as determined by a toxin assay. The central laboratory result was used for the primary endpoint analysis.
  - Assessment by the Investigator that the clinical condition of the subject warranted treatment.

Study Success Criterion: The primary measure of efficacy was the relative risk (RR) of CDI recurrence up to 8 Weeks after initiation of treatment. The success criterion is the upper bound of 95% confidence interval (CI) of relative risk (RR) of recurrence (SER-109 vs placebo) being <0.833.

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind study.

- Randomization

Subjects were randomized in a 1:1 ratio to one of two treatment groups (Treatment Group I [SER-109] or Treatment Group II [placebo]). The randomization was stratified by age (<65 years, ≥65 years) and antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin). The applicant used a forced randomization algorithm to avoid failed randomizations in the unlikely event that the assigned study medication was not available at the site. If supplies for the selected treatment group were not available at the site, the system skipped the randomization number in the selected randomization list and selected the next available minimum randomization number from the randomization list for which treatment supplies were available at the site. During the study, 6 subjects had forced randomization.

- Definitions of analysis populations
  - Intent-to-Treat (ITT) Population:
    All subjects who were randomized, including those who were not exposed to any study drug, and will be analyzed based on the treatment to which they were randomized. Subjects randomized using forced randomization will be analyzed according to the original treatment arm they were randomized to and not the one based on the forced randomization algorithm. The primary efficacy population is the ITT Population.
  - Modified Intent-to-Treat (mITT) Population:
    All subjects with recurrent CDI diagnosis who were randomized, received any amount of study drug, whose qualifying CDI episode was confirmed and

clinically controlled by antibiotic treatment before receiving study drug, and who have at least one efficacy evaluation post baseline. Data from the mITT Population were to be analyzed based on the treatment to which they were randomly assigned. Subjects randomized using forced randomization were to be analyzed according to the original treatment arm they were randomized to and not the one based on the forced randomization algorithm.

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

• Sample size planning

The original planned sample size for this study was 160 subjects per treatment group for a total sample size of 320 subjects. However, enrollment in this study was slower than anticipated due to broad open access to FMT. The applicant proposed reducing the size of the trial. In response, FDA recommended that this study maintain an adequate sample size to demonstrate superiority by targeting the upper bound of 95% confidence interval (CI) of relative risk (RR) of recurrence (SER-109 vs placebo) to be <0.833 to potentially support licensure as a single study. In case SERES-012 only demonstrated a statistically significant treatment effect for RR<1, the applicant would need to provide additional independent confirmatory evidence, potentially by conducting another Phase 3 study.

The applicant then changed the planned sample size for this study to 94 subjects per treatment arm or 188 subjects total in Protocol Amendment 7 dated 24 April 2019. This sample size was derived using recurrence rate assumptions based on available information at the time the sample size was re-estimated. A blinded assessment of the CDI recurrences observed in SERES-012 among subjects enrolled who have either experienced a recurrence prior to Day 58 or have been followed for at least 58 days as of 24 March 2019 yielded an estimated overall recurrence rate of 26%. From the open-label SERES-013 study, the SER-109 recurrence rate observed as of 24 March 2019 was 16%. Therefore, based on this information, the placebo recurrence rate was estimated to be 36%, given that the randomization ratio for this study is 1:1.

Assuming a 36% recurrence rate for the control group and a 16% recurrence rate in the SER-109 group, the sample size for this study was determined to provide the following power estimates based on the fixed sequence multiple testing strategy:

o   Hypothesis #1: to test the null hypothesis (H_{0_1}) that the relative risk (RR) of CDI recurrence of SER-109 to placebo is ≥ 1.0 vs the alternative hypothesis (H_{a_1}) that the RR<1.0 at a one-sided significance level of 0.025, the sample size would provide 83% power.

o Hypothesis #2: If Hypothesis #1 was found to be statistically significant, then H_{0_2}: RR≥0.833 vs H_{a_2}: RR<0.833 was to be tested at a one-sided significance level of 0.025. The sample size would provide 62% power to test H_2.

- Statistical Analysis for Primary Efficacy Endpoint

The primary efficacy analysis was performed using the Cochran-Mantel-Haenszel (CMH) test of the RR of SER-109 compared to placebo, stratified by age (<65 years; ≥65 years), and prior antibiotic regimen for the qualifying episode (vancomycin; fidaxomicin). The CMH estimate of the common relative risk, RR_{CMH}, stratified by age and prior antibiotic regimen, and 2-sided CIs were provided. The logarithm of the CMH estimate of the common relative risk, RR_{CMH}, is approximately normal with mean $\log(\rho_0)$ and variance estimate $\hat{\sigma}$, using the Greenland and Robins (1985) variance estimate for the logarithm of RR_{CMH}. Therefore, the Z-statistic for the Cochran-Mantel-Haenszel estimate for testing the relative risk ρ was defined as $Z = [(\log(RR_{CMH}) - \log(\rho_0)]/\hat{\sigma}$. The Z-statistic has an approximately normal distribution with mean 0 and standard error 1 under the null hypothesis $\rho = \rho_0$. For the primary efficacy endpoint, the null hypothesis will be tested at both $\rho_0 = 1$ and $\rho_0 = 0.833$.

The applicant also proposed to perform the following sensitivity analyses on the primary efficacy endpoint in the ITT Population:

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

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

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

- Statistical Analysis for Secondary Efficacy Endpoints

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

The number and percentage of subjects with recurrence of CDI determined by a PCR algorithm up to 8 weeks (Day 58) were presented by treatment group in the ITT and mITT Populations. RRs and differences in proportions were estimated and tested using the same methods as for the primary efficacy assessment at Week 8 (Day 58).

o Time to Recurrence of CDI Determined by a Toxin Assay

Time to first recurrence of CDI determined by a toxin assay was summarized by treatment group for the ITT and the mITT Populations using the median and 25th and 75th percentiles from Kaplan-Meier analyses. Differences between treatment groups were tested for significance using the log-rank test, stratified by age and prior antibiotic regimen.

  o Time to Recurrence of CDI Determined by a PCR Algorithm

The same analyses described for time to first CDI recurrence determined by a toxin assay were conducted for the analysis of time to first CDI recurrence determined by a PCR algorithm.

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

The number and percentage of subjects with recurrence of CDI determined by a toxin assay up to 4 (Day 30), 12 (Day 87), and 24 weeks after treatment (Day 171) were presented by treatment group in the ITT and mITT Populations. RRs and differences in proportions were estimated and tested using the same methods for the primary efficacy assessment at Week 8 (Day 58).

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

The same analyses described for the recurrence of CDI determined by a toxin assay were conducted for the recurrence of CDI determined by a PCR algorithm up to 4-, 12-, and 24-weeks post-treatment.

- Multiplicity adjustment

Adjustments for multiple testing were made for two hypothesis tests on the primary efficacy endpoint, i.e., hypothesis test #1 for H_{0_1}: RR $\geq$ 1.0 vs. H_{a_1}: RR < 1.0 and hypothesis test #2 for H_{0_2}: RR $\geq$ 0.833 vs. H_{a_2}: RR < 0.833. To maintain an overall 1-sided 0.025 type I error rate, the fixed sequence testing method was used.
  o Hypothesis #1 is tested at the 1-sided 0.025 level. If found to be statistically significant at this level, then Hypothesis #2 is tested at the 1-sided 0.025 level.
  o However, if the primary efficacy endpoint fails to establish superiority, i.e., Hypothesis #1 is not significant at the 1-sided 0.025, then testing of the next hypothesis in this sequence, Hypothesis #2, does not proceed.

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

- Missing data handling
  o Subjects who were lost-to-follow-up, terminated from the study prematurely, or died without a CDI recurrence before 8 weeks after treatment were to be defined as having an unfavorable outcome for the primary analysis. Subjects who missed any contact with the site before Week 8 (phone calls or Week 2 visit) but who did not report 2 or more consecutive days with $\geq$ 3 unformed stools at the subsequent telephone contact or by Week 8 were to be defined as having a favorable outcome for the primary analysis.
  o If the Week 8 visit was missed, subjects were to be considered as having an unfavorable outcome for the primary analysis if they reported 2 or more consecutive days with $\geq$ 3 unformed stools at the next unmissed telephone contact or visit. If any of the 3 components of the CDI recurrence criteria was missing, and the non-missing components met the CDI recurrence criteria, then an unfavorable outcome for the primary analysis was to be imputed.

o However, if some of the 3 components of the CDI recurrence criteria were missing, and at least 1 of the non-missing components did not meet the CDI recurrence criteria, then a favorable outcome for the primary analysis was to be imputed.

o If any of the components of the CDI recurrence criteria was missing, and the non-missing components met the CDI recurrence criteria, then an unfavorable outcome for the primary analysis was to be imputed. However, if some of the components of the CDI recurrence criteria were missing, and at least 1 of the non-missing components did not meet the CDI recurrence criteria, then a favorable outcome for the primary analysis was to be imputed.

- Statistical Methods for Safety Analyses

The safety population was used to summarize all adverse event data, unless otherwise specified. Statistical methods for safety analysis are mainly descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

As shown in Table 2, the majority of subjects (>92%) in both treatment groups were white and non-Hispanic/non-Latino with a median age of 68 years (range, 18–100 years). The demographics and baseline characteristics were similar between the 2 treatment groups except for the inclusion of more female subjects in the SER-109 group (60/89 [67.4%]) compared to placebo (49/93 [52.7%]).

Table 2 Demographics and Baseline Characteristics, ITT Population

Characteristics	Statistic	SER-109 N=89	Placebo N=93	Total N=182
Age (Years)	Mean (SD)	65.6 (16.5)	65.5 (16.7)	65.5 (16.5)
	Median	66.0	69.0	68.0
	Min; Max	21; 100	18; 96	18; 100
Age Class, n (%)	<65 years	41 (46.1)	38 (40.9)	79 (43.4)
	≥65 years	48 (53.9)	55 (59.1)	103 (56.6)
Sex, n (%)	Male	29 (32.6)	44 (47.3)	73 (40.1)
	Female	60 (67.4)	49 (52.7)	109 (59.9)
Ethnicity, n (%)	Hispanic or Latino	5 (5.6)	6 (6.5)	11 (6.0)
	Not Hispanic or Latino	84 (94.4)	87 (93.5)	171 (94.0)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race n (%)	American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	1 (1.1)	0 (0.0)	1 (0.5)
	Black or African American	4 (4.5)	4 (4.3)	8 (4.4)

Characteristics	Statistic	SER-109 N=89	Placebo N=93	Total N=182
	Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
	White	82 (92.1)	88 (94.6)	170 (93.4)
	Other	2 (2.2)	1 (1.1)	3 (1.6)
Number of Previous CDI Episodes, n (%)	2	49 (55.1)	61 (65.6)	110 (60.4)
	3	27 (30.3)	21 (22.6)	48 (26.4)
	4	5 (5.6)	6 (6.5)	11 (6.0)
	≥5	7 (7.9)	5 (5.4)	12 (6.6)
	Missing	1 (1.1)	0 (0.0)	1 (0.5)
Prior Antibiotic Regimen, n (%)	Vancomycin	64 (71.9)	69 (74.2)	133 (73.1)
	Fidaxomicin	25 (28.1)	24 (25.8)	49 (26.9)
Prior FMT History, n (%)	Yes	5 (5.6)	5 (5.4)	10 (5.5)
	No	84 (94.4)	88 (94.6)	172 (94.5)

Source: Adapted from Table 7 in Study SERES-012 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition
Figure 1 shows subject disposition in Study SERES-012:
- Two-hundred eighty-one (281) subjects were screened for entry into the study, of whom 182 subjects passed screening and were enrolled. All the 182 enrolled subjects were randomized to either SER-109 group or placebo) group.
- A total of 90 subjects received oral doses of SER-109 and a total of 92 subjects received matching placebo. For the Safety Population, subjects were analyzed according to the treatment they actually received. The Safety Population comprised 90 subjects in the SER-109 group and 92 subjects in the placebo group.
- During the study, 6 subjects had forced randomization, as below:
  - Two subjects ((b) (6)   ) were originally assigned SER-109, but allocated to placebo due to forced randomization. These subjects were analyzed in the SER-109 group.
  - Three subjects ((b) (6)   ) were originally assigned placebo, but allocated into SER-109 due to forced randomization. These subjects were analyzed in the placebo group.
  - One subject (#(b) (6)) was originally assigned to SER-109 Donor Lot 4 but received Lot 3. This subject was analyzed in the SER-109 group and analyzed in Lot 4 subgroup.

Reviewer Comment*: In the applicant's subgroup analysis by donor lot, subject #*(b) (6) *was included in the Lot 4 subgroup (originally assigned) rather than Lot 3 subgroup (actually received). This analysis approach may be questionable because the intention to treat a subject is based on the planned treatment regimen rather than donor lot. Nevertheless, the subgroup analysis results are not meaningfully changed by including the subject in the lot actually received.*

These subjects were analyzed according to the original treatment group to which they were assigned for the Intent-To-Treat (ITT) and modified ITT (mITT) Populations as per the SAP and as discussed in the FDA correspondence dated 06 October 2017. The ITT Population comprised 89 subjects in the SER-109 group, and 93 subjects in the placebo group.

- Forced randomizations were considered to be major protocol deviations, and therefore subjects randomized using forced randomization were excluded from the Per Protocol Week 8 (PP8) and PP Week 24 (PP24) Populations.

- A total of 49/182 (26.9%) subjects discontinued prematurely from the study, including 12/89 (13.5%) subjects in the SER-109 group and 37/93 (39.8%) subjects in the placebo group. The most common reason for withdrawal in the SER-109 group and placebo was RCDI (4 and 27 subjects, respectively).

Figure 1 Disposition of Subjects in SERES-012, All Screened Subjects
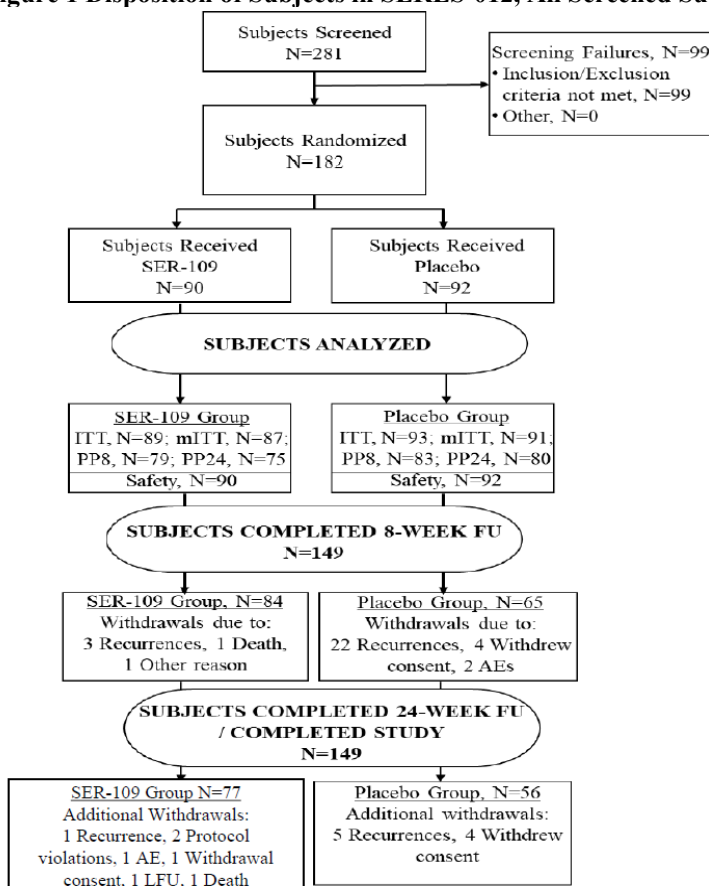
Note: AE=adverse event; FU=follow up; ITT=Intent-to-Treat; LFU=lost to follow up; mITT=modified ITT; PP8/PP24=Per Protocol Week 8/Week24
Note: Subject # (b) (6) died after withdrawing consent, and this event is not reflected in the death totals.
Source: Modified by reviewer from Figure 2 in Study SERES-012 CSR

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy endpoint was CDI recurrence in subjects who received SER-109 or placebo as determined by a toxin assay up to 8 weeks after initiation of treatment. A recurrence was defined as ≥3 unformed stools per day for 2 consecutive days and the requirement that subjects continued to have diarrhea until antibiotic treatment was 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 warranted antibiotic treatment.

The primary efficacy endpoint results are summarized in Table 3. In the ITT population, CDI recurrence was observed in 11/89 (12.4%) subjects in the SER-109 group and 37/93 (39.8%) subjects in the placebo group at Week 8. The relative risk (RR) of recurrence with SER-109 as compared to placebo was 0.32 (95% CI: 0.18, 0.58).

The upper bound of the 95% CI for RR (0.58) was lower than the pre-specified success threshold of 0.833, indicating a successful demonstration of superiority. The one-sided hypothesis tests showed statistical significance ($p<0.001$) for both hypothesis test #1 (H_{0_1}: RR ≥ 1.0 vs. H_{a_1}: RR < 1.0) and hypothesis test 2 (H_{0_2}: RR ≥ 0.833 vs. H_{a_2}: RR < 0.833).

Table 3 C. difficile Infection Recurrence Rates and Relative Risk with Recurrence at 8 weeks (up to Day 58) as Determined by a Toxin Assay (Primary Efficacy Endpoint), ITT Population

	SER-109 N=89	Placebo N=93
Number of Subjects with CDI Recurrence [1], n (%)	11 (12.4)	37 (39.8)
Number of Subjects without CDI Recurrence, n (%)	78 (87.6)	56 (60.2)
Relative Risk (RR) [2]	0.32	
95% CI for RR	0.18, 0.58	
One-sided *P*-value for H0: RR≥1	<0.001	
One-sided *P*-value for H0: RR≥0.833	<0.001	

Note: [1] Subjects who were lost to follow-up, terminated the study prematurely, or died without a recorded recurrence before the end of the time interval were assumed to have had a recurrence. [2] Relative risk is defined as the SER-109 recurrence rate divided by the placebo recurrence rate.
Source: Modified from Table 10 in Study SERES-012 CSR.

Reviewer Comments:

- *I was able to replicate these analysis results using the submitted data.*
- *In the primary efficacy endpoint analysis, the applicant's determination of CDI recurrence appears to be consistent with the algorithm for CDI recurrence determination and imputation pre-specified in the study protocol.*
- *Table 3 presents the final analysis of the primary efficacy endpoint that was conducted at the final database lock when all subjects had completed 24-week follow-up. In this analysis, 6 subjects who had undergone forced randomization were analyzed according to their original treatment assignment per the SAP and the correspondence between the applicant and CBER.*
- *In Study SERES-012 CSR, the applicant also presented the results from the 12-Week Interim Analysis that was performed at the 12-week interim database lock when all subjects had completed 12 weeks of follow-up. This was done as per the protocol to provide the results of the primary outcome analysis and the safety analysis at 8 weeks. Since this interim analysis was conducted after all subjects had completed 12 weeks of follow-up, the occurrence of this interim analysis would not have an impact on the final analysis for the primary efficacy endpoint (at 8 weeks) from the multiplicity control perspective. Considering that the forced randomization events were unknown at the 12-Week interim analysis, my review memo is focused on the final analysis.*

The applicant also evaluated the difference in CDI recurrence rate at 8 weeks after adjustment for age group (<65 years, ≥65 years) and prior antibiotic regimen (vancomycin, fidaxomicin). The difference in CDI recurrence was -26.78% (95% CI, -38.34%, -13.99%) between the SER-109 group and the placebo group.

The applicant conducted the following sensitivity analyses on the primary efficacy endpoint:
- Analyzed with the modification that subjects who were lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence on or before Day 58 were considered to have a favorable outcome in both treatment groups. The applicant reported a statistically significant lower risk of recurrence with SER-109 treatment as compared with placebo: RR=0.31 (95%CI, 0.16, 0.58).
- Analyzed with the modification that subjects who were lost-to-follow-up, terminated the study prematurely, or died without having a CDI recurrence on or before Day 58 in the SER-109 group were considered to have an unfavorable outcome, whereas placebo subjects under these conditions were considered to have a favorable outcome. The applicant reported a statistically significant lower risk of recurrence with SER-109 treatment as compared with placebo: RR=0.34 (95%CI, 0.19, 0.62).
- Analyzed without adjustment for stratification by age and prior antibiotic regimen, whereby all subjects who were lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence by Week 8 were considered to have a favorable outcome. The applicant reported a statistically significant lower risk of recurrence with SER-109 treatment as compared with placebo: RR=0.31 (95%CI, 0.17, 0.57).

These sensitivity analyses showed a similar trend of treatment effect as the primary analysis.

6.1.11.2 Analyses of Secondary Endpoints
- CDI Recurrence by PCR Algorithm Up to 4, 8, 12, and 24 Weeks After Treatment
The RR of recurrence, as determined by PCR algorithm, was significantly lower with SER-109 treatment as compared with placebo at all timepoints (Table 4).

Table 4 C. difficile Infection Recurrence Rates and Relative Risk with Recurrence Determined Using a PCR Algorithm, ITT Population

Time Interval After Dose Statistic	SER-109 N=89	Placebo N=93
4 Weeks (up to Day 30)		
Number of Subjects with CDI Recurrence, n (%)	10 (11.2)	31 (33.3)
RR (95% CI)	0.35 (0.19, 0.67)	
8 Weeks (up to Day 58)		
Number of Subjects with CDI Recurrence, n (%)	11 (12.4)	37 (39.8)
RR (95% CI)	0.32 (0.18, 0.58)	

Time Interval After Dose Statistic	SER-109 N=89	Placebo N=93
12 Weeks (up to Day 87)		
Number of Subjects with CDI Recurrence, n (%)	16 (18.0)	43 (46.2)
RR (95% CI)	0.40 (0.24, 0.65)	
24 Weeks (up to Day 171)		
Number of Subjects with CDI Recurrence, n (%)	20 (22.5)	45 (48.4)
RR (95% CI)	0.48 (0.31, 0.74)	

Source: Adapted from Table 17 in Study SERES-012 CSR

- CDI Recurrence by Toxin Assay up to 4, 12, and 24 Weeks After Treatment

The RR of recurrence was significantly lower in the SER-109 group compared with placebo at all timepoints (Table 5).

Table 5 CDI Recurrence Rates by Toxin Assay through 24 Weeks, ITT Population

Time Interval After Dose Statistic	SER-109 N=89	Placebo N=93
4 Weeks (up to Day 30)		
Number of Subjects with CDI Recurrence, n (%)	10 (11.2)	31 (33.3)
RR (95% CI)	0.35 (0.19, 0.67)	
8 Weeks (up to Day 58)		
Number of Subjects with CDI Recurrence, n (%)	11 (12.4)	37 (39.8)
RR (95% CI)	0.32 (0.18, 0.58)	
12 Weeks (up to Day 87)		
Number of Subjects with CDI Recurrence, n (%)	16 (18.0)	43 (46.2)
RR (95% CI)	0.40 (0.24, 0.65)	
24 Weeks (up to Day 171)		
Number of Subjects with CDI Recurrence, n (%)	19 (21.3)	44 (47.3)
RR (95% CI)	0.46 (0.30, 0.73)	

Source: Adapted from Table 18 in Study SERES-012 CSR

- Time to CDI Recurrence as Determined by Toxin Assay

Time to recurrence of CDI is summarized by treatment group in the ITT Population in Figure 2. In this analysis, subjects who completed the study and did not experience a CDI recurrence by the end of the follow-up period were censored on the date of last contact. Subjects who were lost to follow-up or who terminated the study prematurely before experiencing a CDI recurrence were censored on the date of last contact. Subjects who died before having a CDI recurrence were censored on the date of death. Subjects who were assessed to have a CDI recurrence due to missing or incomplete data for 1 or more of the 3 components of CDI recurrence were not counted as an event but censored on their last date of contact. The applicant indicated that a significant difference was

observed between the 2 treatment groups for Kaplan-Meier estimates of time to CDI recurrence (log-rank test P<0.001).

Figure 2 Survival Function for Time to CDI Recurrence: Kaplan-Meier Plot, ITT Population
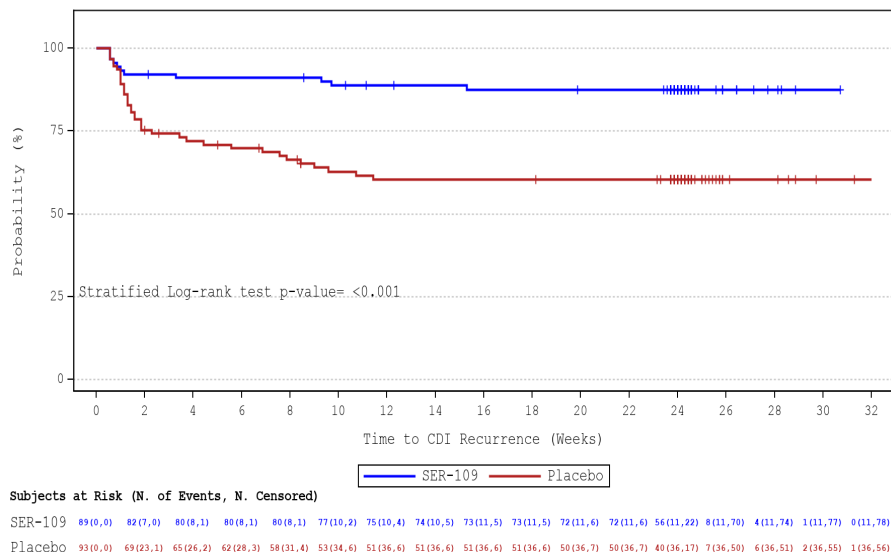
Source: Figure 3 in Study SERES-012 CSR

- Time to CDI Recurrence as Determined by PCR Algorithm

The applicant indicated that the time to recurrence analysis by PCR algorithm was consistent with that based on toxin assay. A significant difference was observed between the 2 treatment groups for Kaplan-Meier estimates of time to CDI recurrence (log-rank test p<0.001).

6.1.11.3 Subpopulation Analyses

The applicant conducted subgroup analysis by age and by Prior Antibiotic Regimen.
- Age: At 8 weeks, the recurrence rates were 7.3% and 30.8% in the SER-109 group and the placebo group, respectively, in the <65 years age group. The recurrence rates were 16.7% and 46.3% in the SER-109 group and the placebo group, respectively, in the ≥65 years age group.
- Sex: At 8 weeks, the recurrence rates were 13.8% and 29.5% in the SER-109 group and the placebo group, respectively, among the male subjects. The recurrence rates were 11.7% and 49.0% in the SER-109 group and the placebo group among the female subjects.
- Race: The majority of the study population in Study SERES-012 were white (93.4%) and non-Hispanic (94.0%). The subgroup analyses for other racial groups were based on a limited number of subjects and do not provide interpretable information.
- Prior Antibiotic Regimen: At 8 weeks, the recurrence rate was 15.6% and 37.7% in the SER-109 group and the placebo group, respectively, in the Vancomycin subgroup. The recurrence rate was 4.0% and 45.8% in the SER-109 group and the placebo group, respectively, in the Fidaxomicin subgroup.

These subgroup analyses showed a similar trend of treatment effect as the primary analysis.

6.1.11.4 Dropouts and/or Discontinuations

The applicant handled missing data based on the imputation algorithm pre-specified in the study protocol. The applicant performed pre-specified sensitivity analyses to evaluate the impact of the different imputation approaches (Section 6.1.11.1 Analyses of Primary Endpoint). The sensitivity analyses showed a similar trend of treatment effect as the primary analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

The overall summary of TEAEs by treatment and time interval (1-10, 11-14, 15-58, and 59-168 Days) from first administration of study drug is summarized in Table 6. A total of 84/90 (93.3%) subjects in the SER-109 group and 84/92 (91.3%) subjects in the placebo group experienced a total of 529 and 598 TEAEs, respectively. A total of 46/90 (51.1%) subjects in the SER-109 group and 48/92 (52.2%) subjects in the placebo group experienced a total of 224 and 228 TEAEs respectively, which were considered by the Investigator to be related or possibly related to study drug. A total of 15/90 (16.7%) subjects in the SER-109 group and 19/92 (20.7%) subjects in the placebo group experienced a total of 26 and 32 SAEs respectively, none of which was considered by the Investigator to be study drug-related.

Table 6 Overall Summary of Treatment-Emergent Adverse Events, Safety Population

Days from Start of Study Drug	1-10 days		11-14 days		15-58 days		59-168 days		Total	
-	SER-109 N=90	Placebo N=92	SER-109 N=90	Placebo N=89	SER-109 N=90	Placebo N=87	SER-109 N=85	Placebo N=64	SER-109 NT=90	Placebo NT=92
Number of TEAEs	408	492	24	16	82	80	15	10	529	598
Subjects with TEAEs	76(84.4)	81(88.0)	18(20.0)	13(14.6)	44(48.9)	43(49.4)	10(11.8)	6(9.4)	84(93.3)	84(91 3)
Number of Study Drug Related or Possibly Related TEAEs	211	220	7	3	6	5	0	0	224	228
Subjects with Study Drug Related or Possibly Related TEAEs	44(48.9)	47(51.1)	6(6.7)	3(3.4)	6(6.7)	5(5.7)	0(0.0)	0(0.0)	46(51.1)	48(52 2)
Number of Serious TEAEs	0	8	3	4	8	10	15	10	26	32
Subjects with Serious TEAEs	0(0.0)	7(7.6)	2(2.2)	4(4.5)	6(6.7)	8(9.2)	10(11.8)	6(9.4)	15(16.7)	19(20.7)
Number of Serious TEAEs Related or Possibly Related to Study Drug	0	0	0	0	0	0	0	0	0	0
Subjects with Serious TEAEs Related or Possibly Related to	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Days from Start of Study Drug	1-10 days		11-14 days		15-58 days		59-168 days		Total	
-	SER-109 N=90	Placebo N=92	SER-109 N=90	Placebo N=89	SER-109 N=90	Placebo N=87	SER-109 N=85	Placebo N=64	SER-109 NT=90	Placebo NT=92
Study Drug										
Number of TEAEs Leading to Study Withdrawal	0	3	0	1	0	1	1	0	1	5
Subjects with TEAEs Leading to Study Withdrawal	0(0.0)	1(1.1)	0(0.0)	1(1.1)	0(0.0)	1(1.1)	1(1.2)	0(0.0)	1(1.1)	2(2.2)

Source: adapted from Table 33 in Study SERES-012 CSR

The most commonly observed TEAEs by MedDRA SOC and PT were similar in nature and event rates between the SER-109 and placebo group. The most common types of TEAEs by MedDRA SOC were GI disorders (SER-109, 79/90 [87.8%]; placebo 80/92 [87.0%]), followed by general disorders and administration site conditions (SER-109, 57/90 [63.3%]; placebo 65/92 [70.7%]). TEAEs by MedDRA PT occurring in >50% of subjects in both treatment groups included flatulence, fatigue, abdominal distension, and abdominal pain.

Numerically higher rates of nausea, flatulence, abdominal pain, vomiting, decreased appetite, and C. difficile colitis were observed in the placebo group vs SER-109 group. The applicant suggested that symptoms due to CDI recurrence contributed to the higher rates of GI events among placebo recipients.

There were more UTI events in the SER-109 group—8/90 (8.9%) subjects (9 events) versus 1/92 (1.1%) subject (2 events) in the placebo group; none of the events were related to
study drug treatment.

6.1.12.1 Methods
Descriptive methods were used for safety analysis.

6.1.12.3 Deaths
Three subjects in the SER-109 group died during study participation, and none of the deaths were considered to be related to study drug by the Investigator.

6.1.12.4 Nonfatal Serious Adverse Events
A total of 15/90 (16.7%) subjects in the SER-109 group and 19/92 (20.7%) subjects in the placebo group experienced a total of 26 and 32 SAEs respectively, none of which was considered by the Investigator to be study drug-related.

6.1.12.5 Adverse Events of Special Interest (AESI)
A total of 4/90 (4.4%) subjects in the SER-109 group and 3/92 (3.3%) subjects in the placebo group
experienced a total of 4 and 3 AESIs respectively, none of which was considered by the

Investigator to be study drug related.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

A total of 1/90 (1.1%) subjects in the SER-109 group and 2/92 (2.2%) subjects in the placebo group
experienced a total of 1 and 5 TEAEs leading to study withdrawal, respectively. One subject in each treatment group experienced an SAE that led to early withdrawal.

6.2 Study SERES-013

Title: 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)

6.2.1 Objectives (Primary, Secondary, etc)

- 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

- Primary Safety Objective

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

6.2.2 Design Overview

This study comprised 2 open-label cohorts. The study duration for both cohorts was approximately 27 weeks, including a 3-week screening period, an 8-week primary efficacy period from initiation of treatment on Day 1, and a 16-week follow-up period.

- Cohort 1 comprised subjects previously enrolled in Study SERES-012 who experienced a recurrence of Clostridioides difficile infection (CDI) within 8 weeks after receipt of either SER-109 or placebo. Approximately 30 eligible subjects were planned to be enrolled.
- Cohort 2 was designed to examine safety and tolerability in additional adult subjects who received SER-109 at the dose used in SERES-012. Approximately 200 subjects were planned to be enrolled.

6.2.3 Population

- Cohort 1: Eligible subjects had per-protocol RCDI within 8 weeks of receipt of either SER-109 or placebo in SERES-012, and who had responded to 10–21 days of standard-of-care antibiotic treatment for CDI.
- Cohort 2: Eligible subjects had at least 2 prior CDI episodes (including the qualifying episode) and had responded to CDI antibiotic therapy, defined as 10–42 days of treatment with vancomycin or 10–25 days of fidaxomicin (200 mg).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Eligible Cohorts 1and 2 subjects received a single dose of oral SER-109 (3×10^7 SCFU as 4 capsules) on Day 1. Subjects were dispensed a 2-day supply with instructions for at-home administration of a single daily dose in the morning before breakfast on Days 2 and 3.

6.2.6 Sites and Centers

This study was conducted at 72 study sites in North America (64 US; 8 Canada).

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints and Criteria for Study Success

- Primary Efficacy Endpoints
  - For Cohort 1, the primary efficacy endpoint was recurrence of CDI and sustained clinical response as determined by a toxin assay up to 8 weeks after initiation of 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 were the efficacy endpoints.
- Safety Endpoints for both cohorts were as follows: incidence of AEs, laboratory evaluation results, vital sign measurements, and physical examination findings

6.2.9 Statistical Considerations & Statistical Analysis Plan

- Analysis populations
  - Intent-to-Treat (ITT) Population: all enrolled subjects.
  - Modified Intent-to-Treat (mITT) Population: 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. For subjects in Cohort 1, subjects must have had RCDI diagnosis that occurred on the SERES-012 trial. For subjects in Cohort 2, subjects with a RCDI diagnosis should have ≥2 CDI episodes prior to screening, inclusive of the current episode.
  - Safety Population: all enrolled subjects who received any amount of SER-109.
- Sample size planning: The applicant expected that approximately 30 subjects were anticipated to enroll from SERES-012 (Cohort 1). Additionally, 200 subjects with RCDI were planned to enroll in the Open-Label program (Cohort 2) into SERES-013.
- Primary efficacy endpoint analysis: The number and percentage of subjects in each group defined as having CDI recurrence outcomes were reported with exact 95% confidence intervals (CIs) for each group.
- Missing data handling:
  - For the primary endpoint for both Cohorts 1 and 2, subjects who were lost to follow-up, terminated from the study prematurely, or died without a CDI

recurrence before 8 weeks (Day 58) after treatment were defined as having CDI recurrence for the primary analysis.

o Data from the C. difficile toxin assay (EIA or CCNA), performed at the central laboratory, was used for the primary endpoint analysis. If the results of the C. difficile toxin assay from the central laboratory were missing, then the results of the C. difficile toxin test performed by a CLIA-certified local laboratory using an FDA-approved toxin test was used, if available.

o If any one of the components of the CDI recurrence criteria were missing, and the non-missing components met the CDI recurrence criteria (e.g., a positive toxin test), then CDI recurrence for the primary analysis was imputed. However, if some of the components of the CDI recurrence criteria were missing, and at least 1 of the non-missing components did not meet the CDI recurrence criteria (e.g., not meeting diarrhea criteria), then a CDI non-recurrence (i.e., sustained clinical response) for the primary analysis was imputed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Table 7 Demographics and Baseline Characteristics, ITT / Safety Population

Characteristic	Statistic	Cohort 1 (N=29)	Cohort 2 (N=234)	Total (N=263)
Age (Years)	Mean (SD)	71.7 (12.5)	63.1 (15.8)	64.0 (15.7)
	Median (Min, Max)	73.0 (35, 96)	64.0 (22, 96)	65.0 (22, 96)
Age Class, n (%)	<65 years	8 (27.6)	118 (50.4)	126 (47.9)
	≥65 years	21 (72.4)	116 (49.6)	137 (52.1)
Sex, n (%)	Male	11 (37.9)	72 (30.8)	83 (31.6)
	Female	18 (62.1)	162 (69.2)	180 (68.4)
Ethnicity, n (%)	Hispanic or Latino	0	20 (8.5)	20 (7.6)
	Not Hispanic or Latino	29 (100.0)	214 (91.5)	243 (92.4)
Race, n (%)	American Indian or Alaska Native	0	1 (0.4)	1 (0.4)
	Asian	0	5 (2.1)	5 (1.9)
	Black or African American	0	14 (6.0)	14 (5.3)
	Native Hawaiian or other Pacific Islander	0	0	0
	White	29 (100.0)	214 (91.5)	243 (92.4)
	Other	0	0	0
Number of Previous	1	0	77 (32.9)	77 (29.3)

Characteristic	Statistic	Cohort 1 (N=29)	Cohort 2 (N=234)	Total (N=263)
CDI Episodes, n (%)				
	2	0	99 (42.3)	99 (37.6)
	≥2	29 (100.0)	157 (67.1)	186 (70.7)
	≥3	29 (100.0)	58 (24.8)	87 (33.1)
Prior Antibiotic Regimen, n (%)	Vancomycin	22 (75.9)	169 (72.2)	191 (72.6)
	Fidaxomicin	7 (24.1)	65 (27.8)	72 (27.4)

Source: Adapted from Table 5 in Study SERES-013 CSR

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.2.10.1.3 Subject Disposition
- In Cohort 1, 31 subjects were screened for entry into the study, of whom 29 (93.5%) passed screening. All 29 subjects enrolled in Cohort 1 were included in the ITT/Safety Population, and 23 subjects were included in mITT Population. A total of 27 (93.1%) Cohort 1 subjects completed the study. All 29 subjects completed through Week 8 follow-up and 2 subjects (from SERES-012 placebo arm rollover) withdrew consent during subsequent follow-up.
- In Cohort 2, 320 subjects were screened for entry into the study, of whom 234 (73.1%) passed screening. All 234 enrolled subjects in Cohort 2 were included in the ITT/Safety Population, and 225 (96.2%) were included in the mITT population. A total of 222 (94.9%) Cohort 2 subjects completed the study. Twelve subjects withdrew from the study, of whom 6 withdrew before Week 8 (5 died and 1 withdrew consent) and 6 withdrew during subsequent follow-up (3 withdrew consent and 3 died).

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint
The primary efficacy endpoint was CDI recurrence as determined by toxin assay up to Week 8 for Cohort 1 and up to Weeks 8 and 12 for Cohort 2.

Cohort 1: Of the 29 subjects, 4 subjects (13.8%; 95% CI 3.9, 31.7) had CDI recurrence up to Week 8, all of which were observed recurrences, and none imputed.

Cohort 2: Of the 234 subjects, 19 subjects (8.1%; 95% CI 5.0, 12.4) had CDI recurrence up to Week 8, of which 12 (5.1%) subjects had observed recurrences and 7 (3.0%) subjects had imputed recurrences (4 early terminations; 3 with missing component). Up to Week 12, 23 subjects (9.8%; 95% CI 6.3, 14.4) had CDI recurrence, of which 14 (6.0%) subjects had observed recurrences and 9 (3.8%) subjects had imputed recurrences (5 early terminations; 4 with missing component).

Overall (Cohorts 1 and 2): Of the 263 subjects, 23 subjects (8.7%; 95% CI 5.6, 12.8) had CDI recurrence up to Week 8, of which 16 (6.1%) subjects had observed recurrences and 7 (2.7%) subjects had imputed recurrences (4 early terminations; 3 with missing component). Up to Week 12, 28 subjects (10.6%; 95% CI 7.2, 15.0) had CDI recurrence, of which 18 (6.8%) subjects had observed recurrences and 10 (3.8%) subjects had imputed recurrences (6 early terminations; 4 with missing component).

6.2.11.2 Analyses of Secondary Endpoints

Secondary endpoints were specified only for Cohort 1. Considering the size of Cohort 1 (29 subjects) and open-label nature of the study, the secondary endpoint analyses are of exploratory nature. The results are not presented in this memo.

6.2.11.3 Subpopulation Analyses

- Age (<65 years, ≥65 years): CDI recurrence rate in the ≥65 years and <65 years age subgroups were 13.1% (18/137) and 4.0% (5/126), respectively.
- Sex: Approximately 2/3 of the overall population were female. CDI recurrence rate among females was 7.8% (14/180) compared to that among males of 10.8% (9/83).
- Race: Majority (>90%) of the overall population was White. Black or African American race was associated with a trend of higher CDI recurrence (21.4%, 3/14 subjects). On the contrary, none of the 5 Asian subjects had a CDI recurrence up to Week 8.
- Antibiotic treatment for the qualifying CDI episode (vancomycin, fidaxomicin): More than 70% of subjects had received vancomycin treatment for the qualifying CDI episode, and the remaining had received fidaxomicin. The CDI recurrence rates were similar between vancomycin (8.9%, 17/191 subjects) and fidaxomicin (8.3%, 6/72 subjects) subgroups.

6.2.11.4 Dropouts and/or Discontinuations

Please see section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

As shown in Table 8, 141 (53.6%) subjects experienced a total of 476 TEAEs. Thirty-two (12.2%) subjects experienced a total of 82 TEAEs that were considered by the investigator to be related or possibly related to study drug. Thirty-three (12.5%) subjects experienced a total of 77 SAEs; all of which were deemed not related to the study drug by the investigator. Most TEAEs (90%) were mild or moderate in severity. There were no TEAEs leading to study withdrawal. Eight subjects (3.0%) died during the study, and all were considered not related to study drug by the investigators.

Table 8 Overall Summary of Treatment-Emergent Adverse Events, Safety Population

Days from Start of Study Drug: Any Statistic	Cohort 1 (NT=29) n (%)	Cohort 2 (NT=234) n (%)	Total (NT=263) n (%)
Number of TEAEs	53	423	476
Subjects with TEAEs	19 (65.5)	122 (52.1)	141 (53.6)
Number of Study Drug Related or Possibly Related TEAEs	12	70	82
Subjects with Study Drug Related or Possibly Related TEAEs	5 (17.2)	27 (11.5)	32 (12 2)
Number of Serious TEAEs	1	76	77
Subjects with Serious TEAEs	1 (3.4)	32 (13.7)	33 (12 5)
Number of Serious TEAEs Related or Possibly Related to Study Drug	0	0	0
Subjects with Serious TEAEs Related or Possibly Related to Study Drug	0	0	0
Number of TEAEs Leading to Study Withdrawal	0	0	0
Subjects with TEAEs Leading to Study Withdrawal	0	0	0
Subjects with TEAEs Leading to Death	0	8 (3.4)	8 (3.0)

Source: Adapted from Table 27 in Study SERES-013 CSR

6.2.12.1 Methods

Descriptive methods were used for the safety analysis.

6.2.12.3 Deaths

There were 8 deaths in the study, and all were considered not related to study drug by the investigators.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 33 (12.5%) subjects experienced a total of 77 SAEs, none of which was considered by the investigator to be study drug related.

6.2.12.5 Adverse Events of Special Interest (AESI)

In this study, any invasive infection was designated as an AESI. Overall, 17 (6.5%) subjects experienced a total of 23 AESIs. All AESIs were deemed not related to the study drug by the investigators.

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

There were no TEAEs leading to study withdrawal.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The primary data that support the safety and tolerability of SER-109 are from the randomized, placebo-controlled Phase 3 study SERES-012 and integrated data for all subjects who received SER-109 in SERES-012 and/or SERES-013. A total of 349 subjects who received SER-109 at the target dose in studies SERES-012 and SERES-013 are included in the integrated safety analyses; 327 of these subjects completed 24 weeks of follow up.

The applicant also provided supportive safety data from the randomized, controlled Phase 2 study SERES-004 compared with placebo and integrated data for all subjects who received SER-109 in SERES-004 and/or SERES-005. A total of 111 subjects received SER-109 at non-target doses in studies SERES-004 and SERES-005. This memo will not discuss these non-target dose studies in detail.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Studies SERES-012 (randomized, placebo-controlled Phase 3 study) and SERES-013 (open-label study).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The SERES-012/SERES-013 integrated dataset includes 349 subjects. In the integrated dataset, 327/349 subjects (93.7%) completed study participation through Week 24.

Subjects in SERES-012 and SERES-013 were administered single oral daily doses of SER-109 (3×107 SCFU) or matching placebo (SERES-012 only) as 4 capsules on 3 consecutive days (12 capsules total). In the SERES-012/SERES-013 integrated dataset, 99.1% of subjects (346/349) received all scheduled doses and capsules of SER-109 (12 or 24 capsules total, for subjects with 1 or 2 treatment regimens, respectively). Subjects were followed for safety in both SERES-012 and SERES-013 for 24 weeks after administration of study treatment. The median duration of follow-up in SERES-012 was 169.0 and 168.0 days in SER-109 and placebo subjects, respectively. The median duration of follow-up in the SERES-012/SERES-013 integrated dataset was 169.0 days (range: 5 to 232 days).

In the SERES-012/SERES-013 integrated dataset, subjects were primarily White (92.3%) and not Hispanic or Latino (92.6%) (Table 9). Approximately 69% of subjects were female, which was similar to the SER-109 arm in SERES-012 (68.9%). The mean age of subjects was 64.2 years (range: 21-100 years).

Table 9 Demographics and baseline characteristics in Target Dose Studies SERES-012 and SERES-013

	SERES-012 SER-109 (N=90)	SERES-012 Placebo (N=92)	Overall SER-109 Exposure[a] (SERES-012/-013) (N=349)
Age (years)			
Mean (SD)	65.8 (16.39)	65.3 (16.75)	64.2 (15.75)
Median (Min, Max)	67.0 (21, 100)	68.0 (18, 96)	66.0 (21, 100)
Age Group, n (%)			
< 65 years	40 (44.4)	39 (42.4)	166 (47.6)
≥ 65 years	50 (55.6)	53 (57.6)	183 (52.4)
Sex, n (%)			
Male	28 (31.1)	45 (48.9)	109 (31.2)
Female	62 (68.9)	47 (51.1)	240 (68.8)
Race, n (%)			
American Indian or Alaska Native	0	0	1 (0.3)
Asian	1 (1.1)	0	6 (1.7)
Black or African American	4 (4.4)	4 (4.3)	18 (5.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	83 (92.2)	87 (94.6)	322 (92.3)
Other	2 (2.2)	1 (1.1)	2 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	6 (6.7)	5 (5.4)	26 (7.4)
Non-Hispanic or Latino	84 (93.3)	87 (94.6)	323 (92.6)
Number of Previous CDI Episodes (not including the qualifying episode)			
1	0	0	77 (22.1)
2	51 (56.7)	59 (64.1)	150 (43.0)
≥ 3	38 (42.2)	33 (35.9)	121 (34.7)
Missing	1 (1.1)	0	1 (0.3)
Prior Antibiotic Regimen (for the qualifying episode)			
Vancomycin	65 (72.2)	68 (73.9)	252 (72.2)
Fidaxomicin	25 (27.8)	24 (26.1)	97 (27.8)

Note: a Includes subjects who received one (N = 345) or two (N = 4) SER-109 treatment regimens in SERES-012 and SERES-013.
Source: Adapted from Tables 11 and 12 in the Integrated Safety Summary

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The solicited reporting of AEs was performed in Study SERES-012, but the solicited reporting was not performed in Study SERES-013. This difference may be attributed to a higher incidence of events observed in both treatment groups in Study SERES-012 compared with Study SERES-013 alone or the SERES-012/SERES-013 integrated safety dataset.

8.4 Safety Results

8.4.1 Deaths

A total of 11 subjects died due to fatal TEAEs during participation in SERES-012 or SERES-013. Three subjects in the SER-109 group in SERES-012 died due to unrelated events. In SERES-013, 8 subjects experienced a fatal TEAE. All fatal TEAEs in SERES-013 were considered unrelated to study drug by the investigator.

8.4.2 Nonfatal Serious Adverse Events

In the SERES-012/SERES-013 integrated dataset, 13.8% of subjects had at least one SAE. The most frequently reported SAEs were UTI (1.7%), cellulitis (1.1%), and C. difficile colitis (1.1%).

8.4.3 Study Dropouts/Discontinuations

In the SERES-012/SERES-013 integrated dataset, 327/349 subjects (93.7%) completed study participation through Week 24. The primary reasons for discontinuation were death (2.9%) and consent withdrawal (2.0%).

8.4.4 Common Adverse Events

In the SERES-012/SERES-013 integrated dataset, a total of 1007 events were reported in 221 subjects (63.3%) (Table 10). Study drug related TEAEs were reported in 22.1% of subjects, and 13.8% of subjects had at least 1 SAE. No SAEs were considered related to study drug by the investigator. One subject (0.3%) experienced a TEAE that led to study withdrawal.

Table 10 Overall Summary of Treatment-Emergent Adverse Events in Target Dose Studies SERES-012 and SERES-013

	SERES-012 SER-109 (N=90) n (%)	SERES-012 Placebo (N=92) n (%)	Overall SER-109 Exposure[a] (SERES-012/-013) (N=349) n (%)
Number of TEAEs	529	598	1007
Subjects with at Least 1 TEAE [b]	84 (93.3)	84 (91.3)	221 (63.3)
Subjects with Study Drug-Related [c] TEAEs [b]	46 (51.1)	48 (52.2)	77 (22.1)
Subjects with SAEs (Serious TEAEs)	15 (16.7)	19 (20.7)	48 (13.8)
Subjects with Study Drug Related [c] SAEs (Serious TEAEs)	0	0	0
Subjects with Treatment-Emergent AESIs [d]	9 (10.0)	3 (3.3)	28 (8.0)
Subjects with Study Drug Related [c] Treatment-Emergent AESI	0	0	0
Subjects with TEAEs Leading to Study Withdrawal	1 (1.1)	2 (2.2)	1 (0.3)
Subjects with SAEs (Serious TEAEs) Leading to Study Withdrawal	1 (1.1)	1 (1.1)	1 (0.3)
Subjects with TEAEs Leading to Death	3 (3.3)	0	11 (3.2)

a. Includes subjects who received one (N = 345) or two (N = 4) SER-109 treatment regimens in SERES-012 and SERES-013.
b. Solicited AEs were collected on Days 4-10 in SERES-012 only.
c Table includes TEAEs that were considered to be related or possibly related to study treatment according to the investigator.
Source: Table 17 in the Integrated Safety Summary

Most subjects with TEAEs in SERES-012 or SERES-013 had an event in the GI Disorders or the General Disorders and Administrative Site Conditions system organ class (SOCs) (Table 11).

Common TEAEs in the SERES-012/SERES-013 integrated dataset were flatulence, diarrhea, abdominal pain, fatigue, and abdominal distension.

Table 11 Treatment-Emergent Adverse Events Reported in at Least 5% of Subjects in Any Treatment Group in Target Dose Studies SERES-012 and SERES-013

System Organ Class Preferred Term	SERES-012 SER-109 (N=90) n (%)	SERES-012 Placebo (N=92) n (%)	SERES-013 SER-109 (N=263) n (%)	Overall SER-109 Exposure [a] (SERES-012/-013) (N=349) n (%)
Number of Subjects with at Least 1 TEAE [c]	84 (93.3)	84 (91.3)	141 (53.6)	221 (63.3)
Gastrointestinal Disorders	**79 (87.8)**	**80 (87.0)**	**104 (39.5)**	**181 (51.9)**

System Organ Class Preferred Term	SERES-012 SER-109 (N=90) n (%)	SERES-012 Placebo (N=92) n (%)	SERES-013 SER-109 (N=263) n (%)	Overall SER-109 Exposure [a] (SERES-012/-013) (N=349) n (%)
Flatulence	63 (70.0)	70 (76.1)	20 (7.6)	83 (23.8)
Abdominal distension	49 (54.4)	49 (53.3)	11 (4.2)	59 (16.9)
Abdominal pain	46 (51.1)	56 (60.9)	19 (7.2)	64 (18.3)
Constipation	28 (31.1)	22 (23.9)	7 (2.7)	35 (10.0)
Diarrhea	22 (24.4)	20 (21.7)	60 (22.8)	81 (23.2)
Nausea	16 (17.8)	30 (32.6)	20 (7.6)	36 (10.3)
Vomiting	3 (3.3)	10 (10.9)	3 (1.1)	6 (1.7)
General Disorders and Administration Site Conditions	**57 (63.3)**	**65 (70.7)**	**23 (8.7)**	**80 (22.9)**
Fatigue	53 (58.9)	58 (63.0)	12 (4.6)	65 (18.6)
Chills	21 (23.3)	22 (23.9)	2 (0.8)	23 (6.6)
Metabolism and Nutrition Disorders	**29 (32.2)**	**36 (39.1)**	**11 (4.2)**	**40 (11.5)**
Decreased appetite	26 (28.9)	34 (37.0)	6 (2.3)	32 (9.2)
Infections and Infestations	**21 (23.3)**	**17 (18.5)**	**40 (15.2)**	**60 (17.2)**
Urinary tract infection	8 (8.9)	1 (1.1)	13 (4.9)	21 (6.0)
C. difficile colitis	1 (1.1)	8 (8.7)	3 (1.1)	4 (1.1)

Note: Solicited AEs were collected on Days 4-10 in SERES-012 only.
a. Includes subjects who received one (N = 345) or two (N = 4) SER-109 treatment regimens in SERES-012 and SERES-013.
Source: Table 8 in Summary of Clinical Safety

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy:
Study SERES-012 was a Phase 3 multicenter, randomized, double blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of SER-109 vs. placebo to reduce recurrence of Clostridium difficile Infection (CDI) in adults who have received antibacterial drug treatment for recurrent. The primary efficacy endpoint analysis in the ITT population resulted in CDI recurrence resulted in 11/89 (12.4%) subjects in the SER-109 group and 37/93 (39.8%) subjects in the placebo group at Week 8. The relative risk of recurrence with SER-109 as compared to placebo was 0.32 (95% CI: 0.18, 0.58). The upper bound of the 95% CI of the relative risk was 0.58, which is

lower than 0.833, the study success threshold that CBER agreed could be considered substantial evidence of effectiveness from a single study to support licensure.

Safety:
- Study SERES-012 showed similar overall safety between the SER-109 and placebo groups: 84/90 (93.3%) subjects in the SER-109 group and 84/92 (91.3%) subjects in the placebo group experienced a total of 529 and 598 TEAEs, respectively. The most commonly observed TEAEs by MedDRA SOC and PT were similar in nature and event rates between the SER-109 and placebo group. There were more UTI events in the SER-109 group—8/90 (8.9%) subjects (9 events) versus 1/92 (1.1%) subject (2 events) in the placebo group; none of the events were considered related to study drug treatment. Overall, the subjects receiving SER-109 showed similar safety to those receiving placebo in Study SERES-12.
- A higher incidence of events was observed in the GI Disorders or the General Disorders and Administrative Site Conditions system organ class (SOCs) in both treatment groups in SERES-012 compared with SERES-013. The differences were due to the solicited reporting of AEs in SERES-012, which was not performed in SERES-013. Nevertheless, SER-109 showed similar safety to its concurrent placebo control in Study SERES-12.

10.2 Conclusions and Recommendations

Overall, the Phase 3 study SERES-012 met the statistical success threshold that CBER agreed could provide substantial evidence of effectiveness from a single adequate and well-controlled trial. The subjects receiving SER-109 showed similar safety to those receiving placebo in study SERES-12. No major safety concern was identified from the other studies.