

BLA Clinical Review Memorandum

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| Division / Office | DVRPA/ OVRP |
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| Reviewer Name(s) | Joohee Lee, MD |
| Review Completion Date / Stamped Date | April 26, 2023 |
| Supervisory Concurrence | Kathleen Hise, MD Maria Allende, MD Joseph Toerner, MD |
| Applicant | Seres Therapeutics, Inc. |
| Established Name | SER-109 (Fecal Microbiota Spores, Live-brpk) |
| (Proposed) Trade Name | VOWST |
| Pharmacologic Class | Live Therapeutics |
| Formulation(s), including Adjuvants, etc. | SER-109 (Fecal Microbiota Spores, Live-oral capsules) |
| Dosage Form(s) and Route(s) of Administration | Capsule, for oral administration |
| Dosing Regimen | Four capsules of SER-109 (3×10^7 SCFU) daily for three consecutive days |
| Indication(s) and Intended Population(s) | To prevent the recurrence of <i>Clostridioides difficile</i> infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI) |
| Orphan Designated (Yes/No) | Yes |

TABLE OF CONTENTS

| | |
|--|-----------|
| GLOSSARY | 5 |
| 1. EXECUTIVE SUMMARY..... | 5 |
| 1.1 Demographic Information: Subgroup Demographics and Analysis Summary..... | 10 |
| 1.2 Patient Experience Data | 12 |
| 2. CLINICAL AND REGULATORY BACKGROUND | 12 |
| 2.1 Disease or Health-Related Condition(s) Studied | 12 |
| 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)..... | 14 |
| 2.3 Safety and Efficacy of Pharmacologically Related Products | 15 |
| 2.4 Previous Human Experience with the Product (Including Foreign Experience) | 15 |
| 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission .. | 15 |
| 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES | 16 |
| 3.1 Submission Quality and Completeness | 16 |
| 3.2 Compliance with Good Clinical Practices and Submission Integrity..... | 16 |
| 3.3 Financial Disclosures | 17 |
| 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | 18 |
| 4.1 Chemistry, Manufacturing, and Controls | 18 |
| 4.2 Assay Validation..... | 19 |
| 4.3 Nonclinical Pharmacology/Toxicology | 19 |
| 4.4 Clinical Pharmacology | 19 |
| 4.4.1 Mechanism of Action | 20 |
| 4.4.2 Human Pharmacodynamics (PD)..... | 20 |
| 4.4.3 Human Pharmacokinetics (PK) | 20 |
| 4.5 Statistical..... | 20 |
| 4.6 Pharmacovigilance..... | 20 |
| 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW ... | 20 |
| 5.1 Review Strategy..... | 20 |
| 5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review..... | 21 |
| 5.3 Table of Studies/Clinical Trials..... | 22 |
| 5.4 Consultations | 23 |
| 5.5 Literature Reviewed | 23 |
| 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS..... | 24 |
| 6.1 Trial #1: SERES-012 | 24 |
| 6.1.1 Objectives (Primary, Secondary, etc.)..... | 25 |
| 6.1.2 Design Overview | 26 |
| 6.1.3 Population..... | 26 |
| 6.1.4 Study Treatments or Agents Mandated by the Protocol | 27 |
| 6.1.5 Directions for Use | 28 |
| 6.1.6 Sites and Centers | 28 |
| 6.1.7 Surveillance/Monitoring | 28 |
| 6.1.8 Endpoints and Criteria for Study Success..... | 29 |
| 6.1.9 Statistical Considerations & Statistical Analysis Plan | 30 |
| 6.1.10 Study Population and Disposition..... | 31 |
| 6.1.11 Efficacy Analyses | 37 |
| 6.1.12 Safety Analyses..... | 44 |
| 6.1.13 Study Summary and Conclusions | 55 |
| 6.2 Trial #2: SERES-013 | 55 |

| | |
|---|-----------|
| 6.2.1 Objectives (Primary, Secondary, etc.)..... | 56 |
| 6.2.2 Design Overview | 56 |
| 6.2.3 Population..... | 57 |
| 6.2.4 Study Treatments or Agents Mandated by the Protocol | 58 |
| 6.2.5 Directions for Use | 58 |
| 6.2.6 Sites and Centers..... | 58 |
| 6.2.8 Endpoints and Criteria for Study Success..... | 59 |
| 6.2.9 Statistical Considerations & Statistical Analysis Plan | 59 |
| 6.2.10 Study Population and Disposition..... | 59 |
| 6.2.11 Efficacy Analyses | 64 |
| 6.2.12 Safety Analyses..... | 68 |
| 6.2.13 Study Summary and Conclusions | 77 |
| 6.3 Trial #3: SERES-004 | 77 |
| 6.3.1 Objectives (Primary, Secondary, etc.)..... | 77 |
| 6.3.2 Design Overview | 78 |
| 6.4 Trial #4: SERES-005 | 79 |
| 6.4.1 Objectives (Primary, Secondary, etc.)..... | 79 |
| 6.4.2 Design Overview | 80 |
| 6.5 Trial #5: SERES-001 | 81 |
| 6.5.1 Objectives (Primary, Secondary, etc.)..... | 81 |
| 6.5.2 Design Overview | 81 |
| 7. INTEGRATED OVERVIEW OF EFFICACY | 82 |
| 8. INTEGRATED OVERVIEW OF SAFETY | 82 |
| 8.1 Safety Assessment Methods | 82 |
| 8.2 Safety Database..... | 83 |
| 8.2.1 Studies/Clinical Trials Used to Evaluate Safety | 83 |
| 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations | 84 |
| 8.2.3 Categorization of Adverse Events..... | 85 |
| 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials..... | 85 |
| 8.4 Safety Results..... | 85 |
| 8.4.1 Deaths | 86 |
| 8.4.2 Nonfatal Serious Adverse Events..... | 89 |
| 8.4.3 Study Dropouts/Discontinuations | 89 |
| 8.4.4 Common Adverse Events..... | 89 |
| 8.4.5 Clinical Test Results | 91 |
| 8.4.6 Systemic Adverse Events..... | 91 |
| 8.4.7 Local Reactogenicity | 92 |
| 8.4.8 Adverse Events of Special Interest | 92 |
| 8.5 Additional Safety Evaluations | 93 |
| 8.5.1 Dose Dependency for Adverse Events | 93 |
| 8.5.2 Time Dependency for Adverse Events..... | 93 |
| 8.5.3 Product-Demographic Interactions..... | 94 |
| 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound | 95 |
| 8.6 Safety Conclusions | 95 |
| 9. ADDITIONAL CLINICAL ISSUES | 96 |
| 9.1 Special Populations..... | 96 |
| 9.1.1 Human Reproduction and Pregnancy Data..... | 96 |
| 9.1.2 Use During Lactation..... | 96 |
| 9.1.3 Pediatric Use and PREA Considerations | 96 |
| 9.1.4 Immunocompromised Patients | 96 |
| 9.1.5 Geriatric Use..... | 97 |

| | |
|--|------------|
| 10. CONCLUSIONS | 97 |
| 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS | 100 |
| 11.1 Risk-Benefit Considerations..... | 100 |
| 11.2 Risk-Benefit Summary and Assessment | 103 |
| 11.3 Discussion of Regulatory Options..... | 103 |
| 11.4 Recommendations on Regulatory Actions..... | 103 |
| 11.5 Labeling Review and Recommendations | 103 |
| 11.6 Recommendations on Postmarketing Actions | 104 |

GLOSSARY

| | |
|------------|---|
| AE | adverse event |
| AESI | adverse event of special interest |
| BIMO | Bioresearch Monitoring |
| BLA | Biologics License Application |
| CDI | <i>Clostridioides difficile</i> (<i>C. difficile</i>) infection |
| CCNA | cell cytotoxicity neutralization assay |
| CHF | congestive heart failure |
| CI | confidence interval |
| COVID-19 | coronavirus disease 2019 |
| EIA | enzyme immunoassay |
| EQ-5D-5L | EuroQol 5 Dimension 5 Level |
| FMT | fecal microbiota transplantation |
| GERD | gastroesophageal reflux disease |
| GI | gastrointestinal |
| HRQoL | Health Related Quality of Life |
| IDSA | Infectious Diseases Society of America |
| IND | investigational new drug |
| ITT | intent-to-treat |
| PCR | polymerase chain reaction |
| PP | per-protocol |
| PT | Preferred Term |
| rCDI | recurrent <i>Clostridioides difficile</i> (<i>C. difficile</i>) infection |
| RR | relative risk |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SCFU | spore colony forming units |
| SER-109 | investigational oral microbiome product |
| SOC | System Organ Class |
| SporQs | spore equivalents |
| TEAE | treatment-emergent adverse event |
| UBM | unformed bowel movement |
| UTI | urinary tract infection |
| VAS | Visual Analog Scale |

1. EXECUTIVE SUMMARY

Seres Therapeutics, Inc. (the Applicant), submitted a Biologics License Application (BLA) to the US Food and Drug Administration (FDA) to support licensure of SER-109, a fecal microbiota spore suspension encapsulated for oral administration (proprietary name VOWST). SER-109 is manufactured from human fecal matter sourced from qualified donors and tested for a panel of transmissible pathogens. The spore suspension is generated by treating fecal matter with ethanol to kill organisms that are not spores, followed by removal of particulates and residual ethanol. The proposed indication for SER-109 is to “prevent the recurrence of *Clostridioides difficile* infection (rCDI) in individuals 18 years of age and older, following antibacterial treatment for recurrent *Clostridioides difficile* infection (rCDI).” SER-109 is supplied in a capsule. Each capsule of SER-109 contains between 1×10^6 and 3×10^7 spore colony forming units

(SCFU) in 92 ± 4% glycerol in saline. The dosage is 4 capsules taken orally once daily for 3 consecutive days. SER-109 is initiated 2 to 4 days after completing antibacterial treatment for rCDI and after taking a laxative (10 ounces of magnesium citrate or 8.5 ounces of polyethylene glycol electrolyte solution) on the preceding evening.

Recurrent CDI is defined as an episode of CDI that occurs within 8 weeks of a previous episode (provided that symptoms from the previous episode resolved) and can be serious or life threatening (Surawicz et al. 2013). rCDI may be due to relapse of a previous episode of CDI by the same strain or reinfection by a different strain (Tang-Feldman et al. 2003). Risk factors for rCDI include age >65 years, antibiotics use, gastric acid suppression, hypervirulent strain (NAP1/BI/027 – produces larger amount of toxins A and B), renal insufficiency, history of previous CDI, previous severe CDI, prolonged hospital stays and lack of adaptive immune responses to toxins A and B (Song et al. 2019). rCDI occurs in about 20%-35% of individuals who experience an initial episode of CDI, and approximately 40%-60% of those with a first recurrence will experience a second recurrence (Hopkins et al. 2018). rCDI complications include dehydration, hypotension, kidney failure, severe diarrhea and rarely, toxic megacolon, colonic rupture, septicemia and death. Published chart reviews of outpatient and inpatient populations with rCDI report 6- to 12-month mortality rates ranging between 9.3% and 36% (Olsen et al. 2015).

Treatment options for rCDI are limited. Standard-of-care antibacterial therapy options for rCDI include fidaxomicin and vancomycin; the regimens can be complex and prolonged. Bezlotoxumab, a human monoclonal antibody directed against *Clostridioides difficile* toxin B administered intravenously, was the first US-licensed product (approved in 2016) indicated for reduction in recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence. Rebyota, a fecal microbiota enema suspension prepared from human stool, was approved in 2022 and is also indicated for the prevention of recurrence of CDI in individuals 18 years of age and older, following antibiotic treatment for rCDI.

This BLA included data from five clinical studies: two placebo-controlled studies (Phase 2 study SERES-004 and Phase 3 study SERES-012) and three prospective open-label studies (SERES-001, SERES-005, SERES-013). Of these, two studies (SERES-012 and SERES-013) evaluated the 3-day dosing regimen for licensure. SERES-004 evaluated a 1-day regimen of SER-109, which did not meet success criteria for efficacy. As a result, only the safety data from these SERES-004 and associated open-label study SERES-005 were discussed in the Integrated Summary of Safety (ISS). The results from SERES-001 were treated as background information for this BLA because the study was conducted outside of an IND, evaluated 1-day and 2-day regimens of an earlier formulation of SER-109, and had important differences in study design from the studies conducted under IND.

FDA and the Applicant agreed that a single randomized, double-blind, placebo-controlled Phase 3 trial (SERES-012) that demonstrated the efficacy of SER-109 based on a pre-specified margin of statistical significance with respect to relative risk (RR) of CDI recurrence with SER-109 compared to placebo would be acceptable for meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation. FDA also agreed that SERES-013 would provide additional supportive safety data and ensure that there would be a minimum safety database of 300 recipients of the 3-day regimen of SER-109.

In SERES-012, subjects who had had three or more episodes of *C. difficile* infection (inclusive of the qualifying acute episode) received SER-109 or placebo (four capsules daily for 3 days) after standard-of-care antibiotic treatment. The primary efficacy objective was to demonstrate the efficacy of SER-109 as compared with placebo in reducing the risk of *C. difficile* infection recurrence up to 8 weeks after treatment. Diagnosis by toxin testing was performed at trial entry, and randomization was stratified according to age (<65 years or ≥65 years) and antibiotic agent received (vancomycin or fidaxomicin). FDA agreed that an upper limit of the 95% confidence interval of the RR of CDI recurrence rate in the SER-109 arm compared to the placebo arm that was ≤ 0.833 would provide adequate evidence of effectiveness for SER-109 for the proposed indication. When recruitment challenges precluded enrollment of a proposed 320 subjects, the Applicant revised the sample size to 188. The study terminated enrollment after accrual of 182 subjects due to the challenges in clinical trial conduct in the setting of the COVID-19 pandemic. The primary efficacy endpoint was evaluated in the SERES-012 intent-to-treat (ITT) population consisting of 182 subjects, with 89 SER-109 recipients and 93 placebo recipients. The subjects had a mean age of 65.5 years (range, 18-100 years), 93% were white, 60% were female, and 73% had received vancomycin. The primary efficacy endpoint was CDI recurrence through 8 weeks after treatment. Subjects were assessed for recurrence, which was defined as ≥3 unformed stools per day for 2 consecutive days with continued diarrhea until antibacterial treatment was initiated, a positive *C. difficile* test on a stool sample determined by a toxin assay, and assessment by the investigator that the subject warranted antibacterial treatment. Following 8 weeks of treatment, there were statistically significantly fewer SER-109 recipients with CDI recurrence (11 of 89 or 12.4%) than placebo recipients (37 of 93, or 39.8%). The point estimate of the RR of CDI recurrence (RR) with SER-109 compared to placebo in the intent-to-treat (ITT) population was 0.32 (95% CI: 0.18, 0.58). The upper bound of 0.58 met the pre-specified treatment success criterion of ≤ 0.833. The analysis in the per-protocol (PP) population was similar, with a RR of 0.30 (95% CI: 0.16, 0.56).

Safety evaluations included unsolicited adverse events (AEs), adverse events of special interest (AESIs; namely invasive infections), and serious adverse events (SAEs), which were prospectively collected for up to 24 weeks after treatment. Solicited AEs using diary cards were collected for 7 days after treatment in SERES-012. Most of the of the safety database for the 3-day regimen of SER-109 was obtained from SERES-013, an open-label extension trial associated with SERES-012. Subjects with CDI recurrence within 8 weeks of completing study drug were eligible to roll over to receive SER-109 (Cohort 1). Subsequently, the protocol was revised to include a cohort of *de novo* adult subjects with 2 (rather than 3) or more episodes of CDI (Cohort 2) to fulfill the minimum agreed upon safety database of 300 recipients of the 3-day regimen of SER-109. The ISS considered combined unsolicited treatment-emergent adverse events (TEAEs) from paired studies of the 3-day regimen (SERES-012/SERES-013) and a study of the 1-day regimen (SERES-004/SERES-005).

In an analysis of AEs occurring within 8 weeks after blinded treatment in SERES-012 (the only study that obtained solicited AEs), the most common adverse reactions (defined as AEs assessed as definitely, possibly, or probably related to SER-109 by the investigator) reported by ≥5% of SER-109 recipients and at a rate greater than that reported by placebo recipients included: abdominal distension (31.1% of SER-109 recipients and 29.3% of placebo recipients), fatigue (22.2% and 21.7%), constipation (16.7% and 10.9%), chills (11.1% and 8.7%), and diarrhea (10.0% and 4.3%). Most adverse reactions occurred within the first week after treatment and lasted for a median

duration of 5 days or less. Rates of subjects with at least one adverse reaction declined from 48.9% and 51.1% during the first week after completing treatment in the SER-109 and placebo arms, respectively, to 6.7% and 3.4% during the second week after treatment. Rates plateaued at 6.7% and 5.7% during the third week through eighth week after treatment, and to 0% in both arms after 8 weeks and through 6 months of follow-up. The severity profile of the solicited adverse reactions (collected in SERES-012 only) were generally similar among SER-109 and placebo recipients.

Safety data (unsolicited TEAEs, AESIs, SAEs) from a total of 460 subjects exposed to SER-109, with 349 who received the 3-day regimen (SERES-012 and SERES-013) and 111 who received the 1-day regimen (SERES-004 and SERES-005) were evaluated in regimen-specific pairs (see Section 8. Integrated Overview of Safety). In SERES-012/-013 (3-day regimen), the proportion of subjects with at least one unsolicited treatment-emergent adverse event (TEAE) was 57.0% (199/349) among SER-109 recipients and 66.3% (61/92) among placebo recipients. In SERES-004/-005 (1-day regimen), the rate of TEAEs was 80.2% (89/111) among SER-109 recipients and 69.0% (20/29) among placebo recipients.

In the SERES-012/SERES-013 integrated safety dataset, there were 7 events with MedDRA PTs that included “bacteremia” or “sepsis” in 7 subjects. One case was culture-negative, while the others had blood or urine cultures that grew *Escherichia coli* (n=3), *Pseudomonas aeruginosa*, *Serratia marcescens*, *Abiotrophia defectiva*, or *Proteus mirabilis*. None of these AESIs were considered related or possibly related to SER-109. They were attributed to subject’s intercurrent medical illnesses or pre-existing conditions (e.g., prolonged ventilator-associated pneumonia in the ICU with acute coronavirus infection, chronic indwelling foley, hemodialysis catheter, therapeutic immunosuppression). Furthermore, the organisms isolated from blood cultures were aerobes and non-spore formers. In the SERES-004/SERES-005 integrated safety database, a total of 8 subjects (7.2%; 8/111) had AESIs, namely cellulitis (4.5%; n=5), sinusitis (1.8%; n=2), and sepsis (1.8%; n=2). One subject had numerous intercurrent infections: rCDI, recurrent cellulitis, UTI, and pneumonia. The other subject’s sepsis was attributed to diarrhea, colitis, but available cultures (blood) had no growth.

Across SERES-012 and SERES-013, 13.8% (48/349) of SER-109 recipients and 20.7% (19/92) of placebo recipients reported a SAE within 6 months of completing treatment. The most frequently reported SAE in SER-109 recipients was UTI (3.3%) and in placebo recipients it was *C. difficile* colitis (7.6%). None of these events were considered related to the study drug. Across SERES-004 and SERES-005, 17.1% (19/111) of SER-109 recipients and 10.3% (3/29) of placebo recipients reported an SAE. The most frequently reported SAE in SERES-004/-005 was diarrhea.

Across controlled studies SERES-012 and SERES-004, death occurred in 3.3% (3/90) and 1.7% (1/59) of SER-109 recipients. There were no deaths reported for placebo recipients. The three deaths in SERES-012 did not occur during study drug administration (all occurred after the completion of three days of therapy) and were attributable to acute events, pre-existing conditions, and progression of a malignancy (see [Section 6.1.12.3](#)). The 1 death that was observed in SERES-004 (1.7%) in the SER-109 recipient was due to progression of a malignancy (see [Section 6.2.12.3](#)). None of the deaths were considered related to the SER-109 by study investigators and most of the narratives strongly implicate the role of pre-existing conditions or acute events. There was no temporal clustering of the deaths relative to SER-109 treatment.

Furthermore, when compared to published rates of mortality in rCDI populations, which vary from 6% to 55% (Lessa et al. 2015; Olsen et al. 2015; Feuerstadt et al. 2022), the mortality rates observed in SERES-012 and SERES-004 are within reported ranges. The absence of deaths among the 92 placebo recipients in SERES-012 and the 30 placebo recipients in SERES-004 may have been due to small sample size.

In the uncontrolled studies of open-label administration of SER-109, there were 12 additional deaths reported. As with SERES-012 and SERES-004, the patient populations enrolled in these other trials were generally considered to have serious chronic medical conditions that predisposed them to adverse outcomes, including mortality. The 12 deaths had confounding factors associated with their clinical cases, and some cases did not have complete information. Among the deaths with a concurrent bacterial infection, when available the culture results did not represent a bacterial pathogen contained in SER-109. There is no direct comparison group (i.e., no placebo group) with which to draw definitive conclusions about the potential for a mortality imbalance. As noted above in the clinical review of rCDI, high rates of mortality (26 to 36% within 6 months of CDI treatment) are observed in these patients (Olsen et al. 2015). Although definitive conclusions cannot be made about the lack of attribution of the study drug to the observation of the deaths, the FDA's assessment is that it is highly unlikely that the deaths were related to SER-109 administration for the reasons stated above.

Conclusions

- rCDI is a serious condition associated with high rates of morbidity and mortality. There is an unmet medical need because currently available treatment options are limited and can be complex and prolonged.
- Data from SERES-012 demonstrate that SER-109 is effective in preventing rCDI in individuals 18 years of age and older who respond to antibacterial treatment for rCDI and take the 3-day regimen of SER-109 within 2 to 4 days of completion of antibacterial treatment, preceded by a bowel cleanse the day prior. The primary efficacy analysis in the ITT population met the pre-specified success criterion of an upper bound of the 95% CI of the RR of rCDI with SER-109 relative to placebo that was 0.58, which is less than 0.833. Through 8 weeks after treatment, rCDI in SER-109 recipients was lower compared to that in placebo recipients (12.4% compared to 39.8%). The analysis in the per-protocol population was similar, with a RR of 0.30.
- Most adverse reactions associated with SER-109 in SERES-012 were gastrointestinal, mostly mild or moderate in severity, and occurred within 1 week of completing SER-109.
- There was an imbalance in urinary tract infections observed in SERES-012 (8/90 SER-109 recipients versus 1/92 placebo recipients). The time of onset varied widely, ranging between Study Day 2 and 157. For those with available urine culture data (6 out of the 8 SER-109 recipients), the culprit organisms were gram-negative uropathogens or enterococci, which are not contained in SER-109.
- In the controlled studies, mortality rates were 3.3% (SERES-012: 3/90 SER-109 recipients vs 0/92 placebo recipients) and 1.7% (SERES-004: 1/59 vs 0/30). Of the 16 deaths that occurred among SER-109 recipients in the phase 2 and phase 3 drug development program, 12 deaths occurred in the uncontrolled studies SERES-013 (3.1%; 8/263) and SERES-005 (5.6%; 4/72). These rates are on the lower end of published mortality ranges of 9.3% to 36% in similar populations

with rCDI (Lessa et al. 2015; Olsen et al. 2015; Feuerstadt et al. 2022). Although the lack of a comparator arm and multiple confounders limit a definitive assessment of causality, the narrative review indicated that the deaths were due to chronic medical condition(s) or acute events reflecting individual subjects' comorbidities and were considered unrelated to SER-109.

- In summary, this reviewer concludes that the benefit-risk balance for SER-109 is favorable for the indication being requested by the Applicant.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Section 1.1 on demographic information and subgroup analyses is included early in the template clinical review for ease in identifying information about the safety and efficacy in certain subgroups. The clinical development program included five prospective studies (SERES-001, SERES-004, SERES-005, SERES-012, SERES-013), which enrolled a total of 573 unique subjects, with 490 who received open-label or blinded SER-109 (349 of whom received the 3-day regimen of SER-109). Subjects who participated in SERES-004 and SERES-012 and who experienced rCDI prior to Week 8 after treatment were eligible to roll over to the associated open-label studies, SERES-005 and SERES-013, respectively. Each study included 24 weeks of follow-up after administration of study drug. Subgroup analyses from SERES-012 are descriptive analyses without pre-specified success criteria.

Of the 349 subjects who received the 3-day regimen of SER-109 being licensed, 327 completed up to 24 weeks of follow-up, with median duration of 169.0 days (range: 5 to 232 days). The median age was 66 years. Most were White (92.3%), not Hispanic or Latino (92.6%), female (68.8%). The age strata were balanced, with 52.8% of subjects ≥65 years of age. The numbers of subjects in other racial groups (second most common being Black [5.2%]) were too small to perform meaningful efficacy and safety analyses by race.

Subgroup Analysis of Treatment Success Within 8 Weeks (ITT population), SERES-012
The relative risk (RR) of CDI 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 RR was 0.58, which is lower than 0.833, the study success threshold that FDA agreed could be considered substantial evidence of effectiveness from a single study, which in this case is SERES-012. [Table 1](#) presents subgroup analyses of efficacy among the 182 subjects in SERES-012 (89 in the SER-109 arm and 93 in the placebo arm) by age strata (<65 years versus ≥65 years), antibacterial therapy for CDI episode at entry (vancomycin versus fidaxomicin), sex, and number of total CDI episodes (3 versus >3 CDI episodes). The RR of CDI recurrence ranged between 0.09 (for fidaxomicin) and 0.47 (for males). For race, RR could only be estimated for White subjects, which was 0.29.

Table 1. Relative Risk (RR) of CDI Recurrence at Week 8, Subgroups for Analysis, ITT Population, SERES-012

| Subgroup | Recurrence SER-109 N=89 | Recurrence Placebo N=93 | Relative Risk ^a |
|---------------|-------------------------------|-------------------------------|----------------------------|
| <65 years old | 7.3% (3/41) | 30.8% (12/39) | 0.24 |
| ≥65 years old | 16.7% (8/48) | 46.3% (25/54) | 0.36 |
| Vancomycin | 15.6% (10/64) | 37.7% (26/69) | 0.41 |
| Fidaxomicin | 4.0% (1/25) | 45.8% (11/24) | 0.09 |

| Subgroup | Recurrence SER-109 N=89 | Recurrence Placebo N=93 | Relative Risk ^a |
|------------------------------------|-------------------------------|-------------------------------|----------------------------|
| Male | 13.8 (4/29) | 29.5 (13/44) | 0.47 |
| Female | 11.7% (7/60) | 49.0% (24/49) | 0.24 |
| 3 prior CDI episodes ^c | 14.8% (4/27) | 47.6% (10/21) | 0.31 |
| >3 prior CDI episodes ^d | 25.0% (3/12) | 45.5% (5/11) | 0.55 |

Source: Figure 14.2.7 and Table 14.2.2.3.1 from SERES-012 CSR

*This data missing for 1 SER-109 recipient

^aRelative risk is defined as the SER-109 recurrence rate divided by the placebo recurrence rate.

^cLimited to subjects with a total of 4 CDI episodes at study entry; the denominators do not add up to total of 89 SER-109 recipients and 93 placebo recipients because this subgroup analysis does not include group of those with 2 prior (i.e., 3 total) CDI episodes at study entry

^dLimited to subjects with a total of > 4 CDI episodes at study entry

Safety Analyses by Sex, Age Subgroup

The Applicant conducted subgroup analyses of AEs and adverse reactions based on sex and age (<65 years, ≥65 years). Analyses of treatment emergent adverse events among sex and age group showed no substantive differences in safety across the respective subgroups, except with respect to urinary tract infections, as shown in [Table 2](#).

The profiles of TEAEs in SER-109 recipients based on sex and age strata were similar. For instance, with respect to sex:

- In SERES-012, the most frequently reported TEAEs in male SER-109 recipients were solicited AEs of flatulence (64.3%), fatigue (57.1%), abdominal pain (46.4%), and abdominal distension (46.4%). In females, the most frequently reported TEAEs were also solicited AEs, including flatulence (72.6%), fatigue (59.7%), abdominal distension (58.1%), and abdominal pain (53.2%). Similar results were observed for subgroups among placebo recipients in SERES-012.
- In the SERES-012/-013 integrated dataset, the most frequently reported TEAEs in male subjects were diarrhea (24.8%), flatulence (23.9%), and fatigue (20.2%) (Table 84). In female subjects, flatulence (23.8%), diarrhea (22.5%), abdominal pain (19.6%), abdominal distension (17.9%), and fatigue (17.9%) were most frequently reported.

Within the integrated dataset of SERES-012/-013, there was higher incidence of SAEs in male SER-109 recipients (22.9%) compared to female SER-109 recipients (9.6%) and in older subjects (≥ 65 years old) than younger subjects (< 65 years old). However, this imbalance was less pronounced in the placebo-controlled study SERES-012. In the integrated safety set, the higher incidence of SAEs in males was largely driven by single cases (e.g., aspiration pneumonia, syncope, urosepsis) that did not occur in female subjects, and the higher incidence in older adults ran in parallel with underlying medical conditions. Otherwise, the safety profile of SER-109 in the pre-specified subgroups did not reveal any patterns that raised product-specific safety concerns.

Table 2. Treatment-Emergent Adverse Events Among SER-109 Recipients by Sex and Age Group, Integrated Safety Population, SERES-012/-013

| Subjects with ≥ 1 of the following events | Females N=240 | Males N=109 | < 65 years old N=166 | ≥ 65 years old N=183 |
|---|------------------|----------------|-------------------------|-------------------------|
| Any TEAE | 146 (60.8) | 75 (68.8) | 103 (62.0) | 118 (64.5) |
| Urinary Tract Infection | 16 (6.7) | 5 (4.6) | 6 (3.6) | 15 (8.2) |

| Subjects with ≥ 1 of the following events | Females N=240 | Males N=109 | < 65 years old N=166 | ≥ 65 years old N=183 |
|---|------------------|----------------|-------------------------|-------------------------|
| Serious Adverse Event | 23 (9.6) | 25 (22.9) | 14 (8.4) | 34 (18.6) |

Source: Tables 82 - 85 from Integrated Summary of Safety, Section 5.3 in STN 125757/1

1.2 Patient Experience Data

Data Submitted in the Application

| Check if Submitted | Type of Data | Section Where Discussed, if Applicable |
|-------------------------------------|--|--|
| <input checked="" type="checkbox"/> | Patient-reported outcome | Sections 2.1, 6.1.11.5 |
| <input type="checkbox"/> | Observer-reported outcome | |
| <input type="checkbox"/> | Clinician-reported outcome | |
| <input type="checkbox"/> | Performance outcome | |
| <input type="checkbox"/> | Patient-focused drug development meeting summary | |
| <input type="checkbox"/> | FDA Patient Listening Session | |
| <input type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| <input type="checkbox"/> | Observational survey studies | |
| <input type="checkbox"/> | Natural history studies | |
| <input type="checkbox"/> | Patient preference studies | |
| <input type="checkbox"/> | Other: (please specify) | |
| <input type="checkbox"/> | If no patient experience data were submitted by Applicant, indicate here. | |
| Check if Considered | Type of Data | Section Where Discussed, if Applicable |
| <input type="checkbox"/> | Perspectives shared at patient stakeholder meeting | |
| <input type="checkbox"/> | Patient-focused drug development meeting | |
| <input type="checkbox"/> | FDA Patient Listening Session | |
| <input type="checkbox"/> | Other stakeholder meeting summary report | |
| <input type="checkbox"/> | Observational survey studies | |
| <input type="checkbox"/> | Other: (please specify) | |

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Clostridioides difficile (*C. difficile*) is a spore-forming, gram-positive anaerobic bacterium that causes colitis, typically after disruption of the human gastrointestinal (GI) microbiome by antibiotic therapy. In the disrupted gut microbiome, *C. difficile* colonizes the GI tract and its spores germinate and proliferate into toxin-producing vegetative bacteria within the colon. These toxins invade epithelial cells and disrupt the

cytoskeleton, resulting in damage to the epithelial barrier and promoting mucosal inflammation .

CDI is one of the most common health care-associated infections and a significant cause of morbidity and mortality, especially among older adult hospitalized patients. In the United States, CDI is associated with 15,000 to 30,000 deaths annually, with acute inpatient costs exceeding \$4.8 billion . Population-based surveillance of CDI in 10 US sites identified 15,512 cases in 2017, including 7,973 healthcare-associated and 7,539 community-associated cases (Guh et al. 2020). Globally, CDI incidence rate ranges from 1.1 to 631.8 per 100,000 population per year (Balsells et al. 2019). The Centers for Disease Control and Prevention (CDC) consider CDI to be an urgent, antibiotic resistance threat (McDonald et al. 2018). Globally, CDI incidence rate ranges from 1.1 to 631.8 per 100,000 population per year (Balsells et al. 2019).

Approximately 10% to 30% of patients will develop rCDI after an initial episode of CDI, and each recurrence increases the risk for subsequent recurrence, with reported recurrence rates of 65% after three episodes of CDI (McDonald et al. 2018). rCDI is defined as an episode of CDI occurring within 8 weeks of a previous episode. rCDI may be due to relapse of previous CDI by the same strain or reinfection by a different strain. The most frequently reported risk factors for rCDI include age >65 years (Deshpande et al. 2015), antibiotic use for non-CDI after CDI diagnosis leading to disruption of the native intestinal microbiome, gastric acid suppression, infection with a hypervirulent strain (e.g., NAP1/BI/027, which produces a larger amount of toxins A and B), severe underlying disease, renal insufficiency, immunosuppression, inflammatory bowel disease, history of previous CDI, previous CDI severity, prolonged hospital stays, and lack of adaptive immune responses to toxins A and B .

Clinical Manifestations, Diagnosis and Treatment

CDI causes manifestations ranging from an asymptomatic carriage to fulminant disease with toxic megacolon . The most common signs and symptoms of moderate CDI are watery diarrhea >3 times a day for more than one day, mild abdominal cramping and tenderness. CDI complications include dehydration and kidney failure from significant loss of fluids and electrolytes due to severe diarrhea, which can result in hypotension. Other complications include bowel perforation, peritonitis, and death from even mild to moderate infection if not treated promptly. Surgical intervention with colectomy may be required when aggressive medical management is unsuccessful.

Diagnosis

According to Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), the diagnostic criteria for CDI include new-onset diarrhea (≥ 3 unformed stools in 24 hours without an alternative etiology), and positive stool test for toxicogenic *C. diff* or toxins, or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis. An algorithmic approach to testing is recommended, including highly sensitive tests, such as glutamate dehydrogenase (GDH) followed by confirmation with more specific tests, including enzyme immunoassays (EIAs) to detect toxins A and B and nucleic acid amplification testing (McDonald et al. 2018; Kelly et al. 2021).

Quality-of-life scores in patients with rCDI are lower compared to patients with a first episode of CDI, and consistently decrease with increasing number of CDI episodes

(Garey et al. 2016). In considering the benefits and harms of treatment for rCDI, the expert panel contributing to the development of the Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America judged, based on clinical experience, that patients experiencing rCDI will invariably put a high value on avoidance of a subsequent CDI episode (Johnson et al. 2021).

The Applicant submitted health-related quality of life and health outcomes assessed throughout the study SERES-012 via the CDI-specific Cdiff32 Health Related Quality of Life (HRQoL) and EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaires. These data were exploratory and were not intended to support any labeling efficacy claims. The HRQoL at 24 weeks and the EQ-5D-5L at 8 weeks after starting SER-109 compared to placebo were analyzed as exploratory endpoints. The HRqOL questionnaire consists of 32 questions regarding physical (general and specific complaints), mental (future and current anxiety), and social (relationships) domains of daily living. Each question is scored on a 5-point scale, from 0 (most positive) to 100 (most negative) in increments of 25, and the total score is divided by 32. The EQ-5D-5L is a brief questionnaire comprising 5 dimensions/questions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored from 1 (no problems) to 5 (extreme problems).

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

An initial episode of CDI is often successfully managed by fluid replacement, discontinuation of antibiotics if possible, and initiation of first-line antibacterial therapy with oral fidaxomicin or vancomycin. According to clinical practice guidelines published in 2021, fidaxomicin rather than vancomycin is the recommended first-line therapy for adult patients with an initial CDI episode, although vancomycin is an acceptable alternative. Second-line agents include metronidazole, nitazoxanide, rifamycin, and cytotoxin binding agents such as cholestyramine or colestipol (Johnson et al. 2021).

For adult patients with a recurrent CDI episode, fidaxomicin (standard or extended-pulsed regimen) is recommended as first-line therapy, although vancomycin (standard or tapered and pulsed regimen) is an acceptable alternative. Bezlotoxumab (Zinplava), a human monoclonal antibody directed against toxin B, was approved on October 21, 2016 for reduction in recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at high risk for CDI recurrence. For patients with a recurrent CDI episode within the last 6 months, bezlotoxumab is recommended as a co-intervention along with standard or extended-pulsed standard-of-care antibiotics such as fidaxomicin or vancomycin. For patients with more than one recurrence, treatment options may also include a course of rifaximin if a standard course of vancomycin was used (Johnson et al. 2021).

In Phase 3 trials, patients with a history of congestive heart failure had an increased risk of heart failure with use of bezlotoxumab compared to placebo (12.7% vs 4.8%) as well as an increased risk of death (19.5% vs 12.5%). Therefore, in patients with a history of congestive heart failure (CHF), the package insert advises under Section 5 [Warnings and Precautions] that bezlotoxumab should be reserved for use when the benefit outweighs the risk.

2.3 Safety and Efficacy of Pharmacologically Related Products

Fecal microbiota transplantation (FMT) is recommended by various gastroenterology and infectious diseases practice guidelines and has been widely used, especially in the past ~10 years, as an unapproved product for this purpose, and FMT has been available as an unapproved therapy for rCDI under FDA's investigational new drug (IND) enforcement discretion policy since July 2013. A draft guidance was released on March 2016, outlining IND requirements for use of FMT obtained from stool banks to treat CDI not responsive to standard therapies. The draft guidance was finalized in November 2022. No large-scale studies evaluating efficacy or safety of FMT administered to individuals under enforcement discretion have been submitted to the Agency for review. However, results of randomized, placebo-controlled trials of FMT products administered to individuals under enforcement discretion have been reported in the literature (van Nood et al. 2013; Kelly et al. 2016; Lee et al. 2016; Hota et al. 2017; Hvas et al. 2019).

FDA has issued multiple safety communications based on safety reports from specific investigational FMT products or safety concerns that resulted in revisions to donor screening and stool testing practices across all investigational FMT products. FDA safety communications to date include:

- June 13, 2019: risk of serious or life-threatening infections due to transmission of multi-drug resistant organisms (FDA 2019).
- March 12, 2020: risk of serious or life-threatening infections due to infections caused by enteropathogenic *Escherichia coli* and Shiga toxin-producing *Escherichia coli*, including events that occurred following investigational use of FMT, suspected to be due to transmission of these pathogenic organisms from the FMT product (FDA 2020a).
- March 23, 2020: potential risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) due to the documented presence of SARS-CoV-2 ribonucleic acid and/or SARS-CoV-2 virus in stool of infected individuals (FDA 2020b).
- August 22, 2022: potential risk of transmission of monkeypox virus due to the documented presence of monkeypox virus DNA in rectal swabs and/or stool samples from infected individuals (FDA 2022).

On November 30, 2022, the FDA approved RBX2660 (proprietary name Rebyota), a fecal microbiota suspension for intrarectal use to prevent rCDI in individuals 18 years of age and older, following antibacterial treatment for CDI. RBX2660 is prepared from human stool collected from prescreened, qualified donors and tested for prespecified pathogens and other infectious agents. It is supplied as a pre-packaged single dose in an enema bag.

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

Not applicable

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

- **Pre-IND teleconference (June 2014):** Discussion focused on preparing an IND for evaluating SER- 109 for preventing recurrences of CDI and including CMC information.

- **IND submission (December 2014):** Seres submitted a phase 3 protocol that was placed on clinical hold because of insufficient manufacturing information and the phase 1 clinical data (from open-label study SERES-001) was not considered to be sufficient to support a phase 3 trial.
- **Breakthrough Therapy (BT) request #1 (December 2014):** FDA denied this initial BT request because the IND was on clinical hold.
- **BT request #2 (May 2015):** This request was granted on 6/11/15 because of the favorable results from trial SERES-001 when compared to historical control data, which was submitted with this second BT request.
- **Orphan Drug Designation (August 2015):** SER-109 received Orphan Drug Designation for the proposed indication of treatment of recurrent *C. difficile* infection (rCDI) for a subset of individuals with rCDI (estimated prevalence of 163,000 using the reported prevalence in 2011 by the CDC (453,000 cases), the 2015 US population (320 million), and the upper boundary of percentage of recurrence after initial CDI (35%).
- **End-of-Phase 2 (EOP2) meeting (January 2017)** In brief, post hoc analyses from the Sponsor's completed clinical development program provided support for a selection of a dosing regimen to bring forward to a phase 3 trial.
- **Pre-BLA Meeting Request (November 2021)** – For the Integrated Safety Summary, we requested that the data for the 3-day regimen be presented separately from the data for the 1-day regimen.
- **Priority Review Request (October 2022):** Priority review was granted based on the rationale that if approved, SER-109 would offer significant improvements in the safety of a preventative treatment for CDI recurrence. In addition, its oral route of administration suitable for an outpatient setting was considered a clinically important improvement.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This BLA submission was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant stated that the clinical studies SERES-001, SERES-004, SERES-005, SERES-012 and SERES-013 were conducted in accordance with the study protocols and submitted according to relevant regulations in 21 CFR Part 11, 50, 54, 56 and 312 and 45 CFR 160 and 164, and the ICH E6 Good Clinical Practice: Consolidated Guidance; and applicable Health Canada regulations for the protection of human subjects, and with the ethical principles that have their origin in the Declaration of Helsinki.

The Applicant stated that the informed consent form was reviewed and approved by an institutional review board.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of one foreign and three domestic clinical investigators who participated in the conduct of SERES-012. The

inspections did not reveal substantiative issues that impact the data submitted in this original BLA. [Table 3](#) lists inspection sites and BIMO inspection classification.

Table 3. Bioresearch Monitoring Inspection Classification

| Site Number and Location | FDA Form 483 Issued | Final Classification |
|---------------------------------|----------------------------|-----------------------------|
| 234 Bountiful UT | No | No Action Indicated (NAI) |
| 302 Greenville, NC | No | NAI |
| 406 Alberta Canada | No | NAI |
| 305 Cleveland, OH | No | NAI |

Source: BIMO Final Discipline Review by Char-Dell Edwards

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 and list of investigators for the clinical studies submitted to the BLA, and certified that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the studies. The Applicant certified that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21 CFR 54.2 were reported.

| |
|---|
| Covered clinical study (name and/or number): SERES-012 and SERES-013 |
| Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Total number of investigators identified: <u>223 (principal) and 743 (sub-investigators)</u> |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u> |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u> |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant) |

| |
|--|
| <p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): _____</p> <p>Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)</p> |
|--|

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

4.1 Chemistry, Manufacturing, and Controls

SER-109 is derived from Donor Human Stool (DHS). The components of the SER-109 Drug Product (DP) are presented in [Table 4](#) below.

Table 4. Components of SER-109 Drug Product

| Component | Grade | Function |
|-----------------|---------|---|
| SER-109 DS | NA | Active ingredient (<i>Firmicutes</i> bacterial spores) |
| Glycerol | (b) (4) | Excipient, non-aqueous |
| Sodium chloride | (b) (4) | Excipient, component of saline solution |
| (b) (4) | (b) (4) | Excipient, component of saline solution |
| Inner capsule | (b) (4) | Primary capsule, sealed to contain liquid formulation |
| (b) (4) | (b) (4) | (b) (4) agent |
| Outer capsule | (b) (4) | Appearance, imprinted with "SER109" in blue ink |

Source: Table 1 in Section 3.2.P.3 from STN 12757/60,

Drug substance (DS) containing *Firmicutes* bacterial spores purified from stool collected from qualified human donors is used in the manufacture of SER-109 DP capsules. DS bacterial spore suspension matrix contains (b) (4) w/w glycerol (b) (4) with (b) (4) w/w saline.

To be eligible for donor screening, individuals must be 18 through 49 years of age. The process by which individuals are screened and qualified to become active stool donors begins with a full health history questionnaire, screening physical exam, entrance blood and stool pathogen screening, and supplemental screening (e.g., nasopharyngeal polymerase chain reaction (PCR) testing for COVID). Once qualified, active donors undergo (b) (4) stool pathogen screening and provide (b) (4) stool donations, all of which undergo stool analysis.

Key components of the 5 events for donor qualification are listed below:

- Event 1: Optional Pre-screening – donor recruiting mechanism
- Event 2: Pre-qualification
 - Full health history questionnaire (FHHQ), which included SARS-CoV-2 and Mpox screening
 - Stool donations over approximately (b) (4) to assess spore levels; candidate is only invited to return for Event 3 (formal start of donation activities) if spore levels are favorable

- Event 3: Donor Qualification (must be completed throughout the donation period before stool material is released)
 - Donor screening lab testing includes (b) (4)
[REDACTED]
 - Stool pathogen testing for parasitic, viral and bacterial pathogens; stool must be negative for screening assay for (b) (4) Shigella/EIEC, (b) (4) *Escherichia coli* strains (b) (4) EPEC, (b) (4), STEC [→ E. coli] (b) (4)
[REDACTED]
- Event 4: (b) (4) Collection
 - (b) (4) health history questionnaire to verify continued good health
 - (b) (4) screening for GI pathogens and SARS-CoV-2
 - After entering Event 4, donations are collected continuously to ensure frequent monitoring of donor health. To remain qualified, donors should not have unexcused absences from donation of more than (b) (4) continuous days.
- Event 5: (b) (4) Screening
 - Active donors must complete (b) (4) FHHQ, medical physical screening exam, blood and stool screening for pathogens (as outlined under Event 3).
- Other Control measures
 - Every (b) (4) months, donors are screened for kidney and liver function and blood counts at Event 5 to assess the continued good health of the donor
 - At least one Event 5 is required to occur before any donor material is released for manufacturing. In addition, donor material may only be released within the bracketed period of Event 3 - Event 5.

4.2 Assay Validation

Please refer to the CBER Chemistry and Manufacturing Controls memo (Siobhan Cowley, PhD).

4.3 Nonclinical Pharmacology/Toxicology

Non-clinical pharmacology/toxicology studies were not performed. Module 4 was not required for this BLA (Written Response to the pre-BLA questions sent on 2022).

4.4 Clinical Pharmacology

Clinical pharmacology studies were not conducted and not required.

4.4.1 Mechanism of Action

The exact mechanism of action is not fully understood, but it is thought to involve repopulation and restoration of the composition and diversity of the gut microbiome that is disrupted by CDI and antibacterial treatment.

4.4.2 Human Pharmacodynamics (PD)

The Applicant submitted descriptive data on microbiome and metabolome changes based on stool samples from subjects in Studies SERES-012 as well as SERES-001 and SERES-004. Please refer to [Section 6.1](#) and the CBER Chemistry and Manufacturing Controls memo (Siobhan Cowley, PhD) for a summary of the exploratory studies pertaining to product engraftment and resultant changes in the profile of stool microbiome constituents and metabolic products that the Applicant included in this BLA.

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

The statistical reviewer verified the efficacy and sensitivity analyses in SERES-012. Please refer to the CBER statistical memo (Zhong Gao, PhD) for details.

4.6 Pharmacovigilance

The Applicant proposed to conduct routine pharmacovigilance, which consists of adverse event reporting in accordance with 21 CFR 600.80, quarterly periodic safety reports for 3 years, and annual periodic safety reports thereafter. The Applicant agreed to conduct a voluntary safety surveillance post-marketing study to further characterize the safety profile of SER-109. This surveillance study of approximately 750 individuals will be conducted using data from large US healthcare database(s) following feasibility assessment. The primary objective is to characterize the safety of SER-109 in patients with rCDI, including the rates of UTIs and other medically important infections. The proposed primary endpoints are the incidence of UTIs, and incidence of medically important infections, which will be outlined in the final protocol, from the first day of treatment through 24-weeks of follow-up. Tentative milestone dates include final protocol submission on 09/30/2024, study completion by 03/31/2028, and final study report submission by 08/31/2028.

Please refer to the CBER review by Jonathan Reich, MD from the Office of Biostatistics and Epidemiology for details.

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

5.1 Review Strategy

The clinical development program for SER-109 included 5 studies (SERES-001, SERES-004, SERES-005, SERES-012, and SERES-013) submitted to STN 125757. These studies were reviewed under IND 16262. Two Phase 3 studies, SERES-012 and SERES-013, were reviewed to support the safety and efficacy with placebo-controlled SERES-012 being the main phase 3 study evaluated to demonstrate the effectiveness of SER-109. SERES-013 was an open-label extension study that enrolled most of the

subjects to fulfill the minimum safety database for the dosing regimen of SER-109 being licensed. It also provided descriptive efficacy out to 24 weeks. SERES-001 was the first-in-human open-label multi-center study of varying doses and regimens of SER-109; it was not conducted under IND. SERES-004 and SERES-005 were placebo-controlled and open-label extension studies, respectively, of a one-day regimen of SER-109.

The placebo-controlled efficacy and safety data from SERES-012 are presented in Section 6.1. The safety and descriptive efficacy data from SERES-013 are presented in Section 6.2. The other three studies are presented with a high-level summary in Sections 6.3 through 6.5. A summary and discussion of the integrated safety results from SERES-012, SERES-013, SERES-004, and SERES-005 are presented in Section 8. Pooling of safety data were limited to unsolicited AEs, AESIs and SAEs between SERES-012 and SERES-013 (3-day regimen), and SERES-004 and SERES-005 (one-day regimen). Considerations in the interpretation of comparisons between the placebo and SER-109 arms in the ISS populations included:

- Subjects crossing over from both placebo and SER-109 arms to receive open-label SER-109 due to recurrence of CDI, which may reflect increased risk for AEs due to underlying risk factors that predispose to rCDI or co-morbidities attributable to the CDI
- Differences in safety data collection (i.e., AE solicitation limited to SERES-012, prospective collection of AESIs in SERES-012 and SERES-013 and retrospective collection in SERES-004 and SERES-005)
- The open-label nature of many of the SER-109 regimens taken by subjects (n=234 in SERES-013 versus 89 in SERES-012)

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

The following amendments, modules and content were assigned to and reviewed by the clinical reviewer.

- **STN 125757/0** (received May 24, 2022): Part 1 of 2 of the rolling BLA
 - Sections 1.6 (Meetings); 1.7 (Fast Track); 1.12 (Other Correspondence – Request for Comments and Advice, Environmental Analysis and Orphan Drug Designation)
- **STN 125757/1** (received August 26, 2022): Part 2 of 2 of the rolling BLA
 - Sections 1.3 (Administrative information including Debarment Certification and Financial Disclosure); 1.4 (Statement of Right to Reference); 1.6 (Meetings), 1.18 (Proprietary Names)
 - Sections 2.3 (Quality Overall Summary), 2.5 (Clinical Overview); 2.7 (Clinical Summary)
- **STN 125757/7 and 32** (received September 29, 2022 and January 18, 2023): Responses to information request (IR) about the Monkeypox donor screening questionnaire and revised informed consent form
- **STN 125757/38** (received February 8, 2023): Response to request for any updates to subjects with UTI listed as “ongoing”
- **STN 125757/46** (received February 24, 2023): Submission of diary card used to collect solicited AEs in SERES-012

- **STN 125757/54 and 58** (received March 17 and March 24, 2023): Response to requests for additional tabulations of safety data
- **STN 125757/57** (received March 27, 2023): Response to request for *post hoc* analysis of RR of CDI recurrence in subjects with two CDI episodes total
- **STN 125757/60** (received March 31, 2023): Section 3.2.S.2 [Manufacture]
- **STN 125757/62, 67, 68** (received April 4 and 11, 2023): Response to questions regarding source data and number of total investigators
- **STN 125757/72 and 73** (received April 21 and 25, 2023): Finalized patient package insert (PPI) and package insert (PI).

5.3 Table of Studies/Clinical Trials

The Applicant has conducted a total of five clinical studies, which are presented in [Table 5](#) in the order in which they were conducted. Of these, two studies (SERES-012 and SERES-013) evaluated the dose and regimen of SER-109 that is being licensed.

Table 5. Clinical Studies Evaluating the Safety and Efficacy of SER-109 for the Prevention of Recurrent *C. Difficile* Infection

| Study Number | Study Design Study Arm(s): N | Dose and Regimen | Key Eligibility Criteria | Efficacy Endpoint/ Safety Endpoint |
|---------------------------|--|--|--|---|
| SERES-001 (non-IND) | Open-label, first-in-human, Phase 1 Part 1: 15 Part 2: 15 | <u>Part 1</u> 3.4 x 10 ⁷ – 2.3 x 10 ¹⁰ SporQ* for 2 days <u>Part 2</u> 8.6 x 10 ⁷ – 1.9 x 10 ⁸ SporQ* for 1 day | ≥3 CDI episodes | CDI recurrence within 8 weeks of treatment AEs thru week 24 |
| SERES-004 | Phase 2 DBPCRCT SER-109: 59 Placebo: 30 | 1 x 10 ⁸ SporQ* (4 capsules) as single dose for one day | ≥3 CDI episodes | CDI recurrence within 8 weeks of treatment AEs thru week 12 SAEs thru week 24 |
| SERES-005 | Open-label Phase 2 extension Cohort 1: 34 from SERES-004 Cohort 2: 38 from expanded access | 1 x 10 ⁸ SporQ* (4 capsules) as single dose for 1 day | ≥2 CDI episodes | CDI recurrence within 8 weeks of treatment AEs thru week 12 SAEs thru week 24 |
| SERES-012 | Phase 3 DBPCRCT SER-109: 89 Placebo: 93 | 10 ⁷ CFU daily (4 capsules) as single dose for 3 days | ≥3 CDI episodes | CDI recurrence within 8 weeks of treatment AEs thru week 8, SAEs and AESIs thru week 24 |
| SERES-013 | Phase 3 open-label extension and new open-label program Cohort 1: 29 Cohort 2: 234 | 10 ⁷ CFU (4 capsules) as single dose for 3 days | Cohort 1: ≥4 CDI episodes Cohort 2: ≥2 CDI episodes | CDI recurrence within 8 weeks of treatment AEs thru week 8, SAEs thru week 24 |

Source: FDA reviewers

Abbreviations: AE=adverse event, AESI=adverse event of special interest, CDI=*Clostridioides difficile* infection, CFU=colony-forming units, DBPCRCT=double-blind placebo-controlled randomized clinical trial, SAE=serious adverse event

5.4 Consultations

None

5.5 Literature Reviewed

Balsells, E, T Shi, C Leese, I Lyell, J Burrows, C Wiuff, H Campbell, MH Kyaw, and H Nair, 2019, Global burden of Clostridium difficile infections: a systematic review and meta-analysis, *J Glob Health*, 9(1):010407.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: **SERES-012**

[NCT03183128](#): SER-109 Versus Placebo in the Treatment of Adults with Recurrent *Clostridium Difficile* Infection (rCDI) (ECOSPOR III)

6.1.1 Objectives (Primary, Secondary, etc.)

Primary efficacy objective: To evaluate the efficacy of SER-109 versus placebo in the reduction of CDI recurrence rates, determined by a toxin assay, up to 8 weeks after initiation of treatment

Primary safety objective: To evaluate the safety and tolerability of SER-109 versus placebo in subjects with rCDI, defined as a history of ≥ 3 CDI episodes within 12 months, inclusive of the current episode.

Secondary efficacy objectives:

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

Exploratory Objectives

- To compare changes in the composition of the gut microbiome in the SER-109 treatment group to changes in the composition of the gut microbiome in the placebo group from Baseline up to 1, 2, 8, and 24 weeks after initiation of treatment
- To compare changes in the fecal metabolome in the SER-109 treatment group versus in the placebo group from Baseline up to 1, 2, and 8 weeks after initiation of treatment
- To determine the incidence of mortality from all causes up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To determine the incidence of hospitalizations for rCDI up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To determine the incidence of all hospitalizations up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To determine, for subjects who are hospitalized, the total length of stay (days) of hospitalization, including days in the intensive care unit, up to 8 and 24 weeks after initiation of treatment in each of the two treatment groups
- To assess health outcomes, including HRQOL, by using the EQ-5D-5L and the HRQOL survey for CDI (Cdiff32) up to 24 and 8 weeks, respectively, after the initiation of treatment in each of the two treatment groups

6.1.2 Design Overview

This Phase 3, randomized, double-blinded, multi-center trial was powered to evaluate the ability of SER-109 versus placebo to reduce the recurrence of CDI (as determined by a toxin assay rather than PCR, which was the case in SERES-004) relative to placebo up to 8 weeks after study treatment. The statistical criterion for success was to demonstrate that the upper bound of the 95% CI of the estimate of the relative risk of CDI recurrence in SER-109 recipients compared to placebo recipients was less than or equal to 0.833. The study enrolled 182 subjects 18 years of age or older with rCDI, defined as a history of ≥ 3 CDI episodes within 12 months, inclusive of the current episode. Subjects were randomized to an oral dose of SER-109 in 4 capsules once daily for 3 consecutive days or matching placebo.

Reviewer comment: *The Applicant's initial plan was to enroll 320 subjects in SERES-012, but the accrual rate was slow, with an estimated enrollment of 0.057 patients/site/month, whereas the rate of enrollment for their completed Phase 2 study (SERES-004) was 0.18 patients/site/month. Slow enrollment was attributed to the accessibility and greater acceptance of FMT (with approximately 83% of the U.S. population being within a 1-hour drive to a health care facility providing stool bank FMT (Panchal et al. 2018)), misconception among both physicians and patients that FMT is safe and effective (as reflected in an updated clinical practice guidelines from the IDSA which strongly recommends FMT as an option for patients with 2 or more recurrences of CDI based on "moderate evidence," despite a broad range of reported outcomes from uncontrolled data), and reluctance of both physicians and their patients to enter a placebo-controlled study where at best they have a 50% chance of receiving the active drug. Due to these barriers in study enrollment, in May 2018 the Applicant proposed changes to reduce the trial size. The FDA responded that this proposal would be acceptable provided that the success criterion be maintained to demonstrate that upper bound of the 95% CI of the point estimate of the RR of CDI recurrence with SER-109 versus placebo was equal to or less than 0.833. The FDA did not specify the final study size. The final statistical analysis plan (SAP) (dated April 25, 2019) stated target enrollment of 188 subjects. This new sample size was derived from recurrence rate assumptions based on available data from blinded assessment of CDI recurrences in SERES-012 and SERES-013, which estimated the placebo recurrence rate to be 36%. Based on fixed sequence multiple testing, 188 subjects (94 in each arm) would provide 83% power to test the null hypothesis that the RR of CDI recurrence of SER-109 to placebo was 1 or greater at a one-sided significant level of 0.025, and 62% power to test the second null hypothesis that RR was 0.833 or greater at a one-sided significance level of 0.025. SERES-012 closed enrollment when 182 subjects were enrolled due to the COVID-19 pandemic.*

6.1.3 Population

This study enrolled adults 18 years of age or older with rCDI. To be eligible for enrollment, subjects were required to have a qualifying episode of CDI as defined by:

- a. ≥ 3 unformed stools per day for 2 consecutive days
- b. A positive *C. difficile* stool toxin assay. Documentation of a positive *C. difficile* stool test result preferably performed by a central laboratory
- c. The requirement of CDI standard-of-care antibiotic therapy (defined as 10-21 days of treatment with vancomycin [125 mg qid] or fidaxomicin [200 mg bid]).

Note: It was acceptable if subject had started on metronidazole, switched to vancomycin or fidaxomicin and was 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.

Subjects must also have had ≥ 3 episodes of CDI (or, in other words, 2 or more CDI recurrences) within the previous 12 months, inclusive of the current episode, with documented history of ≥ 2 episodes, inclusive of the current (qualifying) episode, including dates, test results, and antibiotic treatments received.

Subjects who were taking probiotics had to agree to discontinue them at the time of consent. All subjects had to agree not to take probiotics for the duration of study participation.

Exclusion criteria included: known or suspected toxic megacolon, known small bowel ileus, use of antibacterial therapy other than standard-of-care antibiotics for the most recent episode of CDI during the screening period, major GI surgery within 3 months of enrollment, any history of total colectomy or bariatric surgery (however, banding and other restrictive procedures which do not disrupt the GI lumen are permitted), active inflammatory bowel disease, unable to stop loperamide, diphenoxylate/atropine, or cholestyramine prior to start of study, receipt of human monoclonal antibody against *C. difficile* toxin within 3 months before study entry, and FMT within the past 3 months.

Reviewer comment: *Protocol Amendment 2 revised the inclusion criteria to include subjects with a history of ≥ 3 CDI episodes within 12 months instead of 9 months, to facilitate subject enrollment given the difficulty in study subject accrual. The eligibility criteria for this study selected for individuals with 2 or more recurrences of CDI (i.e., total of 3 CDI episodes) in the past 12 months which is appropriately representative of the Orphan Drug designation (pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) of SER-109, because it affects fewer than 200,000 subjects. Exclusion criteria appropriately mitigated the potential risks and challenges in assessing the causality of AEs that could be plausibly associated with a stool-based product.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Standard-of-care antibacterial therapy: All 182 enrolled subjects had a qualifying CDI episode treated with 10-21 days of vancomycin or fidaxomicin with confirmed symptom resolution, followed by completion of a bowel cleanse on study Day -1.

Bowel cleanse (Day -1): 10 oz (~300 mL) of oral magnesium citrate followed by overnight fasting for at least 8 hours. Subjects with impaired kidney function who were unable to take magnesium citrate took 250 mL of GoLytely (polyethylene glycol electrolyte solution). The purpose of the bowel cleanse was to promote engraftment of SER-109, which is further described in this BLA as promoting clearance of residual vancomycin or fidaxomicin completed by subjects 2 to 4 days earlier.

Reviewer comment: *While the Applicant has not obtained data demonstrating that the bowel cleanse promotes the clearance of residual vancomycin or fidaxomicin, we did not request this during product development. The purported*

effect of the bowel cleanse is plausible because both antibacterial agents act locally within the GI tract and a bowel cleanse would be expected to facilitate in the mechanical clearance of any contents of the GI tract, including residual vancomycin or fidaxomicin.

On Day 1, 4 study drug capsules were administered orally with at least 8 oz of water (capsules were to be swallowed, not chewed) and subjects were required to continue the fast for an additional hour. This additional fast was intended to ensure operational consistency across the numerous study sites and optimize the setting for monitoring for potential adverse reactions attributable to the study drug. On Days 2 and 3, in-clinic visits or phone calls were used to confirm administration of the second and third doses of the study drug before breakfast.

All enrolled subjects randomly assigned to either SER-109 or placebo were stratified by age (<65 years, ≥65 years) and by antibiotic regimen for the qualifying episode (vancomycin or fidaxomicin).

A total of 90 subjects received oral doses of SER-109 (3×10^7 SCFU) for 3 consecutive days starting on Day 1. One subjects who did not document taking the capsules on Days 2 and 3 was considered to have not completed the regimen. A total of 92 subjects received matching placebo in identical dosing regimen.

Reviewer comment: *Part of the exploratory objectives of SERES-012 was to demonstrate engraftment of SER-109 by characterizing the changes in the composition of the gut microbiome based on whole genome sequencing and quantification of diversity and changes in the composition of the fecal metabolome at multiple time points between Baseline and 24 weeks after treatment. These data were generated using non-validated assays, however, but are supportive of the clinical efficacy data obtained in SERES-012.*

6.1.5 Directions for Use

Take 4 capsules as a single dose with at least 8 fluid ounces of water in the morning before breakfast. Capsules are to be swallowed and not chewed.

6.1.6 Sites and Centers

A total of 182 subjects were enrolled from 56 sites in North America: 51 U.S; 5 Canada. Each site enrolled at least one subject (range 1-13 subjects).

Reviewer comment: *BIMO inspected three domestic and one Canadian site. No significant issues were identified.*

6.1.7 Surveillance/Monitoring

- Clinical assessments: physical exam at screening and on Day 1; laboratory assessments at screening, Day 1, Week 8, recurrence visit(s), and early termination visit.
- Monitoring for CDI recurrence:

- Daily electronic diarrhea log. Subjects with diarrheal symptoms recurred (≥ 3 unformed stools per day over 2 consecutive days) were instructed to contact the investigator and return to the clinic.
- AE monitoring during efficacy period:
 - Weekly phone calls to query for AEs and diarrheal symptoms recorded using an electronic daily diary (Day 1 through Week 8)
 - Patient diary card for solicited AEs (Day 4 through Day 10), specifically gas/flatulence, abdominal distention or bloating, abdominal pain or cramping, nausea, anorexia, vomiting, fatigue, chills or shivering, constipation with grading on a 0 to 3 (severe=noticed symptom and interfered with daily activities), and temperature (measured by thermometer)
- AE monitoring during follow-up period: Phone calls every 4 weeks to query for SAEs, AESIs, and any antibiotic medication and its corresponding indication (Weeks 12, 16, 20, and 24)
- Independent data safety and monitoring committee (DSMC): The DSMC reviewed blinded safety data, namely, suspected unexpected serious adverse reactions (SUSARs) as they occurred, and monthly blinded SAE and AESI listings.
- Study withdrawal/discontinuation: Subjects who voluntarily withdrew, or who were withdrawn, from the study were encouraged to complete the Early Termination Visit for evaluation for rCDI, physical exam, and laboratory assessments.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Ability of SER-109 versus placebo to reduce the recurrence of CDI as determined by a toxin assay (FDA approved test performed in a CLIA-certified lab), relative to placebo up to 8 weeks after study treatment. The pre-specified success criterion was met if the upper bound of the 95% CI of the point estimate of the RR of CDI recurrence in SER-109 recipients compared to placebo recipients was less than or equal to 0.833.

Secondary efficacy endpoints:

- CDI recurrence by PCR algorithm up to 4, 8, 12, and 24 weeks after treatment
- CDI recurrence by toxin assay up to 4, 12, and 24 weeks after treatment
- Time to CDI recurrence as determined by toxin assay
- Time to CDI recurrence as determined by PCR algorithm

Safety endpoints: Safety and tolerability of SER-109 up to 24 weeks after treatment as assessed by:

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

Reviewer comment: In SERES-012, the case definition of CDI recurrence was revised based on previous experience with Phase 2 study SERES-004. In SERES-

004, the case definition required a positive PCR testing which does not discriminate between colonization and an acute infection. This was thought to be a confounder in SERES-004 due to the detection of 75% of all recurrences in both the SER-109 and placebo arms within 20 days after treatment. Therefore, for SERES-012, we agreed upon the following testing algorithm which was conducted at a central laboratory:

(Step 1) *C. difficile* Tox A+B and *C. difficile* glutamate dehydrogenase (GDH)
If both were positive, no further testing was needed. If there was discordance between these two tests, a follow-up *C. difficile* cytotoxicity assay (CCNA) was performed. A positive CCNA test was required for the toxin algorithm to be considered positive. The test models used at the central laboratory for the toxin algorithm were:

- *C. difficile* GDH: (b) (4)
- *C. difficile* Tox A+B: (b) (4)
- *C. difficile* Toxin CCNA: Cell Cytotoxicity Neutralization Assay

In addition to the testing requirement, subjects were required to continue to have 3 or more loose stools up until the time of initiating antibacterial therapy to ensure true infection as opposed to self-limited post-infectious GI symptoms.

Protocol Amendment 6 allowed for subjects with CDI recurrence within first 8 weeks of study to roll over into open-label extension trial immediately upon completion of antibiotic therapy for that recurrent episode (rather than waiting until Week 8 visit) so that all subjects who had a recurrence, especially those randomized to placebo, could access treatment.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size

The initial sample size of 320 was derived using an assumed CDI recurrence rate of 59% in the placebo arm and 30% in the SER-109 arm. The primary efficacy measure is the RR reduction of CDI recurrence within 8 weeks after completion of treatment, defined as $P1/P2$, where P1 is the proportion of subjects with CDI recurrence in the SER-109 group and P2 is the proportion of subjects with CDI recurrence in the placebo group. This sample size was selected to provide sufficient power to demonstrate that the upper bound of the 95% CI of the RR of CDI recurrence in SER-109 recipients compared to placebo recipients was less than or equal to 0.833.

Due to slow study accrual, the Applicant recalculated the sample size from 320 to 188 (Amendment 7) using recurrence rate assumptions based on newly available data, namely blinded assessment of the CDI recurrences observed in SERES-012 (approximately 26%) and the 16% recurrence rate in open-label SERES-013. The placebo recurrence rate was estimated to be 36%, much lower than the original assumed rate of 59%. With 94 subjects in each arm, the study was powered at 83% to detect a statistically significant different ($RR < 1$) and powered at 62% to meet the pre-specified success criterion ($RR \leq 0.8333$)

Reviewer comment: FDA agreed that a single efficacy study would be acceptable if the same success criterion for the upper bound of the 95% CI of the point estimate of the RR of CDI recurrence in SER-109 recipients compared to placebo recipients was ≤ 0.8333 . If a less stringent criterion (i.e., upper bound of the 95% CI of the $RR < 1$) was demonstrated, another placebo-controlled Phase 3 study would have been required.

Statistical Analysis Plan (SAP)

The final version (4.0) of the SAP submitted to FDA is dated April 13, 2020. According to the SAP, the primary analysis was to be performed using the Cochran-Mantel-Haenszel (CMH) test of the RR of SER-109 to placebo, stratified by age (<65 years and ≥65 years) and prior antibacterial regimen for the qualifying episode (vancomycin or fidaxomicin). The RR was analyzed by pre-specified subgroups based on age (<65 years and ≥65 years) and antibacterial therapy received for the qualifying CDI episode at study entry (vancomycin or fidaxomicin). CIs were determined using the Greenland and Robins variance estimate for the natural logarithm of the common RR.

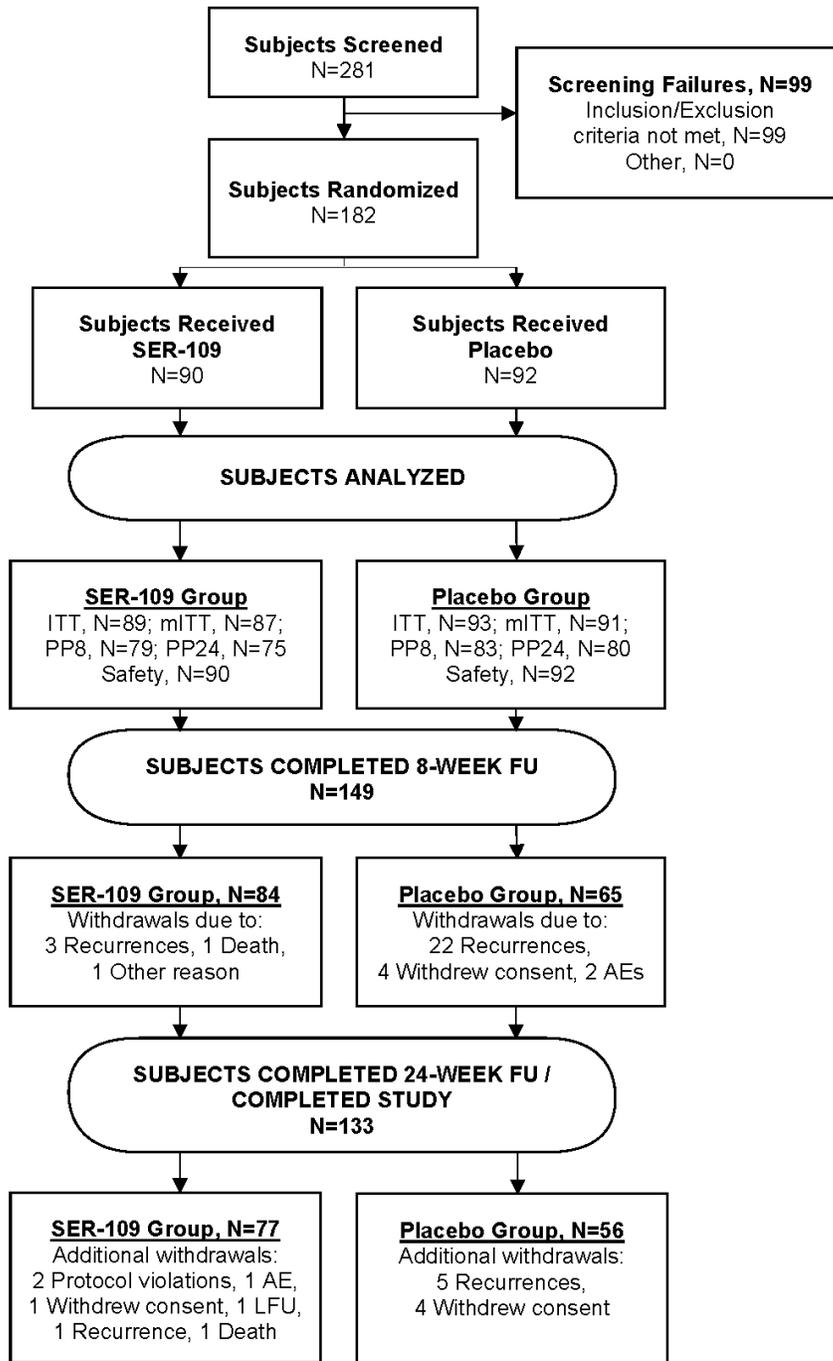
The success criterion for efficacy was to demonstrate that the upper limit of the 95% CI of the RR (P1/P2) was less than or equal to 0.833, which corresponds to an RR reduction by 17%.

6.1.10 Study Population and Disposition

Study period: July 10, 2017 (first subject enrolled) to September 29, 2020 (last subject completed).

Of the 281 subjects screened, 182 subjects were enrolled in the study and analyzed in the primary efficacy analysis. As shown in [Figure 1](#), 91.3% (84/92) of the SER-109 arm and 72.2% (65/90) of the placebo arm remained in the study through 8 weeks after study drug. The most common reason for withdrawal during the 8-week assessment period was CDI recurrence (n=3 in SER-109 arm and 22 in the placebo arm) and rolling over to the open-label treatment study SERES-013. Study completion rate through 6 months of follow-up was also higher in the SER-109 arm (86.7%; n=77/84) than the placebo arm (59.8%; 56/65). The most common reason for discontinuation in both arms during the 6-month interval was CDI recurrence (4.4% (n=4) with SER-109 and 29.3% (n=27) with placebo). The other reasons for discontinuation for SER-109 was an unrelated AE of worsening glioblastoma, and 2 subjects died (due to atrial fibrillation and sepsis in 1 subject and fall and subdural hematoma in 1 subject). In the placebo arm, 2 subjects had AEs (acute respiratory failure in 1 subject and cardiac failure congestive, cardiac failure acute, pulmonary hypertension, and urinary retention in 1 subject). Additional reasons for study withdrawal in the SER-109 group were protocol violation/non-compliance, consent withdrawal, lost to follow-up, and physician discretion (documented under 'other').

Figure 1. Disposition of Subjects, SERES-012



Source: Figure 13 from CSR Addendum 1, version 2, with correction to subject disposition numbers as reported in Figure 2 of the SERES-012 CSR, Version 2, dated 14 May 2021. No statistical outputs were impacted by this correction to the in-text figure.

Abbreviations: 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

Notes: Subject # (b) (6) died after withdrawing consent, and this event is not reflected in the death totals. Subjects allocated using forced randomization were analyzed according to the original treatment group to which they were assigned for the ITT and mITT Populations. These subjects were excluded from PP Populations because forced randomization was considered a major protocol deviation.

6.1.10.1 Populations Enrolled/Analyzed

Table 6. Analysis Populations, SERES-012

| Population | SER-109 | Placebo |
|---|--------------------------------------|--------------------------------------|
| Intent to Treat (ITT; primary efficacy population): All randomized subjects, including those not exposed to study drug; subjects were analyzed as having received the treatment to which they were randomly assigned. ^a | 89 | 93 |
| Modified Intent to Treat (mITT): All randomized subjects who received any amount of study drug, CDI clinically controlled by antibiotics before receiving study drug and at least 1 post-baseline evaluation ^b | 87 | 91 |
| Per Protocol (PP): Subjects from mITT population without major protocol deviations ^c | 79 (Wk 8) 75 (Wk 24) ^d | 83 (Wk 8) 80 (Wk 24) ^d |
| Safety: All randomized subjects who received any amount of study drug; subjects were analyzed according to the treatment actually received rather than what they were assigned to | 90 | 92 |

Source: FDA-generated table from SERES-012 CSR

- Subjects randomized using forced randomization will be analyzed according to original treatment arm they were randomized to and not the one based on the forced randomization algorithm.
- In the mITT population, 2 SER-109 recipients were excluded (Subject # (b) (6) (stool sample was not collected for qualifying episode) and Subject # (b) (6) (vancomycin dosing for qualifying episode not per protocol)) and 2 placebo recipients were excluded: Subject # (b) (6) (vancomycin dosing for qualifying episode not per protocol) and Subject # (b) (6) (used PCR assay and not toxin assay results for qualifying episode).
- Major protocol deviations: subject not meeting eligibility criteria impacting safety or data integrity, no documentation of informed consent prior to screening and enrollment, receipt of prohibited medication for CDI without a recurrence (for those started on antibiotics awaiting central lab results, treatment for more than 3 days considered major deviation), subjects with 3 or more unformed BMs per day for 2 consecutive days with no site contact for recurrence evaluation or missing evidence that symptoms subsided, forced randomization
- Subjects with major protocol deviations were included in the PP24 population.

Reviewer comment: Forced randomization was in place to avoid failed randomizations in the unlikely event that the assigned study medication (SER-109 (including specific lot) or placebo) 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. Seres submitted a correspondence dated Oct 23, 2017 in which FDA agreed with the forced randomization and related analysis population definition. The difference in the number of subjects in each arm based on randomization, 89 versus 90 SER-109 recipients and 93 versus 92 placebo recipients, was due to forced randomization. Two subjects were originally assigned SER-109 but received placebo. These subjects were analyzed as SER-109 recipients for efficacy and as placebo recipients for safety. Three subjects were originally assigned placebo but received SER-109. These subjects were analyzed as placebo recipients for the efficacy analysis and SER-109 recipient for safety.

6.1.10.1.1 Demographics

Table 7 shows the demographic characteristics of the study population in SERES-012, which was comprised of mostly White, not Hispanic adults. Mean and median ages were similar. No major imbalances between treatment groups were identified. There was greater representation of females in the SER-109 arm (68.9%) than in the placebo arm (51.1%). The proportion of subjects in the two age strata were balanced in and across treatment arms. Vancomycin was the more commonly prescribed antibacterial treatment for the qualifying CDI episodes (approximately 70%) across treatment arms, and most

subjects in the SER-109 arm (56.7%) and placebo arm (64.1%) had two prior CDI episodes (i.e., total 3 CDI episodes).

Table 7. Demographic Characteristics, SERES-012, Safety Population

| Characteristic | SER-109 (N=90) | Placebo (N=92) | Total (N=182) |
|---|----------------|----------------|---------------|
| Age (years) | -- | -- | -- |
| Mean (SD) | 65.8 (16.4) | 65.3 (16.8) | 65.5 (16.5) |
| Median | 67.0 | 68.0 | 68.0 |
| Min; Max | 21; 100 | 18; 96 | 18; 100 |
| Age group, n (%) | -- | -- | -- |
| <65 years | 40 (44.4) | 39 (42.4) | 79 (43.4) |
| ≥65 years | 50 (55.6) | 53 (57.6) | 103 (56.6) |
| Sex, n (%) | -- | -- | -- |
| Male | 28 (31.1) | 45 (48.9) | 73 (40.1) |
| Female | 62 (68.9) | 47 (51.1) | 109 (59.9) |
| Ethnicity, n (%) | -- | -- | -- |
| Hispanic or Latino | 6 (6.7) | 5 (5.4) | 11 (6.0) |
| Non-Hispanic or non-Latino | 84 (93.3) | 87 (94.6) | 171 (94.0) |
| Race, n (%) | -- | -- | -- |
| Asian | 1 (1.1) | 0 (0.0) | 1 (0.5) |
| Black or African American | 4 (4.4) | 4 (4.3) | 8 (4.4) |
| White | 83 (92.2) | 87 (94.6) | 170 (93.4) |
| Other | 2 (2.2) | 1 (1.1) | 3 (1.6) |
| Body mass index (kg/m ²) | -- | -- | -- |
| Mean (SD) | 26.86 (6.92) | 26.87 (6.48) | 26.87 (6.68) |
| Median | 26.29 | 25.70 | 26.12 |
| Q1; Q3 | 21.91; 29.12 | 22.05; 30.42 | 22.04; 29.56 |
| Min; Max | 14.7; 47.5 | 14.9; 48.9 | 14.7; 48.9 |
| Number of total CDI episodes ^a , n (%) | -- | -- | -- |
| 3 | 51 (56.7) | 59 (64.1) | 110 (60.4) |
| 4 | 26 (28.9) | 22 (23.9) | 48 (26.4) |
| 5 | 5 (5.6) | 6 (6.5) | 11 (6.0) |
| ≥6 | 7 (7.8) | 5 (5.4) | 12 (6.6) |
| Prior antibiotic regimen, n (%) | -- | -- | -- |
| Vancomycin | 65 (72.2) | 68 (73.9) | 133 (73.1) |
| Fidaxomicin | 25 (27.8) | 24 (26.1) | 49 (26.9) |
| Prior FMT history, n (%) | -- | -- | -- |
| Yes | 5 (5.6) | 5 (5.4) | 10 (5.5) |
| No | 85 (94.4) | 87 (94.6) | 172 (94.5) |
| BI/NAP1/027 status, n (%) | -- | -- | -- |
| BI/NAP1/027 | 11 (12.2) | 9 (9.8) | 20 (11.0) |
| Non-BI/NAP1/027 | 57 (63.3) | 57 (62.0) | 114 (62.6) |
| Missing | 22 (24.4) | 2 (2.3) | 48 (26.4) |

Source: SERES-012 Clinical Study Report, Table 4.1.3.1.1.

Abbreviations : CDI *Clostridioides difficile* infection, FMT fecal microbiota transplantation

a. Includes CDI episode at study entry

Notes: Percentages are based on the number of subjects in the Safety Population. One placebo recipient had missing data for BMI.

Reviewer comment: *This population is representative of the subset of adults with 3 or more CDI episodes. The lack of racial and ethnic diversity could be a limitation to the generalizability of the outcomes. However, the trial enrollment has a large representation of subjects at high risk for recurrence, which is the population of interest. The SER-109 and placebo arms were generally balanced in terms of demographic variables, except for sex. Approximately 69% of SER-*

109 recipients were female while approximately 51% of placebo recipients were female. The greater representation of females in the SER-109 arm has the potential to have impacted outcomes because female sex is a risk factor for CDI recurrence. In the opinion of this reviewer, any bias from this sex imbalance would have been mitigated by balanced representation of other risk factors, namely age greater than 65 years, immunosuppression, chronic kidney disease, and infection with the hypervirulent *C. difficile* ribotype N1/NAP1/027, across treatment groups. Furthermore, potential bias from greater representation of females in the SER-109 arm would not have favored study success. With respect to safety data, the greater representation of females in the SER-109 arm may have contributed to the greater proportion of subjects with UTIs in the SER-109 arm than placebo. The imbalance in UTIs across treatment groups is discussed in [Section 6.1.12.2](#).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A total of 136 (74.7%) subjects in SERES-012 had any significant medical history, with the following conditions in descending order:

- hypertension (54.9%)
- gastroesophageal reflux disease (GERD) (42.9%)
- hyperlipidemia and dyslipidemia (34.6%)
- hypothyroidism (18.1%)

As shown in [Table 8](#), most common coexisting conditions included MedDRA System Organ Classes (SOCs) of *Gastrointestinal disorders* (74.7%), *Vascular disorders* (67.6%), *Metabolism and nutrition disorders* (62.1%), *Psychiatric disorders* (48.9%), *Renal and urinary disorders* (34.6%), *Cardiac disorders* (32.4%), and MedDRA Preferred Terms (PTs) of Type 2 diabetes mellitus (16.5%) and chronic kidney disease (10.4%). Approximately a third of the study population (29.7%; 54/182) were immunocompromised.

Table 8. Medical History, Conditions Reported Among at Least 10% of the Safety Population, SERES-012

| System Organ Class Preferred Term | SER-109 (N=90) n (%) | Placebo (N=92) n (%) | Total (N=182) n (%) |
|------------------------------------|----------------------|----------------------|---------------------|
| Gastrointestinal disorders | 64 (71.1) | 72 (78.3) | 136 (74.7) |
| Surgical and medical procedures | 60 (66.7) | 57 (62.0) | 117 (64.3) |
| Vascular disorders | 58 (64.4) | 65 (70.7) | 123 (67.6) |
| Musculoskeletal, connective tissue | 54 (60.0) | 52 (56.5) | 106 (58.2) |
| Metabolism and nutrition disorders | 52 (57.8) | 61 (66.3) | 113 (62.1) |
| Type 2 diabetes mellitus | 10 (11.1) | 20 (21.7) | 30 (16.5) |
| Infections and infestations | 46 (51.1) | 50 (54.3) | 96 (52.7) |
| Diverticulitis | 8 (8.9) | 2 (2.2) | 10 (5.5) |
| Urinary tract infection | 8 (8.9) | 7 (7.6) | 15 (8.2) |
| Pneumonia | 7 (7.8) | 7 (7.6) | 14 (7.7) |

| System Organ Class Preferred Term | SER-109 (N=90) n (%) | Placebo (N=92) n (%) | Total (N=182) n (%) |
|---|----------------------|----------------------|---------------------|
| Psychiatric disorders | 46 (51.1) | 43 (46.7) | 89 (48.9) |
| Nervous system disorders | 40 (44.4) | 41 (44.6) | 81 (44.5) |
| Renal and urinary disorders | 34 (37.8) | 29 (31.5) | 63 (34.6) |
| Chronic kidney disease | 10 (11.1) | 9 (9.8) | 19 (10.4) |
| Respiratory, thoracic, mediastinal | 31 (34.4) | 45 (48.9) | 76 (41.8) |
| Chronic obstructive pulmonary disease | 4 (4.4) | 13 (14.1) | 17 (9.3) |
| Cardiac disorders | 30 (33.3) | 29 (31.5) | 59 (32.4) |
| Coronary artery disease | 12 (13.3) | 10 (10.9) | 22 (12.1) |
| Atrial fibrillation | 8 (8.9) | 13 (14.1) | 21 (11.5) |
| Cardiac failure congestive | 4 (4.4) | 7 (7.6) | 11 (6.0) |
| Immune system disorders | 27 (30.0) | 22 (23.9) | 49 (26.9) |
| Drug hypersensitivity | 10 (11.1) | 12 (13.0) | 22 (12.1) |
| Endocrine disorders | 24 (26.7) | 21 (22.8) | 45 (24.7) |
| Reproductive system and breast disorders | 24 (26.7) | 20 (21.7) | 44 (24.2) |
| Blood and lymphatic system | 23 (25.6) | 26 (28.3) | 49 (26.9) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 22 (24.4) | 27 (29.3) | 49 (26.9) |
| Hepatobiliary disorders | 13 (14.4) | 16 (17.4) | 29 (15.9) |

Source: SERES-012 Clinical Study Report Table 14.1.4.1, STN 125757/1

Reviewer comment: Based on MedDRA PT term only, the proportion of subjects with type 2 diabetes mellitus was approximately two-fold higher in the placebo arm (21.7%) than the SER-109 arm (11.1%). However, the Applicant conducted a broader query to capture diabetes and we were able to reproduce the statistics of 20.0% in the SER-109 arm and 27.2% in the placebo arm. The other comorbidities had balanced representation across treatment groups: cardiac disease (33.3% in SER-109 arm and 31.5% in placebo arm), immunocompromise/ immunosuppression (28.9% in SER-109 arm and 30.4% in placebo arm), and renal failure/impairment (14.4% in SER-109 arm, 15.2% in placebo arm).

6.1.10.1.3 Subject Disposition

Of the 281 subjects screened for SERES-012, 182 (64.8%) passed screening. All enrolled subjects were stratified by age (<65 years, ≥65 years) and by antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin). For the ITT population, randomizations were analyzed according to the original treatment group to which they were assigned, which accounts for the 89 subjects in the SER-109 arm and 93 subjects in the placebo arm. The safety population, subjects were analyzed according to the study drug received. A total of 49 subjects (12 SER-109 recipients, 37 placebo recipients) discontinued early from the study, with the most common reason being CDI recurrence. All reasons are presented in [Table 9](#).

Table 9. Disposition of Subjects, SERES-012

| Disposition | SER-109 N (%) | Placebo N (%) | Total N (%) |
|--------------------------------|---------------|---------------|-------------|
| Passed screening | | | 182 |
| ITT population ^a | 89 | 93 | 182 |
| Safety population ^b | 90 | 92 | 182 |
| Completed the study | 77 (86.5) | 56 (60.2) | 133 (73.1) |

| Disposition | SER-109 N (%) | Placebo N (%) | Total N (%) |
|-------------------------------|---------------|---------------|-------------|
| Withdrawn from study | 12 (13.5) | 37 (39.8) | 49 (26.9) |
| Reason for withdrawal | -- | -- | -- |
| CDI recurrence | 4 (4.5) | 27 (29.0) | 31 (17.0) |
| Subject withdrawal of consent | 1 (1.1) | 8 (8.6) | 9 (4.9) |
| Adverse event | 1 (1.1) | 2 (2.2) | 3 (1.6) |
| Protocol violation | 2 (2.2) | 0 (0.0) | 2 (1.1) |
| Death | 2 (2.2) | 0 (0.0) | 2 (1.1) |
| Loss to follow-up | 1 (1.1) | 0 (0.0) | 1 (0.5) |
| Other | 1 (1.1) | 0 (0.0) | 1 (0.5) |

Source: Table 14.1.1.1 from SERES-012 CSR, STN 125757/1

a The ITT Population consisted of all subjects who were randomized and was analyzed based on the treatment to which they were randomly assigned. Subjects randomized using forced randomization were analyzed according to the original treatment arm they were randomized to.

b The Safety Population consisted of all randomly assigned subjects who receive any amount of study drug. Subjects will be analyzed according to the treatment they actually received. Subjects randomized using forced randomization were analyzed according to the treatment they actually received.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy assessment was the proportion of subjects who had a CDI recurrent as determined by toxin assay within 8 weeks after treatment. The primary efficacy endpoint was calculated as the CDI recurrence rate in SER-109 recipients divided by the CDI recurrence rate in placebo recipients, which is the point estimate of RR. The pre-specified criterion for efficacy was demonstrated if the upper bound of the corresponding 95% CI of the RR was less than or equal to 0.833. The primary efficacy analysis was conducted in the ITT population at 8 weeks after treatment ([Table 10](#), below).

Reviewer comment: We agreed upon designating prevention of CDI recurrence as the primary efficacy endpoint as expressed by the RR of CDI recurrence with SER-109 relative to placebo. The case definition of CDI recurrence was revised based on the post hoc analysis of Phase 2 study SERES-004, which did not meet success criteria. Revisions were to require a positive toxin assay result as opposed to a positive PCR, which cannot distinguish between colonization and infection, and to require that the diarrhea continue until antibacterial treatment, which was deemed clinically necessary, was initiated. The Applicant hypothesized that the CDI recurrence rate with SER-109 would be halved relative to placebo. The success criterion pertained to the upper limit of the 95% CI around the RR of CDI recurrence. We agreed that an upper limit of 0.833 or less, which corresponds to an RR reduction of approximately 27%, would be a clinically significant margin.

Table 10. C. difficile Infection Recurrence Rates and Relative Risk at 8 weeks (up to Day 58) as Determined by a Toxin Assay (Primary Efficacy Endpoint)

| Time Interval After Dose | SER-109 N=89 | Placebo N=93 |
|---|-----------------|-----------------|
| 8 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 11 (12.4) | 37 (39.8) |
| RR² | 0.32 | -- |

| Time Interval After Dose | SER-109 N=89 | Placebo N=93 |
|----------------------------|-----------------|-----------------|
| 95% CI for RR ³ | 0.18; 0.58 | -- |

Source: SERES-012 Clinical Study Report, Version 2.0; Table 10: *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

Abbreviations: CDI=*C. difficile* infection; CI=confidence interval; RR=relative risk; ITT= intent-to-treat; mITT= modified intent-to-treat

Notes: 4-week 1-sided *P*-value for RR \geq 1: 0.00073. 4-week *P*-value for diff in recur rates: 0.00036. 8-week *P*-value for RR \geq 1: 0.00010. 8-week *P*-value for RR \geq 0.833: 0.00091. 8-week *P*-value for diff in recur and sust resp rates: 0.000027. 12-week *P*-value for RR \geq 1: 0.00013. 24-week *P*-value for RR \geq 1: 0.00041. 12-week *P*-value for diff in recur and sust resp rates: 0.000047. 24-week *P*-value for diff in recur rates: 0.00023. The primary efficacy analysis was performed at the 12-week interim database lock (28 July 2020). At the final database lock (20 October 2020), it was identified that 6 subjects underwent forced randomization, and as per the SAP, these subjects were analyzed according to their original treatment assignment and not the treatment they actually received due to forced randomization. The forced randomizations impacted the ITT, mITT, PP8, and PP24 Populations.

[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. Handling of other types of missing data are provided in the SAP (Appendix 16.1.9).

[2] Relative risk is defined as the SER-109 recurrence rate divided by the Placebo recurrence rate. The Cochran-Mantel-Haenszel (CMH) estimate of the common relative risk, stratified by age group (<65 years, \geq 65 years) and prior antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin), is reported.

[3] The confidence interval was calculated using the Greenland and Robins variance estimate for the natural logarithm of the common relative risk.

Sensitivity analyses conducted with different imputation approaches, presented below, yielded results consistent with the primary efficacy analysis.

1. Subjects lost to follow-up, terminated the study prematurely, or died without having a CDI recurrence on or before Day 58 considered to have a favorable outcome (no CDI recurrence) in both treatment groups: RR=0.31 (95%CI, 0.16, 0.58)
2. 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 (CDI recurrence), whereas Placebo subjects under these conditions were considered to have a favorable outcome (no CDI recurrence): RR=0.34 (95%CI, 0.19, 0.62)
3. No adjustment for stratification by age and prior antibiotic regimen with 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 (no CDI recurrence): RR=0.31 (95%CI, 0.17, 0.57)

Reviewer comment: *A potential direct (e.g., tolerability) or indirect contribution effect of the product leading to missing data or losses of follow-up (e.g., by lack of efficacy) as well as the effect of subgroups cannot be excluded. Because this cannot be excluded, sensitivity analyses were performed and these supported the robustness of the overall efficacy conclusions and overall risk-benefit. These three additional analyses, including worst case/least favorable scenarios presented by imputation approaches 2 and 3, lend strength to the primary efficacy analysis. The point estimates from the sensitivity analyses are similar to the primary efficacy estimate and the 95% CIs are relatively narrow with the upper bounds all under 0.833.*

Efficacy analysis in the per-protocol population, which excluded subjects with major protocol deviations, yielded an RR of 0.30 (95% CI: 0.16, 0.56), similar to the RR of 0.32 (95% CI: 0.18, 0.58) in the ITT population.

6.1.11.2 Analyses of Secondary Endpoints

- RR of CDI recurrence determined using a PCR algorithm up to 8 weeks after initiation of SER-109 compared to placebo
- 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
- Clinical efficacy of each SER-109 lot as compared to placebo up to 8 weeks after initiation of treatment
- 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
- 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

Efficacy was supported by the secondary efficacy endpoint of CDI recurrence rate, as determined by PCR algorithm, at 8 weeks (12.4% vs 39.8%; RR=0.32; 95% CI 0.18, 0.58; P<0.001) in the ITT Population. [Table 11](#) below shows efficacy estimates based on PCR at 4, 8, 12, and 24 weeks after treatment.

Table 11. C. difficile Infection Recurrence Rates and Relative Risk with Recurrence as Determined by PCR Through Week 24, ITT Population, SERES-012

| Time Interval After Dose | SER-109 N=89 | Placebo N=93 |
|---|--------------------|-----------------|
| 4 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 10 (11.2) | 31 (33.3) |
| Number of subjects without CDI recurrence, n (%) | 79 (88.8) | 62 (66.7) |
| RR² | 0.35 | -- |
| 95% CI for RR³ | 0.19 ; 0.67 | -- |
| 8 weeks | -- | -- |
| 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) |
| RR² | 0.32 | -- |
| 95% CI for RR³ | 0.18 ; 0.58 | -- |
| 12 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 16 (18.0) | 43 (46.2) |
| Number of subjects without CDI recurrence, n (%) | 73 (82.0) | 50 (53.8) |
| RR² | 0.40 | -- |
| 95% CI for RR³ | 0.24 ; 0.65 | -- |
| 24 weeks | -- | -- |
| Number of Subjects with CDI recurrence ¹ , n (%) | 20 (22.5) | 45 (48.4) |
| Number of Subjects without CDI recurrence, n (%) | 69 (77.5) | 48 (51.6) |
| RR² | 0.48 | -- |
| 95% CI for RR³ | 0.31 ; 0.74 | -- |

Source: SERES-012 Clinical Study Report, Version 2.0, Table 17: C. difficile Infection Recurrence Rates and Relative Risk with Recurrence Determined Using a PCR Algorithm, ITT Population, Table 14.2.1.2.1
Abbreviations: CI=confidence interval; RR=relative risk

[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. Handling of other types of missing data are provided in the SAP (Appendix 16.1.9).

[2] Relative risk is defined as the SER-109 recurrence rate divided by the Placebo recurrence rate. The Cochran-Mantel-Haenszel (CMH) estimate of the common relative risk, stratified by age group (<65 years, ≥65 years) and prior antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin), is reported.

[3] The confidence interval was calculated using the Greenland and Robins variance estimate for the natural logarithm of the common relative risk.

Reviewer comment: *These analyses align with the primary analyses, which used the more specific toxin-based assay, to define a CDI recurrence. A PCR-based case definition was used in SERES-004, which did not meet the efficacy success criterion, as defined for SERES-012. In the post hoc analysis of this failed study (SERES-004), the high sensitivity of PCR was thought to contribute to the difficult-to-interpret results in the P2 study because it could not discriminate between colonization and re-infection. A similar pattern was likely not seen in SERES-012 because it is a much larger study with 1:1 randomization as opposed to 2:1 in SERES-004; the case definition of recurrence was refined to specify that the diarrhea had to be sustained until the time of initiation of antibacterial therapy. Note that the absolute number of new CDI recurrences after week 8 was similar between treatment groups; these statistical analyses were the cumulative number of CDI recurrences from day 0.*

Another secondary efficacy endpoint was the evaluation of the proportion of subjects who experienced CDI recurrence as determined by toxin assay up to 4, 12, and 24 weeks after treatment. As shown below, most of the CDI recurrences in the SER-109 recipients and placebo recipients occurred by week 4, at 52/6% (10 of 19) and 70.5% (31 of 44), respectively.

Table 12. C. difficile Infection Recurrence Rates and Relative Risk with Recurrence as Determined by a Toxin Assay at Weeks 4, 12, and 24, SERES-012

| Time Interval After Dose | SER-109 N=89 | Placebo N=93 |
|---|-------------------|-----------------|
| 4 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 10 (11.2) | 31 (33.3) |
| RR ² | 0.35 | -- |
| 95% CI for RR ³ | 0.19; 0.67 | -- |
| 12 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 16 (18.0) | 43 (46.2) |
| RR ² | 0.40 | -- |
| 95% CI for RR ³ | 0.24; 0.65 | -- |
| 24 weeks | -- | -- |
| Number of subjects with CDI recurrence ¹ , n (%) | 19 (21.3) | 44 (47.3) |
| RR ² | 0.46 | -- |
| 95% CI for RR ³ | 0.30; 0.73 | -- |

Source: SERES-012 Clinical Study Report, Version 2.0 - (Final analysis) Tables 14.2.1.1.1, 14.2.1.3.1; (Interim analysis) Appendix 16.8 Tables 14.2.1.1.1, 14.2.1.3.1. Table 18: CDI Recurrence Rates by Toxin Assay through 24 Weeks, ITT Population; Table 14.2.1.1.1.

[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. Handling of other types of missing data are provided in the SAP (Appendix 16.1.9).

[2] Relative risk is defined as the SER-109 recurrence rate divided by the Placebo recurrence rate. The Cochran-Mantel-Haenszel (CMH) estimate of the common relative risk, stratified by age group (<65 years, ≥65 years) and prior antibiotic regimen for the qualifying episode (vancomycin, fidaxomicin), is reported.

[3] The confidence interval was calculated using the Greenland and Robins variance estimate for the natural logarithm of the common relative risk.

Reviewer comment: The secondary efficacy analyses show that the efficacy of SER-109 can be detected by 4 weeks after treatment, with an RR and CI similar to those observed at the primary efficacy timepoint of 8 weeks and continues to be detectable and statistically meaningful at 24 weeks out from treatment. Note that the absolute number of new CDI recurrences by toxin assay after week 8 was similar between treatment groups; these statistical analyses were the cumulative number of CDI recurrences from day 0.

6.1.11.3 Subpopulation Analyses

The following tables present descriptive analyses of efficacy based on the pre-randomization variables of age strata (under 65 years of age and 65 years of age and older) and the antibacterial treatment for the CDI episode at study entry.

Table 13. Final Analysis of CDI Recurrence Rates and Relative Risk by Age Group with Recurrence Determined by Toxin Assay, Weeks 4, 8, 12, 24, ITT Population, SERES-012

| Time Interval After Dose | <65 years SER-109 N=41 | <65 years Placebo N=39 | ≥65 years SER-109 N=48 | ≥65 years Placebo N=54 |
|--|------------------------------|------------------------------|------------------------------|------------------------------|
| 4 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 3 (7.3) | 10 (25.6) | 7 (14.6) | 21 (38.9) |
| Relative Risk | 0.29 | | 0.38 | |
| 95% CI | 0.08 ; 0.96 | | 0.18 ; 0.80 | |
| 8 weeks (Primary endpoint) | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 3 (7.3) | 12 (30.8) | 8 (16.7) | 25 (46.3) |
| Relative Risk | 0.24 | | 0.36 | |
| 95% CI | 0.07 ; 0.78 | | 0.18 ; 0.72 | |
| 12 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 6 (14.6) | 13 (33.3) | 10 (20.8) | 30 (55.6) |
| Relative Risk | 0.44 | | 0.38 | |
| 95% CI | 0.19 ; 1.04 | | 0.21 ; 0.68 | |
| 24 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 7 (17.1) | 13 (33.3) | 12 (25.0) | 31 (57.4) |
| Relative Risk | 0.51 | | 0.44 | |
| 95% CI | 0.23 ; 1.15 | | 0.25 ; 0.75 | |

Source: SERES-012 Clinical Study Report Tables 12 and 13.

Reviewer comment: Age-based subgroup efficacy analyses track with that of the total population with respect to the trends over time, which was that the RR point estimate decreases between 4 weeks to 8 weeks after treatment, then increases over 12 and 24 weeks. While there is no substantial difference in the RR by age strata, SERES-012 was not powered to look for differences in efficacy or safety between older and younger adults. For this reason, we did not agree with the Applicant's proposal to state in Section 8.5 [Geriatric Use] that there were no differences in safety or effectiveness in adults 65 years of age and older.

Table 14. Final Analysis of CDI Recurrence Rates by Antibacterial Treatment for the CDI Episode at Entry, with Recurrence Determined by Toxin Assay, Weeks 4, 8, 12, 24, ITT Population, SERES-012

| Time Interval After Dose | Vancomycin SER-109 N=64 | Vancomycin Placebo N=69 | Fidaxomicin SER-109 N=25 | Fidaxomicin Placebo N=24 |
|---|-------------------------------|-------------------------------|--------------------------------|--------------------------------|
| 4 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 10 (15.6) | 22 (31.9) | 0 (0.0) | 9 (37.5) |
| Relative Risk | 0.49 | | 0 | |
| 95% CI | 0.25 ; 0.95 | | Not Estimated | |
| 8 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 10 (15.6) | 26 (37.7) | 1 (4.0) | 11 (45.8) |
| Relative Risk | 0.41 | | 0.09 | |
| 95% CI | 0.22 ; 0.79 | | 0.01 ; 0.63 | |
| 12 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 14 (21.9) | 32 (46.4) | 2 (8.0) | 11 (45.8) |
| Relative Risk | 0.47 | | 0.17 | |
| 95% CI | 0.28 ; 0.80 | | 0.04 ; 0.71 | |
| 24 weeks | -- | -- | -- | -- |
| Number of subjects with CDI recurrence (%) | 16 (25.0) | 33 (47.8) | 3 (12.0) | 11 (45.8) |
| Relative Risk | 0.52 | | 0.26 | |
| 95% CI | 0.32 ; 0.85 | | 0.08 ; 0.82 | |

Source: SERES-012 Clinical Study Report Table 13.

Reviewer comment: Among the subgroup efficacy analyses the Applicant conducted, sex and antibacterial treatment for the CDI episode entry were the two that yielded RR estimates that veered away the most, higher and lower, respectively, from the RR for the ITT population, which was 0.32. Interestingly, the low RR for the fidaxomicin is driven by both the numerator and the denominator (i.e., low recurrence rate among SER-109 recipients and high recurrence rate among placebo recipients). However, this could also have been due to chance and the small size of this subgroup, 49 subjects in total, as reflected in the very wide CI.

6.1.11.4 Dropouts and/or Discontinuations

A total of 49 subjects (26.9%) in SERES-012 dropped out or discontinued, with approximately three times more placebo recipients (39.8%; 37/92) than SER-109 recipients (13.5%; 12/90). The most common reason for withdrawal was CDI recurrence in 31 subjects (17.0%), specifically 4 SER-109 recipients (4.5%) and 27 placebo recipients (29.0%). There were 9 subjects (4.9%), 8 of whom were placebo recipients, who withdrew consent. Three subjects (1.6%), one SER-109 recipient and 2 placebo recipients, withdrew due to an AE. The remaining reasons included protocol violation/non-compliance (2.2%) in 2 SER-109 recipients; death in two subjects (1.1%), both SER-109 recipients; loss to follow-up (0.5%) in one SER-109 recipient; and other (0.5%) in one SER-109 recipient.

6.1.11.5 Exploratory and Post Hoc Analyses

- Changes in stool microbiome assessed via whole metagenomic sequencing (WMS) of stool from SERES-012 study subjects
 - Engraftment (based on detection of new spore-forming species not present at baseline) was significantly higher in SER-109 recipients compared to placebo recipients (weeks 1 through 24).
 - Microbiome diversity (based on beta-diversity) was significantly higher among SER-109 recipients than placebo recipients (weeks 1 through 24).
- Changes in stool metabolome assessed by measuring metabolites of interest
 - Significantly lower primary bile acid (BA) concentrations in stool from SER-109 recipients compared to placebo recipients one week after dosing
 - Significantly higher concentrations of secondary BA among SER-109 recipients compared to placebo recipients 1 to 8 weeks after dosing
 - Significant increases in the concentrations of short chain fatty acid (FA) butyrate and the medium chain FAs valerate and hexanoate, but no significant changes in concentrations of branched chain FA in SER-109 recipients compared to placebo recipients 1 to 8 weeks after dosing

Reviewer comment: *These exploratory studies relied on unvalidated assays to characterize treatment-associated changes in stool microbiome and metabolome. The Applicant was unable to draw conclusions about microbiome and metabolome changes on treatment outcomes. Furthermore, FDA was not involved in the design of these studies and did not review the assays used to generate these data. Therefore, this reviewer cannot comment on the strength of these data.*

- Incidence of all-cause mortality at Week 8 and Week 24 after treatment
 - 3.4% in SER-109 versus 0.0% in placebo
- Incidence of hospitalization at Weeks 8 and 24 after treatment
 - Numerically lower rates of hospitalizations for any reason in the ITT population, SER-109 arm compared with placebo for Week 8 (7.9% versus 17.2%), Week 12 (12.4% versus 19.4%), and Week 24 (16.9% versus 22.6%)
 - Most hospitalizations due to CDI (2 in SER-109 and 7 in placebo) occurred by Week 8
- Total length of stay (days) including in the ICU
 - Mean durations of stay due to any reason were similar, with 2.4 days (SD=9.2) in the SER-109 arm and 2.6 days (SD=7.7) in the placebo arm
 - Mean durations of stay due to CDI were shorter with 0.2 days (SD=1.5) in the SER-109 arm and 0.5 days (SD=2.1) the placebo arm
- Health outcomes: EuroQoL 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) at Week 24 after treatment and the Health-Related Quality of Life survey for CDI (CDiff32 HRQoL) at Week 8 after treatment
 - EQ-5D-5L: (b) (4)

- (b) (4)
Data were not used for labeling claims.
- Cdiff32 HRQoL: (b) (4)
- (b) (4)
Data were not used for labeling claims.

6.1.12 Safety Analyses

6.1.12.1 Methods

All safety analyses were conducted based on the Safety Population (N=182, all randomly assigned subjects who received any amount of study drug). All 90 subjects in SER-109 treatment group and 92 subjects in placebo were included. All subjects in the Safety Population, except 1 (assigned to SER-109, no record of receiving dose on Days 2 and 3), received the total of 3 daily planned dose of study drug containing either SER-109 (3×10^7 SCFU) or matching placebo. Median duration of follow-up in the SER-109 and placebo arms was 169.0 and 168.0 days, respectively.

AEs were assessed by their intensity, severity, and relation to the study treatment. The Common Terminology Criteria for Adverse Events v4.0 (CTCAE) severity grading scale was used for coding AEs except for diarrhea (discussed on the next page).

Solicited AEs were obtained from subjects for 7 days after the last dose of study drug (Days 4-10) using a diary card (see [Figure 2](#)). The diary asked about gas or flatulence, abdominal distention or bloating, abdominal pain or cramping, nausea, anorexia, vomiting, fatigue, chills or shivering, and constipation occurring between study Days 4-10. The grading scale for solicited AEs on Days 4-10 was as follows:

- 0 = no symptom
- 1 = mild: I noticed the symptom. It did not keep me from going about my normal activities.
- 2 = moderate: I noticed the symptom and it kept me from doing some of my normal activities.
- 3 = severe: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do.

Figure 2. Diary Card for Collection of Solicited AEs in SERES-012

| | | | | | | | |
|--|------------------|------------------|------------------|------------------|------------------|------------------|-----------------------|
| Subject Number _____ | | | | | | | |
| <p>Completion Instructions: Each Day <u>circle</u> the most severe intensity for this symptom that you experienced on this day: 0 = no symptom 1 = mild: I noticed the symptom. It did not keep me from going about my normal activities. 2 = moderate: I noticed the symptom and it kept me from doing some of my normal activities. 3 = severe: I noticed the symptom and it kept me from doing activities that I really needed and wanted to do. In the last box, take your oral temperature at the same time each daily and record. Ensure no recent hot or cold beverage or smoking.</p> | | | | | | | |
| | Day 4 Date: | Day 5 Date: | Day 6 Date: | Day 7 Date: | Day 8 Date: | Day 9 Date: | Day 10 Date: _____ |
| Solicited AE | Maximum Grade |
| Gas or flatulence | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Abdominal distention or bloating | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Abdominal pain or cramping | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Nausea | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Anorexia (Loss of appetite) | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Vomiting | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Fatigue | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Chills or Shivering | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Constipation | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 | 0 1 2 3 |
| Temperature | | | | | | | |

SERES-012 Amendment 1_5June2017

Subjects recorded diarrhea using a daily electronic diarrhea log. Criteria for diarrhea severity was as follows:

- mild: 3-4 unformed bowel movements (UBMs) per day
- moderate: 5-6 UBMs per day
- severe: ≥ 7 UBMs per day

Diarrhea that met the protocol definition of CDI recurrence (≥ 3 unformed stools per day over 2 or more consecutive days, a positive *C. difficile* test on a stool sample determined by a toxin assay, and assessment by the Investigator that treatment was required) was NOT be entered as an AE.

Unsolicited AEs were collected weekly for approximately 2 months (Day 58) and monthly thereafter. SAEs and AESIs, which were defined as an invasive infection (e.g., bacteremia, abscess, meningitis), and deaths were monitored throughout the study (through 6 months after treatment).

6.1.12.2 Overview of Adverse Events

The proportion of subjects with at least one TEAE in were similar between the SER-109 arm (84/90; 93.3%) and placebo arm (84/92; 91.3%). Most of the AEs more frequently reported in SER-109 recipients fell under the MedDRA SOC of *Gastrointestinal disorders* and *Infections and infestations*. Most events were reported in the 7 days following completion of the 3-day regimen of SER-109 or placebo, during which pre-specified AEs were collected and graded using a diary card.

Solicited Adverse Events

The proportion of subjects with at least one solicited AE was 80.0% (72/90) in SER-109 recipients and 84.8% (78/92). The 78 SER-109 recipients reported a total of 1343 solicited AEs and the 82 placebo recipients reported a total of 1572 solicited AEs. As shown in [Table 15](#), most SER-109 recipients reported mild solicited AEs (32.2%), followed by moderate (28.9%), and severe (18.9%). Most placebo recipients reported moderate AEs (34.8%), followed by mild (27.2%) and severe (22.8%). However, numerically, most reported solicited AEs were mild (SER-109: 248 of 369; placebo: 259/432).

Table 15. Solicited Adverse Events Collected for 7 Days After Treatment in SERES-012, Safety Population

| Solicited Adverse Event, Maximum Severity | SER-109 (N=90) n(%) | SER-109 Events | Placebo (N=92) n (%) | Placebo Events |
|--|---------------------|----------------|----------------------|----------------|
| Subjects with at least one reported solicited AE | 72 (80.0) | -- | 78 (84.8) | -- |
| Total number of reported solicited AEs | -- | 369 | -- | 432 |
| Mild | 29 (32.2) | 248 | 25 (27.2) | 259 |
| Moderate | 26 (28.9) | 81 | 32 (34.8) | 118 |
| Severe | 17 (18.9) | 40 | 21 (22.8) | 55 |
| Gas or flatulence | | | | -- |
| Mild | 36 (40.0) | 55 | 38 (41.3) | 55 |
| Moderate | 17 (18.9) | 17 | 19 (20.7) | 19 |
| Severe | 8 (8.9) | 8 | 8 (8.7) | 8 |
| Abdominal distention or bloating | | | | |
| Mild | 30 (33.3) | 39 | 22 (23.9) | 34 |
| Moderate | 12 (13.3) | 13 | 22 (23.9) | 23 |
| Severe | 7 (7.8) | 7 | 4 (4.3) | 4 |
| Abdominal pain or cramping | | | | |
| Mild | 25 (27.8) | 38 | 29 (31.5) | 39 |
| Moderate | 14 (15.6) | 16 | 21 (22.8) | 23 |
| Severe | 6 (6.7) | 6 | 6 (6.5) | 6 |
| Nausea | | | | |
| Mild | 6 (6.7) | 9 | 15 (16.3) | 24 |
| Moderate | 5 (5.6) | 5 | 10 (10.9) | 10 |
| Severe | 1 (1.1) | 1 | 5 (5.4) | 5 |
| Anorexia (loss of appetite) | | | | |
| Mild | 18 (20.0) | 22 | 18 (19.6) | 23 |
| Moderate | 5 (5.6) | 7 | 11 (12.0) | 13 |
| Severe | 3 (3.3) | 3 | 5 (5.4) | 7 |
| Vomiting | | | | |
| Mild | 0 (0.0) | 0 | 4 (4.3) | 4 |
| Moderate | 1 (1.1) | 1 | 1 (1.1) | 1 |
| Severe | 0 (0.0) | 0 | 5 (5.4) | 5 |
| Fatigue | | | | |
| Mild | 28 (31.1) | 41 | 32 (34.8) | 43 |
| Moderate | 13 (14.4) | 14 | 12 (13.0) | 15 |
| Severe | 12 (13.3) | 12 | 13 (14.1) | 13 |

| Solicited Adverse Event, Maximum Severity | SER-109 (N=90) n(%) | SER-109 Events | Placebo (N=92) n (%) | Placebo Events |
|---|---------------------|----------------|----------------------|----------------|
| Chills or shivering | | | | |
| Mild | 16 (17.8) | 21 | 13 (14.1) | 16 |
| Moderate | 4 (4.4) | 5 | 4 (4.3) | 6 |
| Severe | 1 (1.1) | 1 | 4 (4.3) | 5 |
| Constipation | | | | |
| Mild | 17 (18.9) | 23 | 14 (15.2) | 21 |
| Moderate | 4 (4.4) | 4 | 5 (5.4) | 8 |
| Severe | 2 (2.2) | 2 | 1 (1.1) | 2 |
| Fever ^a | | | | |

Source: 125757/51 and 53, response to IR

Abbreviation: UBM=unformed bowel movement; AE=adverse event

Notes: Solicited adverse events are captured on a diary card completed by subjects on Days 4 through 10. Percentages are based on the number of subjects in the Safety Population in each treatment group. n provides the number of subjects with the specified solicited AE at the given severity. For multiple occurrences of the same solicited AE for a subject, the solicited AE with the maximum severity is counted for the subject. Events provides the total number of solicited AEs for the given severity.

a. No subjects reported objective fever. Fever severity is based on the CTCAE v4.0, May 2009. Mild fever is defined as 38.0-39.0 degrees C (100.4-102.2 degrees F); moderate fever is defined as >39.0-40.0 degrees C (102.3-104.0 degrees F); and severe fever is defined as >40.0 degrees C (>104.0 degrees F) for <=24 hours.

Unsolicited Adverse Events

Unsolicited AEs occurred in a similar proportion of subjects who received SER-109 (61 [67.8%]) and placebo (61 [66.3%]) over the 6 months of follow-up. These AEs were predominantly under the *Gastrointestinal disorders* SOC, with the most common PT being diarrhea, and Infections and Infestations, with the most common PT of UTI among SER-109 recipients and *Clostridium difficile* colitis among placebo recipients. As shown in [Table 16](#), the proportion of subjects reporting unsolicited AEs was similar across the treatment arms and highest during the first week after treatment, followed by a steady proportion of subjects approximating 13% in the following weeks 2 through 4.

Table 16. Unsolicited AEs During 6 Months of Follow-up, Total and Days 1 through 14, Safety Population, SERES-012

| Event | Days 1-10 SER-109 N=90 | Days 1-10 Placebo N=92 | Days 11-14 SER-109 N=90 | Days 11-14 Placebo N=89 | Days 1-168 SER-109 NT=90 | Days 1-168 Placebo NT=92 |
|--|------------------------------|------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|
| Subjects with ≥1 unsolicited AE, n (%) | 28 (31.1) | 32 (34.8) | 18 (20.0) | 13 (14.6) | 61 (67.8) | 61 (66.3) |
| Events n | 39 | 60 | 24 | 16 | 160 | 166 |
| Mild | 25 | 27 | 9 | 7 | 80 | 82 |
| Moderate | 10 | 25 | 12 | 3 | 56 | 63 |
| Severe | 4 | 8 | 3 | 6 | 24 | 21 |
| SOC Preferred Term | -- | -- | -- | -- | -- | -- |
| Gastrointestinal | 19 (21.1) | 16 (17.4) | 10 (11.1) | 6 (6.7) | 37 (41.1) | 40 (43.5) |
| Diarrhea | 11 (12.2) | 8 (8.7) | 7 (7.8) | 2 (2.2) | 22 (24.4) | 20 (21.7) |
| Constipation | 2 (2.2) | 0 (0.0) | 1 (1.1) | 1 (1.1) | 5 (5.6) | 4 (4.3) |
| Flatulence | 3(3.3) | 5(5.4) | 1(1.1) | 0(0.0) | 5 (5.6) | 6 (6.5) |
| Infections and infestations | 3 (3.3) | 8 (8.7) | 3 (3.3) | 2 (2.2) | 21 (23.3) | 17 (18.5) |
| UTI | 1 (1.1) | 0 (0.0) | 1 (1.1) | 0 (0.0) | 8 (8.9) | 1 (1.1) |

Source: Tables 14.3.1.3.1 b1 and b2, Amendment 51 Abbreviations: AE=adverse event; SOC=System Organ Class; UTI=urinary tract infection; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term
Notes: Percentages are based on the number of subjects in the Safety Population in each treatment group. N=number of subjects in the Safety Population who were in the study at the beginning of the specified time interval; NT=total number of subjects in the Safety Population. For each level of summarization, a subject contributes only once to the count for a given TEAE on the SOC level and on the PT level within SOC. SOC and PT are coded using the MedDRA coding dictionary, v20.0 (March 2017). Solicited adverse events were those of 'Abdominal pain or cramping' (PTs Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness); 'Abdominal distension or bloating' (PT 'Abdominal distension'); 'Constipation' (PT 'Constipation'); 'Gas or flatulence' (PT 'Flatulence'); 'Nausea' (PT 'Nausea'); 'Vomiting' (PT 'Vomiting'); 'Chills or shivering' (PT 'Chills'); 'Fatigue' (PT 'Fatigue'); 'Anorexia or loss of appetite' (PT 'Decreased appetite'); 'Fever' (PT Fever, Pyrexia) and reported by the subject when solicited via diary (during Days 4-10 in SERES-012). All other adverse events were considered unsolicited.

Table 17: Unsolicited AEs During 6 Months of Follow-Up, Days 15 through 168, Safety Population, SERES-012

| Event | Days 15-21 SER-109 N=90 | Days 15-21 Placebo N=87 | Days 22-28 SER-109 N=89 | Days 22-28 Placebo N=85 | Days 29-58 SER-109 N=89 | Days 29-58 Placebo N=83 | Days 59-168 SER-109 N=85 | Days 59-168 Placebo N=64 |
|---------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|
| Subjects with ≥1 unsolicited AE n (%) | 10 (11.1) | 12 (13.8) | 13 (14.6) | 11 (12.9) | 34 (38.2) | 29 (34.9) | 10 (11.8) | 6 (9.4) |
| Events n | 10 | 12 | 14 | 16 | 59 | 52 | 15 | 10 |
| Mild | 5 | 6 | 9 | 8 | 32 | 30 | 0 | 4 |
| Moderate | 2 | 5 | 4 | 7 | 22 | 18 | 6 | 5 |
| Severe | 3 | 1 | 0 | 1 | 5 | 4 | 9 | 1 |

| Event | Days 15-21 SER-109 N=90 | Days 15-21 Placebo N=87 | Days 22-28 SER-109 N=89 | Days 22-28 Placebo N=85 | Days 29-58 SER-109 N=89 | Days 29-58 Placebo N=83 | Days 59-168 SER-109 N=85 | Days 59-168 Placebo N=64 |
|-----------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------------------------|
| SOC Preferred Term | -- | -- | -- | -- | -- | -- | -- | -- |
| Gastrointestinal | 6 (6.7) | 10 (11.5) | 6 (6.7) | 5 (5.9) | 15 (16.9) | 15 (18.1) | 0 (0.0) | 1 (1.6) |
| Diarrhea | 3 (3.3) | 6 (6.9) | 4 (4.5) | 1 (1.2) | 10 (11.2) | 9 (10.8) | 0 (0.0) | 0 (0.0) |
| Constipation | 0 (0.0) | 1 (1.1) | 1 (1.1) | 1 (1.2) | 2 (2.2) | 1 (1.2) | 0 (0.0) | 0 (0.0) |
| Flatulence | 0(0.0) | 0(0.0) | 0(0.0) | 0 (0.0) | 1 (1.1) | 1 (1.2) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | 2 (2.2) | 0 (0.0) | 4 (4.5) | 1 (1.2) | 10 (11.2) | 6 (7.2) | 5 (5.9) | 3 (4.7) |
| UTI | 0 (0.0) | 0 (0.0) | 2(2.2) | 1(1.2) | 2(2.2) | 1(1.2) | 3(3.5) | 0(0.0) |

Source: Table14.3.1.2.1 ISS a., STN 125757/54

UTIs occurred more frequently SER-109 arm (8.9%; 8 subjects had 9 events) than the placebo arm (1.1%; 1 placebo recipient had 2 events). [Table 18](#) presents clinical details for each case. None of the UTIs were considered related to the study drug. Most subjects had urine culture results; they were not obtained in one SER-109 recipient and not available in one SER-109 recipient and the one placebo recipient. The recovered organisms were either Gram negative bacilli or enterococci (commonly associated with UTIs); these vegetative bacteria are not found in SER-109.

Table 18. On-Study Urinary Tract Infection Events, SERES-012

| Group | Sex/ Age (yrs) | Clinical History | Start- Stop Days | Severity | SAE | Urine Culture | Treatment |
|---------|----------------------|---|------------------------|-----------------------|-----|--|--|
| SER-109 | M/69 | Ongoing hematuria, diabetes mellitus | 99-103 | Severe ^a | Yes | <i>Klebsiella</i> | Amikacin (500mg; IV; 1 dose); meropenem (500mg QD; 5 days); vancomycin (1g; IV, 1 dose) |
| SER-109 | F/49 | Recurrent UTI, multiple sclerosis, indwelling Foley catheter | 13-15 69-72 | Moderate ^b | Yes | 1. Multiple organisms 2. <i>Raoultella ornithinolytica</i> and <i>P. aeruginosa</i> | Ceftazidime (1g Q8H; IV; 3 days) Gentamicin sulfate (IV; 320mg, Q24H; 2 days); ceftriaxone sodium (1g IV QD; 9 days) |
| SER-109 | F/80 | UTI | 60-94 | Moderate | Yes | <i>E. coli</i> | Initial treatment with unknown IV antibiotic; followed by ciprofloxacin (250mg BID; 5 days); levofloxacin (500mg QD; 6 days) plus additional ciprofloxacin |
| SER-109 | F/59 | Ongoing overactive bladder requiring treatment, diabetes mellitus | 54-65 | Severe | No | Normal urogenital flora | ceftriaxone 1g QD; IV; 2 days); nitrofurantoin (50mg; QD; 8 days) |
| SER-109 | M/66 | Renal transplant, diabetes mellitus | 22-35 | Moderate | No | <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>Enterococcus</i> | Ertapenem (1g; IM; QD; 3 days); ampicillin (500mg; QOD; 7 days); cefepime (500mg; QOD; IM; 6 days) |
| SER-109 | F/55 | Ongoing overactive bladder requiring treatment | 27-37 | Mild | No | No information available | None |
| SER-109 | F/85 | Bladder prolapse surgery, ongoing chronic interstitial cystitis | 8-19 | Moderate | No | <i>E. coli</i> | Ciprofloxacin (250mg; BID; 6 days) |

| Group | Sex/ Age (yrs) | Clinical History | Start- Stop Days | Severity | SAE | Urine Culture | Treatment |
|---------|----------------------|----------------------------|------------------------|----------|-----|---|--|
| | | (2000) requiring treatment | | | | | |
| SER-109 | F/77 | Stroke, diverticulosis, | 38-62 ^c | Moderate | No | + nitrites, +++leucocytes, moderate pus, ++bacteria on UA No culture obtained | Fosfomycin (3g; QD; 1 dose) |
| Placebo | F/71 | Recurrent UTI | 26-28 51-71 | Moderate | No | No information available | Ciprofloxacin (400mg; IV; 1 dose); ertapenem (0.5g; QD; IV; 3 days); linezolid (Zyvox; 600mg; BID; 7 days) ciprofloxacin (500mg; QD; 15 days) |

Source: SERES-012 CSR Table 34 and updated table from response to information request submitted to 125757/38

a. Subject (b) (6) had an additional event of cystitis on Day 160 in association with hemodialysis-catheter-associated Gram-negat ve sepsis. There were different organisms identified from the urine (Klebsiella) and blood (Serratia marcescens) cultures.

b. This subject also had bacteremia starting Day 70 with blood culture showing E. coli

c. UTI presumed to have resolved based on absence of any additional antibiotics following Fosfomycin, which was given on Day 6

Reviewer comment: *The imbalance in UTIs across treatment arms cannot be attributed to skewed distribution of baseline comorbidities, such as immunocompromise or underlying renal disease, which were balanced. However, there was a greater proportion of female subjects in the SER-109 arm, which may have contributed to the imbalance as UTIs are substantially more common in women than men. Another contributing factor may have been the study size. With respect to causality, none of the organisms detected by culture with available microbiology data (not obtained in one SER-109 recipient and not available for one SER-109 recipient and the once placebo recipient with UTI), were related to those in the study drug, but to common uropathogens like gram negative bacilli or enterococci, which are not found in SER-109. The narratives indicate that there was no temporal clustering observed and the infections occurred in individuals with predisposing conditions. The Applicant points out that the rate of UTIs in the placebo arm is lower than expected for this population of older individuals. The imbalance in UTIs was not included in product labeling for the reasons supporting unrelatedness to SER-109, as described earlier in this comment.*

Adverse Reactions

Adverse reactions, which were AEs considered possibly related to the study drug, are presented in [Table 19](#). The most common adverse reactions reported in at least 5% of subjects and more frequent in the SER-109 arm were abdominal distension (31.1%; 28/90),

Table 19. Related or Possibly Related Treatment-Emergent Adverse Events by Preferred Term, Safety Population, SERES-012

| Preferred Term | Total Days 1-168 SER-109 N _T =90 | Total Days 1-168 Placebo N _T =92 | Days 1-10 SER-109 N=90 | Days 1-10 Placebo N=92 | Days 11-14 SER-109 N=90 | Days 11-14 Placebo N=89 |
|--------------------------------------|---|---|------------------------|------------------------|-------------------------|-------------------------|
| Subjects with at Least 1 TEAE | 46(51.1) | 48(52.2) | 44(48.9) | 47(51.1) | 6(6.7) | 3(3.4) |
| Flatulence | 39(43.3) | 41(44.6) | 39(43.3) | 41(44.6) | 0(0.0) | 0(0.0) |
| Abdominal distension | 28(31.1) | 27(29.3) | 28(31.1) | 27(29.3) | 1(1.1) | 1(1.1) |
| Abdominal pain | 25(27.8) | 33(35.9) | 25(27.8) | 33(35.9) | 1(1.1) | 0(0.0) |
| Fatigue | 20(22.2) | 21(22.8) | 20(22.2) | 21(22.8) | 0(0.0) | 0(0.0) |
| Constipation | 15(16.7) | 10(10.9) | 14(15.6) | 10(10.9) | 1(1.1) | 0(0.0) |
| Decreased appetite | 13(14.4) | 19(20.7) | 13(14.4) | 19(20.7) | 1(1.1) | 0(0.0) |
| Chills | 10(11.1) | 8(8.7) | 10(11.1) | 8(8.7) | 0(0.0) | 0(0.0) |
| Diarrhea | 9(10.0) | 4(4.3) | 7(7.8) | 1(1.1) | 3(3.3) | 1(1.1) |
| Nausea | 9(10.0) | 12(13.0) | 9(10.0) | 12(13.0) | 0(0.0) | 0(0.0) |
| Vomiting | 2(2.2) | 3(3.3) | 2(2.2) | 3(3.3) | 0(0.0) | 0(0.0) |

Source: Table 36 from SERES-012 Clinical Study Report p. 159

Notes: Percentages are based on the number of subjects in the Safety Population in each treatment group.

N=number of subjects in the Safety Population who were in the study at the beginning of the specified time interval;

NT=total number of subjects in the Safety Population. For each level of summarization, a subject contributed only once to the count for a given TEAE on the PT level. PT is coded using MedDRA coding dictionary, v20.0 (March 2017). All TEAEs were collected and summarized from time of randomization up to Week 8; from Week 8 up to Week 24, only SAEs and AESIs were collected and summarized.

Reviewer comment: *These adverse reactions comprise solicited and unsolicited AEs. Adverse reactions occurring in more than 5% of subjects included flatulence, abdominal distension, abdominal pain, fatigue, constipation, decreased appetite, chills, diarrhea and nausea. However, only those occurring at a greater frequency in SER-109 recipients than in placebo recipients were reported in the package insert. The total number of events from days 1 to day 168 are presented in columns 2 and 3. There were too few events after day 14 to draw meaningful conclusions about differences between the treatment groups.*

6.1.12.3 Deaths

Three deaths occurred in SERES-012, all in SER-109 recipients (n=90; 3.3%). None were considered related to the study drug.

An 87-year-old White NH female with a medical history including myocardial infarction, atrial fibrillation, stent placement and cardiac pacemaker on anticoagulants apixaban and clopidogrel lost her balance and fell while attempting to get into a car) on Study Day 9. She reported a headache early on Study Day 10 and was subsequently seen in an emergency room, round to have left subdural bleed on CT and was hospitalized. The bleed progressed with midline shift and uncal herniation. Following transfer to the ICU, neurosurgery advised against emergent surgical drainage due to comorbidities and recommended waiting for hematoma to break down and possibly consider drainage via burr hole. Her family opted for palliative care. She died on Study Day 12.

A 66 yo Other NH male with multiple comorbidities including cardiovascular disease, diabetes, renal transplant with immunosuppressive treatment, end-stage renal disease, dialysis, history of sepsis (2018, *Pseudomonas aeruginosa*), recent UTI in February 2019, cultures showed greater than 100,000 CFU/mL of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterococcus species*. He was transferred to the ER in the setting of unexplained hypotension during dialysis on Day 54 (3/5/2019). In addition to cardiac assessment, he had a sepsis workup and was started on Vancomycin (one dose), piperacillin-tazobactam (5-day course) and doxycycline (2-day course). No organisms were identified for this current episode. He went into atrial fibrillation with rapid ventricular response and passed away on Study Day 60.

A 66 yo man with a history of glioblastoma (WHO grade IV) with neurologic impairment due to chemotherapy, colon cancer stage 3 (adenocarcinoma of ascending colon) with metastasis to intra-abdominal lymph node, hemicolectomy and postoperative ileus and generalized abdominal pain who had confusion and fever to 104.3 at home and found to have worsening of a glioblastoma with mass effect and hemorrhage on imaging. Fever subsided without antibiotics. He died on Study Day 164 after transitioning to hospice care approximately one month prior.

Reviewer comment: *This reviewer agrees with the assessment that the deaths were very likely to be unrelated to SER-109, but due to physical trauma and pre-existing conditions.*

6.1.12.4 Nonfatal Serious Adverse Events

SAEs occurred in 16.7% (n=15) of SER-109 recipients and 21.7% (n=19) of placebo recipients. None of the SAEs were attributed to the study drug, but to underlying medical conditions or concurrent illness. Non-fatal SAEs accounted for 12 of the 15 cases while all 19 SAEs in placebo recipients were non-fatal; details are presented below.

SER-109

1. 69-year-old White NH male with multiple hospitalizations worsening of hematuria (moderate) on Days 41-68, gastroenteritis (moderate) on Days 52-54, UTI (severe) on Days 99-103, and cystitis (severe) and gram-negative sepsis (severe) on Days 160-171

2. 49 yo White NH female with intermittent vertigo (moderate) requiring hospitalization on Day 58, ongoing
3. 61 yo Black NH male with hypoglycemia (severe) requiring hospitalization on Day 58, ongoing
4. 49 yo White NH female with multiple sclerosis and indwelling foley catheter with UTI vs colonization of catheter (moderate) on Days 13-15 (moderate), CDI recurrence (severe) on Days 15-22, UTI with *Pseudomonas aeruginosa* and *Raoultella ornithinolytica* (moderate) on Days 69-72 and *E. coli* bacteremia (moderate, AESI) and CDI recurrence (severe) for which she was hospitalized on Days 70-75
5. 77 yo White NH male hospitalized Day 32-37 with hypokalemia (moderate) attributed to diarrhea and *C. difficile* that resolved on Day 72 without treatment
6. 92 yo White NH female hospitalized with exacerbation of chronic diastolic HF (moderate) on Days 121-123
7. 80 yo White NH female with UTI (moderate) hospitalized on Day 60-64, and readmitted 8 days later for same UTI despite completion of 5 day course of ciprofloxacin after initial treatment with IV antibiotic (not specified)
8. 68 yo White NH female with medically serious event of breast cancer (Day 110 – ongoing)
9. 79yo White NH female with exacerbation of depression (severe) and hospitalized on Days 67-70
10. 80 yo White NH female hospitalized with acute gastroenteritis (severe) on Days 132-142
11. 59 yo White NH female hospitalized with TIA (moderate) Days 54-58
12. 87 yo White NH male hospitalized with abdominal wall abscess (moderate) Days 86-125

Placebo

1. 83 yo White NH female hospitalized with diarrhea due to CDI (severe) on Days 9-17
2. 78 yo White NH female hospitalized with COPD exacerbation (moderate) on Days 67-78
3. 72 yo White NH male with worsening CHF days 44-45, left elbow cellulitis (mild) on Days 91-93, peripheral vascular disease and chronic venous stasis of lower extremities (mild) on Days 92-93, diarrhea due to CDI recurrence (mild) on Days 109-112 and diarrhea due to CDI recurrence (mild) again on Days 129-132.
4. 75 yo White NH male diarrhea due to recurrent CDI (severe) on Days 5-8
5. 59 yo White NH female with respiratory failure, hypercapnic hypoxic (severe) on Days 6-8 and acute respiratory failure (severe) Days 14-17
6. 53 yo Black NH female with medically important serious event scleritis (severe) Days 11-62
7. 87 yo White Hispanic male with diarrhea (severe) due to CDI recurrence on Days 11-27, then again diarrhea (severe) due to CDI recurrence on Days 41-62
8. 69 yo Black NH male with intermittent left sided chest pain (moderate) on Days 28-30, nonspecific abdominal pain (moderate) on Days 132-133
9. 48 yo White NH male with acute colitis due to ETEC (moderate) on Days 147-151

10. 93 yo White NH male with AV block/complete heart block (moderate) on Days 7-10, worsening of hyponatremia (moderate) on Days 23-29, worsening general weakness (moderate) on Days 51-58
11. 57 yo White NH male with hospitalized with diabetic heel ulcer (moderate) on Days 7-15
12. 80 yo White NH female hospitalized with acute on chronic atrial fib (severe) on Days 7-10 and diarrhea due to rCDI (severe) on Days 7-10
13. 76 yo White NH male with RLE cellulitis (severe) on days 84-90 and right lower extremity osteomyelitis (moderate) on Days 84-127
14. 67 yo White NH female with diarrhea due to rCDI (moderate) Days 13-23 and acute kidney injury (mild) on Days 18-19
15. 71 yo White NH female with acute encephalopathy (severe) on Days 26-28
16. 61 yo White NH male with alcohol poisoning (moderate) on Days 46-49 and syncope secondary to intoxication (moderate) on Days 47-49
17. 69 yo White NH male with acute cholecystitis (moderate) on Days 139-148
18. 69 yo White NH male with GI bleeding (severe) on Days 41-45
19. 74 yo White NH female hospitalized with severe diarrhea due to CDI on Days 5-9

6.1.12.5 Adverse Events of Special Interest (AESI)

Invasive infections were monitored as an AESI. In SERES-012, 4 SER-109 recipients and 3 placebo recipients experienced AESIs listed below. None were attributed to the study drug.

SER-109

1. 69 yo White NH male with diabetes and end stage renal failure with worsening of pre-existing hematuria (Day 41-68), gastroenteritis suspected viral (Day 52-54), *Klebsiella pneumoniae* UTI on Day 99-103, and hemodialysis catheter-associated *Serratia marascens* bacteremia (severe) on Days 160-171
2. 49 yo White NH female with *E. coli* bacteremia (moderate) on Days 70-75
3. 65 yo Other NH male with suspected sepsis (no growth on blood culture) on Days 54-59
4. 87 yo White NH male with recurrence of abdominal wall abscess (moderate) on Day 86-125, with incision drainage sample that showed 3+ *Strep viridans*, anginosus group. This subject had a prior abdominal wall abscess 7 months prior to SER-109 treatment which grew out *Klebsiella oxytoca*.

Placebo

1. 72 yo White NH male on immunosuppression with left elbow cellulitis (mild) on Days 91-93
2. 57 yo White NH male with diabetic foot, right heel ulcer (moderate) on Days 7-15
3. 76 yo White NH male with diabetes and history of cellulitis with RLE osteomyelitis (moderate) on Days 84-127. Initial cellulitis affected site of 5th toe amputation for diabetic foot ulcer. Wound culture positive for *Streptococcus agalactiae* and bone culture positive for *Staphylococcus saprophyticus*.

Reviewer comment: The Applicant conducted a retrospective review of all studies under IND as part of preparing the ISS. With this retrospective review, the proportion of SER-109 recipients with AESI increased to 10.0%, due to counting cases of sinusitis in 3 subjects and cellulitis in 1 subject. Importantly, the most concerning cases of bacteremia and sepsis were identified prospectively.

6.1.12.6 Clinical Test Results

Blood draws at screening included hematology and chemistry profiles to determine study eligibility. None were followed as a part of safety monitoring. Treatment emergent abnormalities in these lab values were uncommon. The proportion of subjects in SERES-012 with at least 1 abnormal value was balanced across SER-109 (7.8%; 7/90) and placebo groups (7.6%; 7/92). The most common abnormalities were observed in up to 2 patients (such as increased creatinine (2.2%; 2/90 in SER-109 arm) and hyperglycemia (2.2%; 2/92 in placebo arm). Stool samples were analyzed at local laboratories if a subject had a suspected CDI recurrence.

6.1.12.7 Dropouts and/or Discontinuations

Three subjects (1.6%) in SERES-012 withdrew due to an AE, all of which were considered unrelated to the study drug. One SER-109 recipient experienced worsening of a pre-existing glioblastoma and withdrew before the Week 20 visit. The subject subsequently died on study Day 164 (see [Section 6.1.12.3](#)). One placebo recipient withdrew on Day 57 due to exacerbations of pre-existing conditions, namely 4 AEs of CHF, acute chronic diastolic heart failure, severe pulmonary hypertension (Day 7), and acute urinary retention (Day 49). The second placebo recipient withdrew due to an SAE of acute respiratory failure on Day 6 (pre-existing condition related to COPD and recurrent pleural effusion) which recovered with treatment on Day 17. The subject withdrew from the study on Day 18.

6.1.13 Study Summary and Conclusions

The primary efficacy analysis in SERES-012 evaluated the CDI recurrence rate after three consecutive days of SER-109 compared to placebo in the ITT population. SERES-012 met the pre-specified success criterion of the upper bound of the 95% CI of the RR of CDI recurrence ≤ 0.8333 . The safety population consisted of subjects who received at least one dose of study drug. TEAEs were most commonly reported in the MedDRA SOC *Gastrointestinal disorders* and were mostly mild to moderate in severity. Approximately a third of subjects in the SER-109 arm (27.8%; 25/90 SER-109 recipients) and placebo arm (32.6%; 30/92) experienced a total of 64 and 76 severe TEAEs, respectively (some individual subjects had more than one TEAE). There was an imbalance in cases of UTI, with 8 SER-109 recipients with 9 events and one placebo recipient with 2 events. This could not be explained by skewed distribution of baseline comorbidities. However, none of the organisms detected by culture with available microbiology data (not obtained in one SER-109 recipient and not available for one SER-109 recipient and the once placebo recipient with UTI), were related to those in the study drug, but to common uropathogens like gram negative bacilli or enterococci, which are not found in SER-109. SERES-012 enrolled patients with serious comorbid conditions and rCDI is associated with higher mortality rates. Three deaths were observed in this trial, which were not associated with administration of SER-109 by the investigator and by FDA's assessment.

6.2 Trial #2: **SERES-013**

[NCT03183141](#): An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Subjects with Recurrent *Clostridioides Difficile* Infection (ECOSPOR IV)

6.2.1 Objectives (Primary, Secondary, etc.)

Cohort 1

Primary efficacy objective: To evaluate SER-109 in the reduction of CDI recurrence rates, 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, 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.

Cohort 2:

Primary safety objective: To evaluate the safety and tolerability of SER-109 in adult subjects with rCDI.

Efficacy objective: To evaluate SER-109 in the reduction of CDI recurrence rates, determined by a toxin assay, up to 8 and 12 weeks after initiation of treatment.

Reviewer comment: *The primary role of open-label SERES-013 in this BLA was to ensure that the Applicant provided a minimum safety database of 300 who received the 3-day regimen of SER-109. The continued assessment of efficacy was an added advantage, but there was no success criterion applied to the results.*

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, and a 16-week follow-up period.

Cohort 1 comprised subjects previously enrolled in Study SERES-012 who experienced a recurrence of CDI within 8 weeks after receipt of either SER-109 or placebo. 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 (i.e., vancomycin [125 mg 4 times a day] and/or fidaxomicin [200 mg twice a day]). Approximately 30 eligible subjects were planned to be enrolled.

Cohort 2 was designed to examine safety and tolerability in adult subjects who received SER-109 at the dose used in SERES-012. 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). Approximately 200 subjects who were not participants in previous studies of SER-109 were planned to be enrolled.

6.2.3 Population

Cohort 1 Key Inclusion Criteria:

- Previously enrolled in Study SERES-012, had CDI recurrence within 8 weeks after receipt of a treatment regimen of SER-109 or placebo.
- The CDI recurrence in Study SERES-012 must have met the protocol definition of ≥ 3 unformed stools per day over 2 consecutive days, a positive *C. difficile* stool toxin assay, the requirement of CDI SOC antibiotic therapy, and an adequate clinical response following antibiotic therapy (< 3 unformed stools in 24 hours for 2 or more consecutive days).

Cohort 1 Main Exclusion Criteria:

- Known or suspected toxic megacolon and/or known small bowel ileus.
- Major GI 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 GI lumen, i.e., restrictive procedures such as banding, are permitted).
- 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.
- Any history of FMT in the past 3 months.

Cohort 2 Main Inclusion Criteria:

- Subjects 18 years of age or older who had one or more CDI recurrence (as confirmed by a *C. difficile* stool toxin or PCR test) and have responded to a course of antibiotic treatment.

Cohort 2 Main Exclusion Criteria:

All exclusion criteria above, plus:

- Previously enrolled in a Seres Therapeutics clinical study. An exception is made for subjects who screened in SERES-012 who did not receive SER-109 and did not previously roll-over to SERES-013.

Reviewer comment: *Adults with their first CDI recurrence were eligible to be enrolled in Cohort 2. The Applicant justified a less stringent criterion of minimum number of CDI recurrences with references to published data indicating similar epidemiology and pathogenesis between those with their first recurrence and those with multiple recurrences, including demographics, risk factors, and underlying microbiome disruption. Furthermore, epidemiologic studies suggest higher risk of subsequent episodes once a person has a recurrence. This reviewer finds this rationale to be reasonable and considers this broader population of individuals with their first recurrence to be representative of the end-user population after licensure. However, the assertion that those with their first recurrence are comparable to those with more recurrences is debatable. For instance, the risk of CDI recurrence in those with their first recurrence is approximately 40%, which is lower than the estimated recurrence risk in those with 2 or more (>60%), as this was the basis for SER-109 receiving Orphan Drug Designation. This, along with the lack of a comparator arm in*

SERES-013, is an important consideration when interpreting the CDI recurrence rates reported in this study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Cohort 1 (SERES-012 subjects who had CDI recurrence within 8 weeks):

Standard-of-care antibiotics (screening period): 10-21 days of vancomycin (125 mg qid) or fidaxomicin (200 mg bid)

Cohort 2 (de novo subjects):

Standard-of-care antibiotics: 10-42 days of treatment with vancomycin or 10-25 days of fidaxomicin.

Both cohorts:

Bowel cleanse (Day -1): 10 oz (~300 mL) of oral magnesium citrate followed by overnight fasting. Subjects with impaired kidney function who were unable to take magnesium citrate took 250 mL of GoLytely (polyethylene glycol electrolyte solution). For subjects enrolled under protocol amendment 3 or earlier with a confirmed recurrence in SERES-012 and completed antibiotics greater than 10 days prior to Week 8 in SERES-012 with resolution of symptoms, a bowel cleanse was not required. This requirement was clarified in amendment 4. There were 13 subjects (4.9%) who did not complete a bowel cleanse prior to open-label treatment with SER-109.

Investigational product (Days 1,2, and 3): 4 capsules of SER-109 (3×10^7 SCFU) or placebo taken as a single oral dose.

6.2.5 Directions for Use

In the morning before breakfast, take 4 capsules as a single dose with at least 8 fluid ounces of water. Capsules are to be swallowed and not chewed.

6.2.6 Sites and Centers

This study was conducted at 72 study sites in North America (64 US; 8 Canada). Each site enrolled at least one subject (range 1-17 subjects).

6.2.7 Surveillance/Monitoring

- Clinical assessments: physical exam and laboratory assessments at screening, Week 8, recurrence visit(s), and early termination visit.
- AE Monitoring:
 - Weekly phone calls to query for AEs and diarrheal symptoms recorded using an electronic daily diary (Day 1 through Week 8)
 - AE monitoring during follow-up period: Phone calls every 4 weeks to query for SAEs, AESIs, and any antibiotic medication and its corresponding indication (Weeks 12, 16, 20, and 24)
- Monitoring for CDI recurrence: Daily electronic diarrhea log. Subjects with diarrheal symptoms recurred (≥ 3 unformed stools per day over 2 consecutive days) were instructed to contact the investigator and return to the clinic.

- Study withdrawal/discontinuation: Subjects who voluntarily withdrew, or who were withdrawn, from the study were encouraged to complete the Early Termination Visit for evaluation for rCDI, physical exam, and laboratory assessments.

6.2.8 Endpoints and Criteria for Study Success

- Safety and tolerability of SER-109 assessed by incidence of AEs, lab results, vital signs, and physical examination findings up to Week 24.
- Efficacy was evaluated descriptively; no formal hypothesis testing was done as there was no comparator arm.
- The primary efficacy endpoint for Cohort 1 was recurrence of CDI as determined by a stool toxin assay up to 8 weeks after treatment.

The primary efficacy endpoint for Cohort 2 was recurrence of CDI as determined by a stool toxin assay up to 8 and 12 weeks after treatment

6.2.9 Statistical Considerations & Statistical Analysis Plan

There were no pre-specified success criteria for efficacy. Efficacy as well as safety data were assessed descriptively.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 263 subjects were enrolled; 29 were in Cohort 1 (SERES-012 subjects, specifically 4 SER-109 recipients and 25 placebo recipients who had CDI recurrences within the first 8 weeks after study drug treatment) and 234 were in Cohort 2 (*de novo* subjects enrolled with revised eligibility criteria, namely reducing the required number of CDI episodes to 2, including the qualifying CDI episode at study entry).

Analysis populations

Table 20. Analysis Population Definitions for SERES-013

| Analysis Population | Definition |
|--|--|
| Intent-to-Treat (ITT) Population | All enrolled subjects N=263 |
| 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 had at least 1 post-baseline evaluation. N=248 (15 excluded) For Cohort 1, subjects with a rCDI diagnosis that occurred on the SERES-012 study, as defined below: <ul style="list-style-type: none"> •Confirmation of the qualifying CDI episode required a positive <i>C. difficile</i> test based on a toxin assay. •Requirements for the qualifying CDI episode to be clinically controlled by antibiotic treatment included: <ul style="list-style-type: none"> –≤2 UBMs for at least 2 days prior to randomization –Receipt of appropriate antibiotic, including adequate treatment duration, for the qualifying episode to roll over on to the SERES-013 Cohort 1 study |

| Analysis Population | Definition |
|---------------------|---|
| | <p>For Cohort 2, subjects with a rCDI diagnosis were to have ≥ 2 CDI episodes prior to Screening, inclusive of the current episode, as defined below:</p> <ul style="list-style-type: none"> • Confirmation of the qualifying CDI episode requires a positive <i>C. difficile</i> test based on a toxin or PCR assay. Earlier protocol versions (up to Amendment 8) required a positive <i>C. difficile</i> test based on a toxin assay only. • Requirements for the qualifying CDI episode to be clinically controlled by antibiotic treatment included: <ul style="list-style-type: none"> - ≤ 2 UBM for at least 2 days prior to randomization - Receipt of appropriate antibiotic, including adequate treatment duration, for the qualifying episode |
| Safety Population | All enrolled subjects who received any amount of SER-109 N=263 |

Source: FDA-generated table

Abbreviations: ITT=intent-to-treat; mITT=modified intent-to-treat; CDI=*C. difficile* infection; rCDI=recurring *C. difficile* infection; UBM=unformed bowel movement

6.2.10.1.1 Demographics

Cohort 1 (N=29) consisted of adult subjects with 3 or more prior CDI episodes (excluding the qualifying recurrence at entry into SERES-013) whereas Cohort 2 (n=234) were subjects with 1 prior CDI episode (excluding the qualifying episode at entry). The two cohorts were similar with respect to age (median age of 65 years, range of 22 through 96 years), balanced representation of the two age strata, slightly more females (68.4%; n=180) than males (31.6%; n=83). Most subjects identified as White and non-Hispanic (92.4%; n=243 for both). Overall, treatment with vancomycin for the qualifying CDI episode at entry was more common (72.6%; n=191) than with fidaxomicin (27.4%; n=72). All subjects in Cohort 1 (from SERES-012) received vancomycin for the CDI recurrence qualifying them for SERES-013. In Cohort 1, the qualifying CDI episode was confirmed by a positive toxin test in 28 of 29 subjects. In Cohort 2, the qualifying CDI episode was confirmed by PCR test alone in 68 subjects (29.3%); the remaining 164 subjects (70.7%) had positive toxin test to confirm the qualifying CDI episode.

Table 21. Demographics and Baseline Characteristics, ITT / Safety Population, SERES-013

| Characteristic | Cohort 1 (N=29) ^a | Cohort 2 (N=234) | Total (N=263) |
|----------------------------------|------------------------------|------------------|---------------|
| Age (Years) | -- | -- | -- |
| n (missing) | 29 (0) | 234 (0) | 263 (0) |
| Mean (SD) | 71.7 (12.46) | 63.1 (15.79) | 64.0 (15.67) |
| Median | 73.0 | 64.0 | 65.0 |
| Min; Max | 35; 96 | 22; 96 | 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 (%) | -- | -- | -- |
| n (missing) | 29 (0) | 234 (0) | 263 (0) |
| Hispanic or Latino | 0 | 20 (8.5) | 20 (7.6) |
| Non-Hispanic or non-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) |

| Characteristic | Cohort 1 (N=29) ^a | Cohort 2 (N=234) | Total (N=263) |
|---|------------------------------|------------------|---------------|
| White | 29 (100.0) | 214 (91.5) | 243 (92.4) |
| Other | 0 | 0 | 0 |
| Number of previous CDI episodes, n (%) ¹ | -- | -- | -- |
| 1 | 0 | 77 (32.9) | 77 (29.3) |
| 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) |
| Prior FMT History, n (%) | -- | -- | -- |
| Yes | 0 | 6 (2.6) | 6 (2.3) |
| No | 29 (100.0) | 228 (97.4) | 257 (97.7) |
| BI/NAP1/027 status, n (%) | -- | -- | -- |
| BI/NAP1/027 | 3 (10.3) | 18 (7.7) | 21 (8.0) |
| Non-BI/NAP1/027 | 25 (86.2) | 56 (23.9) | 81 (30.8) |
| Missing/NA | 1 (3.4) | 160 (68.4) | 161 (61.2) |
| SER-109 donor lot, n (%) | -- | -- | -- |
| Donor 1 | 21 (72.4) | 94 (40.2) | 115 (43.7) |
| Donor 2 | 0 | 39 (16.7) | 39 (14.8) |
| Donor 3 | 0 | 22 (9.4) | 22 (8.4) |
| Donor 4 | 8 (27.6) | 35 (15.0) | 43 (16.3) |
| Donor 5 | 0 | 44 (18.8) | 44 (16.7) |
| Bowel cleanse, n (%) | -- | -- | -- |
| Yes | 19 (65.5) | 231 (98.7) | 250 (95.1) |
| No | 10 (34.5) | 3 (1.3) | 13 (4.9) |
| Enrollment, n (%) ² | -- | -- | -- |
| Prior to Amendment 8 | 29 (100.0) | 119 (50.9) | 148 (56.3) |
| Post to Amendment 8 | 0 | 115 (49.1) | 115 (43.7) |
| Qualifying CDI episode defined by, n (%) ² | -- | -- | -- |
| PCR alone | 1 (3.4) | 68 (29.3) | 69 (26.4) |
| Toxin with/without PCR | 28 (96.6) | 164 (70.7) | 192 (73.6) |

Source: Seres-013 CSR, Table 14.1.3.1.1, pages 156-158

Abbreviations: PCR=polymerase chain reaction; CDI=C. difficile infection; FMT=fecal microbiota for transplantation; NA=not applicable; SD=standard deviation; Min=minimum; Max=maximum

Notes: Percentages are based on the number of subjects in the Safety Population. Cohort 1 subjects were not required to have a bowel cleanse when antibiotics were completed >10 days prior to SERES-013 enrollment.

a. Randomized treatment arm in SERES-012 (Cohort 1)

1. Number of prior CDI episodes (not including qualifying episode) (1, 2, ≥2, ≥3). All Cohort 1 subjects are included in the category of ≥3 recurrences.

2. All Cohort 1 subjects are enrolled prior to Amendment 8.0.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A total of 259 (98.5%) subjects had any significant medical history, most frequently hypertension (45.6%), GERD (38.8%), anxiety (26.6%), hyperlipidemia (25.9%), depression (24.7%) and hypothyroidism (23.2%). Comorbidities in this study population included: MedDRA SOCs of *Cardiac disorders* (31.2%), *Neoplasms* (21.3%) and *Hepatobiliary disorders* (8.7%); and MedDRA PTs of *Type 2 diabetes mellitus* (10.6%), *Chronic obstructive pulmonary disease* (9.9%) and *Chronic kidney disease* (9.5%).

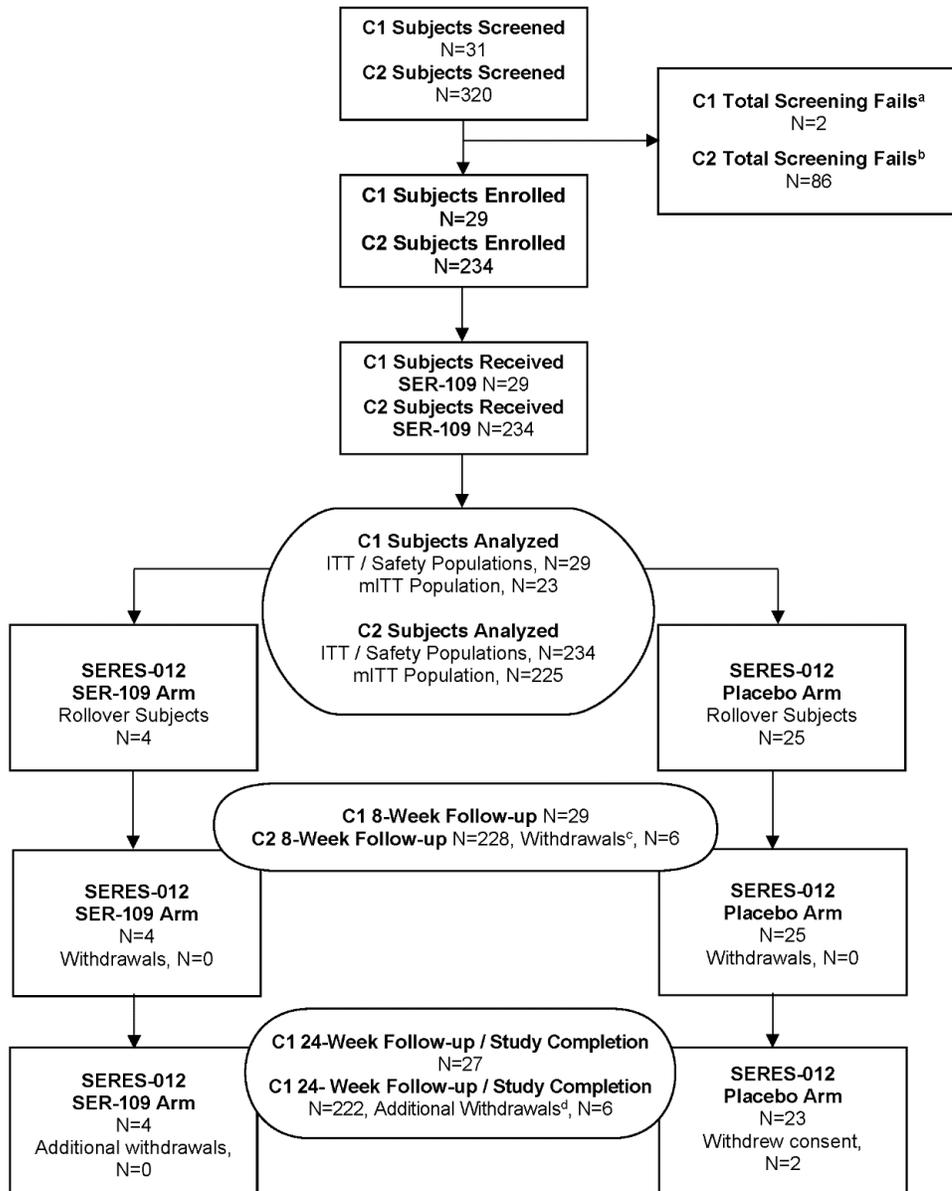
Reviewer comment: Approximately 30% of SERES-013 subjects (all from Cohort 2) had a total of 2 CDI episodes at study entry. However, the population in SERES-013 was similar to that in SERES-012 with respect to mostly vancomycin treatment for the CDI episode at entry, approximately 25% with

history of the virulent ribotype, and mostly not having received FMT before. And as permitted by the initial protocol, a second bowel cleanse was not received by 50% and 32% of subjects who received SER-109 or placebo in SERES-012. The burden of comorbidities, namely chronic cardiovascular and pulmonary conditions, diabetes mellitus, immunocompromise, and chronic kidney disease in the SERES-013 population is comparable to that in the SERES-012 population.

6.2.10.1.3 Subject Disposition

As shown in [Figure 3](#), a total of 263 subjects (Cohort 1: 29; Cohort 2: 234) were enrolled in SERES-013. Of these, 249 (94.7%) completed the study out to Week 24. Among the 14 (5.3%) subjects who withdrew from SERES-013, 8 (3.0%) died and 6 (2.3%) withdrew consent. In terms of timing of discontinuation, 6 (2.3%) subjects withdrew before Week 8 due to death (n=5) and withdrawal of consent (n=1). Eight (3.0%) subjects withdrew before Week 24 due to withdrawal of consent (n=5) and death (n=3). None of the deaths were considered related to SER-109 by study investigators (see [Section 6.2.12.3](#) for details)

Figure 3. Disposition of Subjects, Cohorts 1 and 2 (C1 and C2)



Source: SERES-013 Clinical Study Report, Figs. 1 and 2, Table 14.1.1.1

Abbreviations: C1=Cohort 1; C2=Cohort 2; ITT=Intent-to-Treat; mITT=modified ITT

Notes:

- a. Due to Inclusion/Exclusion criteria requirements, N=2
- b. Due to Inclusion/Exclusion criteria requirements, N=83; Due to other reasons, N=3
- c. Withdrew consent, N=1; Deaths, N=5
- d. Withdrew consent, N=3; Deaths, N=3

Protocol deviations

Among the ITT population (n=263), which was defined as all enrolled subjects, 202 subjects (76.8%) had at least one protocol deviation. A total of 196 (74.5%) had at least one minor protocol deviation, most commonly procedures/test deviations and visit schedule deviations (114 [43.3%] each).

Major protocol deviations were reported for 56 subjects (21.3%). The most common deviation was the use of prohibited medications in 35 subjects (13.3%), which included antibacterials (n=23), antidiarrheals (n=13), and probiotics (n=10), followed by informed consent deviations which included obsolete versions of the ICF signed or ICF not signed at scheduled time in 35 subjects (13.3%). Sixteen subjects (6.1%) had eligibility criteria deviations, such as not having a confirmed CDI episode at entry that met all criteria, receiving an unconventional antibacterial treatment regimen for the CDI episode at entry, and inability to take oral medications.

Treatment compliance

All but two subjects (99.2%) from SERES-013 received all study drug capsules. All subjects from both cohorts received the Day 1 dose. One subject ((b) (6)) had taken Days 2 and 3, but it was not recorded by the study site, and both doses were treated as missed. One subject ((b) (6)) missed Day 3 due to nausea and vomiting. During evaluation in an emergency department, she was found to have a large hiatal hernia with development of gastric volvulus.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the rate of CDI recurrence (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, 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) in the ITT population. For Cohort 1, the CDI recurrence rate was evaluated in subjects through Week 8, and for Cohort 2, it was evaluated through Weeks 8 and 12. RR ratios could not be estimated due to lack of a comparator arm. Efficacy analyses were descriptive.

Monitoring diarrheal symptoms for the purpose of detecting CDI recurrences differed between Cohorts 1 and 2. Cohort 1 subjects were instructed to complete a daily diarrhea log/device. From the date of enrollment to the end of study (Week 24) assessment, subjects were given 24 hours to enter the number of UBMs from the previous day in the electronic diarrhea log, including recording when no UBMs were experienced on any given day. Subjects were instructed to do this daily until the end of the study. However, some missing data was expected. Cohort 2 subjects did not complete a daily log but were queried about diarrheal symptoms (including the day, quality, and frequency) at scheduled telephone calls (on Days 2 and 3 and weekly thereafter through Week 7) and study site visits (Day 1, Week 8, Week 24), as were Cohort 1 subjects. In both cohorts, any subject suspected of having an episode of CDI (≥ 3 unformed stools per day lasting ≥ 2 consecutive days) was asked to arrange for study site or home visit for a *C. difficile* stool toxin test (to be sent to central laboratory).

Reviewer comment: *Where the results of the C. difficile toxin assay from the central laboratory were missing, results of the C. difficile toxin test performed by a Clinical Laboratory Improvement Amendment 7 (CLIA)-certified local laboratory using an FDA-approved toxin test were used, if available, to confirm CDI recurrence. There were no cases of recurrence confirmed based on local laboratory toxin results in SERES-012. However, in SERES-013, recurrences noted in 7 subjects were confirmed based on local laboratory toxin results, using the below test models.*

Handling of missing data for components of the CDI recurrence endpoint were pre-specified. For Cohort 1:

- If the number of UBM was missing on any day from the date of enrollment to the end of the study, the missing UBM counts were assumed to be ≥ 3 .
- If a subject missed entry into the diarrhea log on any day, the study site called the subject to inquire how many UBMs they had on the day entry into the device was missed and reminded them to enter their UBM count every day until the end of the study.
- If entry into the device was missed for 1 day and the subject reported ≥ 3 UBMs for either of the adjacent days, the study site contacted the subject. If the subject reported ≥ 3 UBMs for the missed entry, the subject was asked to return to the study site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.
- If the subject reported having < 3 UBMs on the missed day, then the study site completed the suspected CDI recurrence page in the eCRF without requiring the subject to come to the study site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.
- If entry into the device was missed for ≥ 2 consecutive days and the subject reported 2 consecutive days of ≥ 3 UBMs the next time the study site was able to make contact, the subject was asked to return to the study site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.
- If entry into the device was missed for ≥ 2 consecutive days, but the subject reported not experiencing 2 consecutive days of ≥ 3 UBMs the entire time entry into the diarrhea log was missed at the next contact, then the study site completed the suspected CDI recurrence page in the eCRF, without requiring the subject to come to the study site for a *C. difficile* stool toxin test and clinical evaluation for recurrence of CDI.
- 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.
- 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.
- 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.

As shown in [Table 22](#), at 8 weeks after treatment, the overall recurrence rate in the total population of Cohorts 1 and 2 was 8.7% (23/263) [95% CI 5.6, 12.8]. In Cohort 1, the rate was higher at 13.8% (4/29). All 4 recurrences were in the former placebo recipients

from SERES-012. In Cohort 2 alone, the recurrence rate at 8 weeks was 8.1% (19/234) and drifted up to 9.8% (23/234) at 12 weeks.

Table 22. CDI Recurrence Rates by Toxin Assay at Weeks 8 and 12, ITT population

| Time Interval After Dose Statistic | Cohort 1 (N=29) | Cohort 2 (N=234) | Total N=263 |
|---|--------------------|---------------------|----------------|
| 8 Weeks (up to Day 58) | -- | -- | -- |
| Number of subjects with CDI recurrence, n (%) | 4 (16.0) | 19 (8.1) | 23 (8.7) |
| Number of subjects with observed CDI recurrence, n (%) | 4 (16.0) | 12 (5.1) | 16 (6.1) |
| Number of subjects with imputed CDI recurrence ¹ , n (%) | 0 | 7 (3.0) | 7 (2.7) |
| Imputed CDI recurrence due to loss-to-follow-up, premature termination, or death n (%) | 0 | 4 (1.7) | 4 (1.5) |
| Imputed CDI recurrence due to missing component and non-missing components meet CDI recurrence criteria n(%) | 0 | 3 (1.3) | 3 (1.1) |
| 95% Confidence Interval for subjects with CDI recurrence ² | 3.9; 31.7 | 5.0; 12.4 | 5.6; 12.8 |
| 12 Weeks (up to Day 87) | -- | -- | -- |
| Number of subjects with CDI recurrence, n (%) | 5 (17.2) | 23 (9.8) | 28 (10.6) |
| Number of subjects with observed CDI recurrence, n (%) | 4 (13.8) | 14 (6.0) | 18 (6.8) |
| Number of subjects with imputed CDI recurrence ¹ , n (%) | 1 (3.4) | 9 (3.8) | 10 (3.8) |
| Number of subjects with imputed CDI recurrence ¹ due to lost-to-follow-up, terminated from the study prematurely, or died, n (%) | 1 (3.4) | 5 (2.1) | 6 (2.3) |
| 95% Confidence Interval for subjects with CDI recurrence ² | 5.8; 35.8 | 6.3; 14.4 | 7.2; 15.0 |

Source: Table 11 from SERES-013 CSR

1. Subjects who are lost to follow-up, terminated the study prematurely, or died without a recorded recurrence before the end of the time interval are assumed to have had a recurrence.

2. The confidence interval is calculated using the Clopper-Pearson exact method.

Reviewer comment: Data from these descriptive analyses track with the temporal trend observed in the placebo-controlled SERES-012.

6.2.11.2 Analyses of Secondary Endpoints

For Cohort 1, secondary efficacy endpoints were as follows:

- 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 1 (n=29), the CDI recurrence rate determined by PCR and toxin assay was 13.8% (95% CI: 3.9, 31.7) at Weeks 4 and 8, increased to 17.2% (95% CI: 5.8, 35.8) due to one imputed CDI recurrence, and increased 20.7% (95% CI: 8.0, 39.7) due to another imputed CDI recurrence.

For Cohort 2, secondary efficacy endpoints were not specified. CDI recurrence rates by PCR at Weeks 4, 12, and 24 were 5.3% (95% CI: 2.9, 8.8), 10.6% (95% CI: 7.2, 15.0)

and 13.7% (95% CI: 9.8, 18.4), respectively. Rates by this algorithm were identical to those determined using toxin assay.

6.2.11.3 Subpopulation Analyses

[Table 23](#) summarizes CDI recurrence rates and corresponding 95% CIs. Points of reference include the CDI recurrence rate of 12.4% in SERES-012, and the overall rate of SERES-013 of 8.9%.

Table 23. CDI Recurrence Rates up to 8 Weeks After Treatment Determined by a Toxin Assay by Subgroup, ITT Population

| Baseline Characteristics | Recurrence Rate | 95% CI |
|--|-----------------|---------------|
| Overall | 8.75 | (5.62; 12.83) |
| Age group | -- | -- |
| <65 years old | 3.97 | (1.30; 9.02) |
| ≥65 years old | 13.14 | (7.98; 19.97) |
| Antibiotic regimen stratification | -- | -- |
| Vancomycin | 8.90 | (5.27; 13.87) |
| Fidaxomicin | 8.33 | (3.12; 17.26) |
| Gender | -- | -- |
| Male | 10.84 | (5.08; 19.59) |
| Female | 7.78 | (4.32; 12.71) |
| Race | -- | -- |
| White | 8.23 | (5.10; 12.43) |
| Black or African American | 21.43 | (4.66; 50.80) |
| Asian | 0.00 | (0.00; 52.18) |
| Other | NE | NE |
| Active SER-109 | -- | -- |
| Donor 1 | 8.70 | (4.25; 15.41) |
| Donor 2 | 2.56 | (0.06; 13.48) |
| Donor 3 | 9.09 | (1.12; 29.16) |
| Donor 4 | 11.63 | (3.89; 25.08) |
| Donor 5 | 11.36 | (3.79; 24.56) |
| Number of prior CDI episodes | -- | -- |
| 1 | 6.49 | (2.14; 14.51) |
| 2 | 6.06 | (2.26; 12.73) |
| ≥2 | 9.68 | (5.84; 14.86) |
| ≥3 | 13.79 | (7.34; 22.85) |
| Qualifying episode defined by PCR alone | 4.35 | (0.91; 12.18) |
| Qualifying episode defined by toxin with/without PCR | 10.42 | (6.48; 15.63) |

Source: SERES-013 Clinical Study Report, Version 1.0, Figure 3 pg. 95. Figure 14.2.2

Abbreviations: CDI=*C. difficile* infection; ITT=intent to treat; PCR=polymerase chain reaction

Notes: Subjects who are lost to follow-up, terminated the study prematurely, or died without a recorded recurrence before the end of the time interval are assumed to have had a recurrence. Handling of other types of missing data are provided in the SAP. The 95% confidence interval and recurrence rate (proportion of subjects with CDI recurrence) are calculated using the Clopper-Pearson exact method. Reference Table: 14.2.1.1.3

6.2.11.4 Dropouts and/or Discontinuations

There were 12 subjects who dropped out, with 6 subjects by 8 weeks after treatment, and another 6 by 24 weeks after treatment. Most early dropouts were due to death (n=8) or withdrawal of consent (n=4).

6.2.11.5 Exploratory and Post Hoc Analyses

All-Cause Mortality Through 8 and 24 Weeks After Treatment

There were 8 deaths, all in Cohort 2, in the study. None were considered related to the study drug by investigators. All of them were deemed not related to the study drug by investigators. There was no apparent temporal clustering of the deaths. Five deaths occurred up to Week 8, and 3 additional deaths were reported after Week 12, with a range of 5 days and 132 days after treatment. See [Section 6.2.12.3](#) for details.

Health-Related Quality of Life and Health Outcomes (Cohort 1)

The Cdif21 HRQoL questionnaire was administered to subjects in Cohort 1 (n=29) at baseline, Recurrence Visit, Week 1, and Week 8. (b) (4)

The Cdif21 HRQoL is not qualified by FDA for use in labeling claims.

The EQ-Visual Analog Scale (VAS) was administered to a subset of Cohort 2 (n=115) at Screening and Week 8 and is not qualified by FDA for use in labeling claims. The EQ VAS records the subject's self-reported health on a vertical visual analogue scale, ranging from "worst health you can imagine" to "best health you can imagine." (b) (4)

Reviewer comment: *In the absence of a placebo arm, the interpretability of the reported changes in questionnaire-based outcomes is limited. The bowel cleanse patient satisfaction survey is informative in that it indicates this pre-requisite step for initiating SER-109 treatment is not overly burdensome or prohibitive.*

6.2.12 Safety Analyses

6.2.12.1 Methods

There was no collection of solicited AEs. Unsolicited AEs were collected weekly for approximately 2 months (Day 58). SAEs and AESIs (defined as an invasive infection (e.g., bacteremia, abscess) were collected monthly for the duration of the study (Days 1 through 168). All safety analyses were conducted based on the Safety Population (all randomly assigned subjects who received any amount of study drug).

Most AEs, including SAEs and AESIs, were graded for severity by using the common terminology criteria for AEs Common Terminology Criteria for Adverse Events v4.0 [CTCAE], Publication Date: 28 May 2009). Diarrhea was graded as follows:

- Mild: 3-4 UBMs per day
- Moderate: 5-6 UBMs per day
- Severe: ≥7 UBMs per day

Diarrhea that met the protocol definition of CDI recurrence (≥3 unformed stools per day over 2 or more consecutive days, a positive *C. difficile* test on a stool sample determined by a toxin assay, and assessment by the investigator that treatment was required) was NOT entered as an AE. Events of diarrhea that were not associated with CDI recurrence (e.g., due to food poisoning or flu) were, however, reported as an AE (e.g., Diarrhea [Not CDI related]).

AEs were additionally categorized by relationship to study drug (unrelated, related, or possibly related)

6.2.12.2 Overview of Adverse Events

Solicited AEs were not collected in this study. A total of 141 (53.6%) subjects who received SER-109 reported a total of 476 unsolicited AEs over the duration of the study. None of these AEs resulted in subjects withdrawing from the study. The majority of the AEs were graded as mild (26.6% of subjects) to moderate (17.1%); severe TEAEs were reported by 26 (9.9%) subjects who had a total of 62 events. As shown in [Table 24](#), most subjects reported TEAEs under the *Gastrointestinal disorders* SOC followed by *Infections and infestations* (38 of the 141 reporting TEAEs). PTs under the former SOC were diarrhea (22.8% of all study subjects), flatulence (7.6%), nausea (7.6%) and abdominal pain (6.8%). The most common PT under Infections and infestations were UTI (4.9% of all study subjects; n=13) and cellulitis (2.3%; n=6).

Table 24. Unsolicited AEs in SERES-013

| SERES-013 | Total N_T=263 n (%) | Days 1-10 N=263 n (%) | Days 11-14 N=262 n (%) | Days 15- 21 N=262 n (%) | Days 22- 28 N=261 n (%) | Days 29- 58 N=260 n (%) | Days 59-168 N=257 n (%) |
|---------------------------------------|--|--------------------------------------|---|--|--|--|--|
| Subjects with ≥1 unsolicited AE n (%) | 141 (53.6) | 80 (30.4) | 22 (8.4) | 30 (11.5) | 28 (10.7) | 71 (27.3) | 21 (8.2) |
| Mild | 70 (26.6) | -- | -- | -- | -- | -- | -- |
| Moderate | 45 (17.1) | -- | -- | -- | -- | -- | -- |
| Severe | 26 (9.9) | -- | -- | -- | -- | -- | -- |
| SOC Preferred Term | -- | -- | -- | -- | -- | -- | -- |
| Gastrointestinal disorders | 104 (39.5) | 63 (24.0) | 16 (6.1) | 19 (7.3) | 17 (6.5) | 36 (13.8) | 4 (1.6) |
| Diarrhea | 60 (22.8) | 27 (10.3) | 8 (3.1) | 11 (4.2) | 9 (3.4) | 21 (8.1) | 1 (0.4) |
| Constipation | 7(2.7) | 3(1.1) | 2(0.8) | 0(0.0) | 1(0.4) | 1(0.4) | 0 (0.0) |
| Flatulence | 20 (7.6) | 17 (6.5) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 2 (0.8) | 0 (0.0) |
| Infections and infestations | 38 (14.4) | 6 (2.3) | 3 (1.1) | 5 (1.9) | 5 (1.9) | 18 (6.9) | 12 (4.7) |
| UTI | 13 (4.9) | 4 (1.5) | 2 (0.8) | 2 (0.8) | 0 (0.0) | 6 (2.3) | 1 (0.4) |

Source: Table 14.3.1.3 from SERES-013 CSR and Table 14.3.1.2.1 from response to Information Request submitted as amendment 58 to STN 125757 (received 3/27/2023)

Abbreviations: AE=adverse events; TEAEs=treatment emergent adverse events; SOC=System Organ Class; MedDRA=Medical Dictionary for Regulatory Activities

Notes: Percentages are based on the number of subjects in the Safety Population in each treatment group. N=number of subjects in the Safety Population who are in the study at the beginning of the specified time interval; NT=total number of subjects in the Safety Population. For each level of summarization, a subject contributes only once to the count for a given TEAE on the SOC level and on the PT level within SOC. SOC and PT are coded using the MedDRA coding dictionary, v20.0 (March 2017). All TEAEs will be collected and summarized from the time of initiation of study drug up to Week 8/End of study (early discontinuation that precedes Week 8); from Week 8 up to Week 24/End of Study, only SAEs and AESIs will be collected and summarized. Reference Listing:16.2.7.1

Reviewer comment: *The rate of diarrhea was similar to that observed in SERES-012, while the incidence of the other common AEs was lower in SERES-013 (<10%) compared with SERES-012. This is likely due to the absence of solicited AE reporting in SERES-013. This likely did not affect reporting of diarrhea because subjects were required to keep a diarrhea log for the purpose of monitoring for CDI recurrence.*

Urinary Tract Infections

As summarized in [Table 25](#), UTIs occurred in 15 subjects (all in Cohort 2), with two of them presenting as urosepsis, one of which was associated with a fatality. All subjects received antibacterial treatment.

The majority (84.6%; n=11) of subjects had one of the predisposing risk factors: female sex, prior UTI(s), bladder abnormalities, prostatic hyperplasia, chronic kidney disease or renal stones, Foley catheter or recent catheterization event. Urine culture results were available for 10 subjects. Two of them had no growth; among the 6 with positive results, none of the detected organisms are present in SER-109 and mostly detected common gram negative uropathogens.

Table 25. Treatment-Emergent Urinary Tract Infections, SERES-013

| Sex/Age | Start-Stop Day | Clinical history; UTI course | Severity | SAE | Urine culture | Treatment |
|---------------------------------|------------------|---|----------------|-----|--|--------------------------------------|
| Urosepsis^a | -- | -- | -- | -- | -- | -- |
| 94/M | 111-115 | Chronic kidney disease, benign prostatic hyperplasia; increased frequency, dysuria, rigors and fever | Severe | Yes | >100,000 colonies <i>E coli</i> | ceftriaxone IV to ciprofloxacin oral |
| 69/M | 80-92 105-122 | Prior UTI; fever, pus from foley catheter, no urine output, grogginess | Severe (fatal) | Yes | >100 × 10 ⁶ CFU/L <i>Pseudomonas aeruginosa</i> | Multiple broad spectrum antibiotics |
| Urinary Tract Infections | -- | -- | -- | -- | -- | -- |
| 28/F | 16-29 | No relevant history; burning with urination, flank pain, vaginal burning, cramping, urinary frequency, nausea and low back pain | Moderate | No | Negative | Ceftriaxone; ciprofloxacin |
| 81/F | 13-17 49-53 | Bladder suspension, dementia; burning and frequency of urination | Mild | No | Commensal flora | Fosfomycin, ceftriaxone |

| Sex/Age | Start-Stop Day | Clinical history; UTI course | Severity | SAE | Urine culture | Treatment |
|---------|----------------|--|----------|-----|---|--|
| 48/F | 15-20 | History of UTIs; frequency, dysuria, urgency and hesitancy | Moderate | No | Mixed flora (urogenital), suggesting an improperly collected specimen abnormal | Ciprofloxacin |
| 81/F | 157-163 | Prior hospitalization for UTI. Presented with back pain x2 in preceding year; low-mid back pain | Mild | Yes | >100K <i>Klebsiella oxytoca</i> sensitive to trimethoprim/sulfamethoxazole | Bactrim |
| 75/M | 11-43 | Treated for bladder cancer; prolonged UTI | Mild | No | <i>Klebsiella oxytoca</i> >10,000 but <100,000 CFU/mL | Cephalexin; nitrofurantoin; sulfamethoxazole; trimethoprim |
| 96/F | 2-6 | Long history of prior UTI; dysuria, frequency | Moderate | No | Negative | ceftriaxone IV; cefazolin |
| 86/F | 4-6 35-40 | rUTI; frequency, decreased mental status, increased confusion | Moderate | No | Not done | Fosfomycin |
| 79/F | 8-22 | Urinary and stool incontinence; decreased level of consciousness similar to previous presentation of UTI | Moderate | Yes | Not done | Ceftriaxone, meropenem |
| 68/M | 48-53 | Neurogenic bladder; fever (37.9°C) | Mild | No | <i>Proteus mirabilis</i> ; sensitive to ampicillin, cefotaxime, ciprofloxacin, gentamicin, ceftriaxone, tobramycin; resistant to nitrofurantoin | Nitrofurantoin |
| 56/F | 35-39 | Kidney stones; dysuria, frequency, hematuria | Mild | No | Not available | Macrobid |
| 84/F | 45-56 | Foley catheter during hospitalization; hematuria | Moderate | Yes | >100K <i>E faecium</i> , vancomycin resistant | Meropenem IV |
| 88/M | 3-10 | rUTIs, kidney stones, chronic kidney disease (stage 3) | Mild | No | Not done | Ciprofloxacin |
| 67/F | 31-34 | No relevant history; dysuria and hematuria | Mild | No | 10,000-20,000 CFU/ml <i>Escherichia coli</i> ; 10,000- 20,000 CFU/ml <i>Proteus vulgaris</i> | AZO; doxycycline |

Source: STN 125757/1, Seres-013 CSR Table 32

Abbreviations: CFU=colony forming unit; Hpf=high power field; IV=intravenous; F=female; M=male; rUTI=recurrent urinary tract infection; SAE=serious adverse event; UTI=urinary tract infection

^a Captured as an AESI

Reviewer comment: *This reviewer agrees with the assessment that the UTIs with available culture results are unrelated to SER-109. For the 4 cases where culture was not done or results were not available, older age, female sex, predisposing factors per medical history, and response to empiric antibacterial treatment for a presumed UTI also indicate that these are likely due to common uropathogens.*

Adverse Reactions

Adverse reactions, AEs considered related or possibly related, occurred in 12.2% (32/263) of subjects in SERES-013. The majority were reported within the first week after completion of SER-109 (Study Days 3-10). Adverse reactions were most frequently flatulence (4.2%; n=11 subjects), diarrhea (3.4%; n=9), and nausea (3.0%; n=8 subjects), predominantly mild to moderate in severity. Most subjects with moderate or severe adverse reactions (5.7%; n=15), primarily GI symptoms and fatigue, resolved without intervention.

Hypersensitivity Reactions

One subject, a 44-year-old White female with a medical history significant for multiple drug hypersensitivity reactions, experienced mild facial flushing approximately 30 minutes after the first dose. There were no other cutaneous or respiratory findings or symptoms. Flushing resolved without intervention over approximately 15 minutes. She had similar symptoms as well as subjective throat and jaw tightness after the second and third dose. Vitals were within normal limits. No medications or epinephrine was given. The subject self-medicated with diphenhydramine.

Reviewer comment: *This reviewer agrees with characterizing this subject's reaction as an adverse drug reaction. While reproducible, the symptoms were mild enough for the subject to complete the regimen and were largely subjective. This presentation is not consistent with an IgE-mediated reaction.*

6.2.12.3 Deaths

There were 8 deaths (3.0%) in SERES-013, all from Cohort 2, and none of the deaths occurred during study drug administration. The deaths occurred between 5 and 132 days after completion of treatment. None were considered related to the study drug but due to pre-existing conditions or intercurrent illnesses or, in one case, old age.

- 65 yo White NH male with coronary artery disease, coronary artery bypass graft, CHF, cerebral artery occlusion, chronic obstructive lung disease who was found deceased by police in his home on Day 5. An autopsy was performed and there were no signs of foul play, no evidence of thrombotic events. Death was suspected to be related to his severe dilated cardiomyopathy and possibly acute arrhythmia.
- 64 yo Black NH male HIV, peripheral artery disease, coronary artery disease, systolic and diastolic heart failure, abdominal aneurysm with surgical repair, end stage renal disease on dialysis and on anticoagulant therapy presented to an emergency department three days after completing SER-109 with chest pain, shortness of breath, bilateral leg pain in the setting of missed dialysis for one week. He was found to be in acute decompensated heart failure and was started on daily dialysis. Due to hypoxia, he was placed on BiPAP and transferred to

intensive care. Hospital course was also complicated by thrombocytopenia, for which he received intravenous immunoglobulins on the same day. He was also started on dexamethasone 40 mg. His heart failure was stabilized and he was discharged on Study Day 16. He presented again to the emergency department with cramping abdominal pain, bloody diarrhea, hematemesis, hematochezia, epistaxis, and chest pain on Study Day 22. Chest radiograph showed a possible infiltrate on the left. Nasopharyngeal swab positive for COVID-19, for which he was started on remdesivir and solumedrol. CT of the abdomen and pelvis showed small bowel thickening and diffuse mesenteric edema. Stool was also positive for *C. difficile* toxin A/B. He was started on fidaxomicin and transitioned to vancomycin the following day. Two days later, he reported diffuse abdominal pain and imaging shorted intestinal perforation, which was thought to be in the small bowel and unrelated to his CDI. He was started on broad spectrum antibiotics and was followed by infectious disease, eventually placed on eravacycline for his complex intra-abdominal infection. Cardiology was consulted and he was not considered a surgical candidate. He was made DNR with comfort measures only, and he expired on the same day (Study Day 28). No autopsy was performed. Death was considered due to COVID-19 infection and intestinal perforation (suspected to be small bowel, possibly ischemic, rather than his rCDI). Blood culture from that day eventually grew *Klebsiella oxytoca* and diarrhea was ongoing at the time of death.

- 93 yo White NH female with Parkinson's disease, macular degeneration, deep vein thrombosis with weight of 90 pounds, height 64 inches. At Week 6 study contact, subject's daughter reported that she had been fatigued for past 3 days and being in bed, but with good appetite and without symptoms of diarrhea or bloody stool or fever. She was reported to have passed away during sleep on Day 44. No autopsy was performed. Her death was attributed to natural causes related to age.
- 79 yo White NH female with atrial fibrillation, congestive heart failure, vertebral artery dissection, right upper lung lobectomy and mild cognitive impairment who was found to be less responsive by her daughter 8 days after completing SER-109 (Study Day 11). She was evaluated in an emergency room. Daughter worried about a UTI because she was wearing a pad for (stool and possibly urinary) incontinence at the time. Urine culture was positive for *Citrobacter freundii* and she was started on meropenem along with ceftriaxone. Her diarrhea resolved. Repeat urine culture grew *Candida albicans* in the absence of urinary symptoms, therefore she was not treated for this. Hospitalization was prolonged for management of heart failure. She was discharged on Day 22. Nine days later she was taken to the hospital via ambulance for increasing weakness and confusion. Initial bloodwork showed a serum potassium of 6.2 mmol/l and this was effectively treated in the ER. She was hospitalized. Stool testing with a GI pathogen PCR panel was positive for toxin A+B (PCR accepted for CDI case definition) on she was started on vancomycin on Day 31. Her course was complicated by worsening CHF and increasing oxygen requirements and declining renal function. In the ICU while on 5 L oxygen, approximately 75 minutes after being observed to be in no distress, she was found to be non-responsive and passed away on Day 39. An autopsy was not performed. The attending physician reported the cause of death as unknown, but attributed

multiple acute processes including CHF, CDI, acute kidney injury along with right upper lung lobectomy and dementia.

- 68 yo White NH male with multiple sclerosis, neurogenic bladder with indwelling Foley catheter, recurrent UTIs, decubitus ulcers, chronic inflammatory demyelinating neuropathy, atrial fibrillation, and stroke was found to have a positive urine culture for *Proteus mirabilis*. He was started on nitrofurantoin, to which the organism was later found to be resistant. Documentation did not specify subsequent antibacterial therapy for his UTI. A month later he presented to the ER with grogginess and low urine output. Indwelling catheter was found to be clogged with pus. He was admitted with a diagnosis of urosepsis and acute kidney injury and was later discharged after resolution of these events. He subsequently developed symptoms of pneumonia on Day 105 and was seen again in the ED due to shortness of breath and drowsiness. Wife reported dysphagia with aspiration, but subject was on oral feeds as requested. He developed respiratory failure. In addition to a right lung infiltrate, his urinary catheter was draining dark blood. He was hospitalized and was placed on vasopressors and BiPAP and started on empiric piperacillin/tazobactam. He had CDI recurrence during this hospitalization, which was attributed to broad spectrum antibiotics. Urine culture was also positive for *Pseudomonas aeruginosa*, stool was *C. difficile* toxin positive, and he was found to be positive on MRSA screen. Another urine culture collected approximately 5 weeks later continued to be positive for *Pseudomonas*. His course was also complicated by aspiration and his condition continued to decline while on broad spectrum antibiotics with delirium. His wife requested palliative care and he passed away on Day 122.
- 72 yo White NH male with necrotizing fasciitis and Fournier's gangrene on Day 30 and passed away on Day 55
- 84 yo White NH female with CAD and chronic end-stage heart failure, end-stage renal disease, GI bleed due to duodenal ulcer who passed on Day 115
- 65 yo White NH male with progression of pancreatic cancer on Day 45 and passed on Day 132

6.2.12.4 Nonfatal Serious Adverse Events

There were 34 subjects (12.9%) with non-fatal SAEs.

- 1) 94 yo White NH male who developed urosepsis due to UTI with *E. coli* on Days 111-115
- 2) 59 yo White NH female with transient ischemia attack (TIA) on Day 29-30 and bacterial endocarditis (*Abiotrophia defectiva*) on Days 47-50, CHF on Day 80-84, and exacerbation of CHF on Days 97-100, acute decompensation heart failure on Days 113-144, acute kidney injury on Days 117-127
- 3) 74 yo White NH male with anterior chest wall hematoma on Days 63-67
- 4) 81 yo White NH female with hip fracture on Days 23-32, dehydration due to CDI on Days 49-58, CDI on Day 166-ongoing
- 5) 73 yo White NH male with aspiration pneumonia on Days 18-26 and CDI recurrence on Days 27-31
- 6) 79 yo White Hispanic female with diarrhea on Days 128-131

- 7) 65 yo White NH male with COVID-19 on Days 16-78, E. coli bacteremia on Days 50-61
- 8) 71 yo Black NH male with bronchospasm on Days 68-69, dyspnea on Day 103
- 9) 81 yo White NH female with UTI on Days 157-163
- 10) 82 yo White NH female in motor vehicle accident on Day 37
- 11) 82 yo White NH female with pulmonary embolism on Day 71-ongoing
- 12) 65 yo White NH male with pre-existing severe dilated cardiomyopathy on Day 5
- 13) 64 yo Black NH male with acute decompensated heart failure on Days 6-16, COVID-19 on Days 22-28, diarrhea due to CDI recurrence on Day 26, intestinal perforation on Day 28
- 14) 59 yo Black NH male with syncope Days 56-61
- 15) 50 yo Black NH female with CMV viremia on Day 116-ongoing
- 16) 45 yo White NH male with syncope (attributed to pre-existing condition) on Day 41, diarrhea and secondary dehydration Days 41-47
- 17) 86 yo White NH male with cellulitis and abscess of right foot on Days 41-ongoing, CDI on Days 70-87
- 18) 76 yo White NH male with worsening recurrent cellulitis on Days 148-150, worsening atrial fibrillation Days 160-162
- 19) 84 yo White NH female with purulent cellulitis of left lower extremity, worsening vasculitic infection on Days 107-122
- 20) 63 yo White NH male with small bowel obstruction on Days 67-69
- 21) 96 yo White NH female with gastric volvulus on Days 2-20 and SER-109 stopped, distal esophageal abscess on Days 14-83
- 22) 93 yo White NH female with death due to natural causes on Day 44
- 23) 39 yo White NH female with ectopic pregnancy on Days 89-95
- 24) 79 yo White NH female with UTI on Days 8-22, CDI on Days 31-39
- 25) 68 yo White NH male with urosepsis, acute kidney injury on Days 80-85, nephrolithiasis on Days 83-84, urosepsis again with aspiration pneumonia Days 105-122, bilateral pneumonia Days 121-122
- 26) 73 yo White NH male with worsening of pre-existing anemia Days 20-24
- 27) 57 yo White NH male with bilateral foot cellulitis (recurrence) on Days 110-149, left leg cellulitis recurrence, Days 149-192
- 28) 74 yo White NH male with Bell's Palsy (severe) on Days 7-8
- 29) 54 yo White NH male, chronic recurrent osteomyelitis on Days 31-37
- 30) 55 yo White Hispanic female, elevated amylase and lipase on Days 42-44
- 31) 84 yo White NH female with UTI on Days 45-56, recurrence of CDI on Days 52-66, GI bleed from pyloric ulcer (Day 54- ongoing), thrombocytopenia (Days 76-84)
- 32) 74 yo White NH male: acute ST elevation myocardial infarction on Days 74-76
- 33) 65 yo White NH male with common bile duct obstruction (Days 53-54), streptococcal cholangitis (Days 56-58), ascites, peritonitis and perforated viscus (Day 79-ongoing)
- 34) 67 yo White NH female with Mallory Weiss tear (Days 26-30)

6.2.12.5 Adverse Events of Special Interest (AESI)

Like in SERES-012, SERES-013 prospectively monitored for invasive infections as an AESI. Seventeen subjects (6.5%) experienced a total of 23 AESIs, namely invasive infections, all of which were considered unrelated to the study drug by the investigators. In terms of onset, similar proportion of subjects had AESIs within Week 8 (10 [3.8%] subjects) and after Week 8 (8 [3.1%] subjects). The earliest an AESI was reported was

on Day 14 (distal esophageal abscess, a complication of surgical repair of gastric volvulus). In the 8 subjects (47.1%) with available tissue cultures, the identified microorganisms were not present in SER-109 dose species.

Reviewer comment: *This reviewer agrees that these disparate infections, primarily sinusitis and cellulitis, were not related to the study drug. For the 9 subjects in whom cultures were not done, the narratives indicate alternative etiologies, including pre-existing conditions or acute events unrelated to CDI.*

- 1) 94 yo White NH male with urosepsis due to E. coli UTI (Day 111-115)
- 2) 59 yo White NH female with endocarditis and bacteremia with *Abiotrophia*
- 3) 28 yo White NH female with dental abscess Day 39-41
- 4) 65 yo White NH male with E. coli bacteremia on Day 50-61
- 5) 86 yo White NH male with cellulitis abscess of right foot Day 41-ongoing
- 6) 76 yo White NH male with worsening recurrent cellulitis (Day 148-150)
- 7) 84 yo White NH female with purulent and vasculitic cellulitis of left lower extremity (Day 107-122)
- 8) 96 yo White NH female with distal esophageal abscess (Day 14-83)
- 9) 42 yo White NH female with dental abscess on Day 110-117
- 10) 68 yo White NH male with urosepsis on Day 80-85, then 105-122 (fatal)
- 11) 73 yo White NH male with necrotizing fasciitis and Fournier's gangrene on Days 30-55 (fatal)
- 12) 57 yo White NH male with bilateral foot cellulitis (Days 110-149)
- 13) 42 yo White NH female with bacterial sinus infection on Day 49-72
- 14) 54 yo White NH male with chronic multifocal osteomyelitis of left foot, Day 31-37
- 15) 55 yo White Hispanic female with cellulitis of legs (Days 45-49)
- 16) 65 yo White NH male with strep cholangitis on Days 56-58, peritonitis Day 79-ongoing
- 17) 54 yo White NH male with right leg cellulitis (Days 106-114)

Reviewer comment: *This reviewer agrees that the nonfatal SAEs and AESIs described above were associated with pre-existing conditions or acute events that were not related to the study drug.*

6.2.12.6 Clinical Test Results

Among individual subjects, there were sporadic shifts in hematology and clinical chemistry parameters from normal at baseline to abnormal over the course of the study, none of which were considered related to SER-109. Clinically significant abnormalities were highlighted in specific individuals, and included:

- Thrombocytopenia (n=2)
 - Subject with severe thrombocytopenia on Day 76 and resolved on Day 84 with treatment during hospitalization
 - Subject with moderate thrombocytopenia on Day 9 that resolved on Day 16 with treatment with intravenous immunoglobulins.
- Anemia (n=2)
 - Subject with mild anemia on Day 23 that resolved on Day 32 without treatment.
 - Subject with severe anemia (acute on chronic anemia) on Day 20 that required transfusion of packed red blood cells and resolved on Day 24

- Elevated amylase and lipase: One subject with moderately elevated amylase and lipase on Day 42, with resolution by Day 44 without intervention. There was no corresponding diagnosis.
- Elevated aspartate aminotransferase (AST): One subject with moderately elevated AST on Day 55 that resolved without treatment on Day 84.
- Leukocytosis: One subject with mild leukocytosis on Day 23 that resolved on Day 32 with treatment (Fosfomycin for UTI)

6.2.12.7 Dropouts and/or Discontinuations

There were 14 (5.3%) subjects who withdrew from the study. The common reason was death (3.0%; n=8) followed by withdrawal of consent (2.3%; n=6). Six (2.3%) subjects withdrew before Week 8 due to death (n=5) and withdrawal of consent (n=1). Eight (3.0%) subjects withdrew before Week 24 due to withdrawal of consent (n=5) and death (n=3).

6.2.13 Study Summary and Conclusions

The primary efficacy analysis in open-label study SERES-013 presented the rates of CDI recurrence after three consecutive days of SER-109 in the ITT population, which included all subjects in Cohorts 1 and 2. The overall CDI recurrence rate 8 weeks after treatment in Cohorts 1 and 2 was 8.7% (23/263; 95% CI 5.6, 12.8). In Cohort 2, which consisted of subjects with 2 or more CDI episodes including the qualifying episode at study entry, the recurrence rate at 8 weeks was lower at 8.1% (19/234). Descriptive analyses of recurrence rates by subgroups yielded recurrence rates ranging between 6.1% (subjects with total of 3 CDI episodes, including the one at entry, n=99) to 13.8% (subjects with total of 4 or more CDI episodes, including the one at entry, n=87). The safety population comprised subjects who received at least one dose of SER-109. Over half of the subjects (141 (53.6%; n=141) reported a total of 476 AEs, which were most commonly under the MedDRA SOC *Gastrointestinal disorders* (104 [39.5%]), namely diarrhea (22.5%; n=60), flatulence and nausea (7.6%; n=20) and abdominal pain (6.8%; n=18). Most AEs were graded as mild to moderate in severity (<10% severe AEs). The most common adverse reactions were flatulence (4.2%), diarrhea (3.4%) and nausea (3.0%). None of the SAEs or deaths were considered related to SER-109, and the mortality rate was within an expected rate for this patient population.

6.3 Trial #3: **SERES-004**

[NCT02437487](#): A Randomized, Double Blind, Placebo Controlled, Parallel Group Study of SER 109 to Prevent Recurrent *Clostridium Difficile* (ECOSPOR)

6.3.1 Objectives (Primary, Secondary, etc.)

Primary efficacy objective: To evaluate the efficacy of SER-109 versus placebo in the prevention of rCDI in adult subjects up to 8 weeks after treatment.

Secondary efficacy objectives:

- To compare the time to CDI recurrence in subjects who receive SER-109 or placebo.
- To compare the proportion of subjects experiencing clinical CDI recurrence up to 4 weeks, up to 12 weeks, and up to 24 weeks after treatment.

Safety objective: To evaluate the safety and tolerability of SER-109 in subjects with rCDI.

6.3.2 Design Overview

This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study of the safety, tolerability, and efficacy of SER-109 in adults ≥ 18 years of age with rCDI (defined as a history of ≥ 3 CDI episodes within 9 months, inclusive of the current episode). Subjects were randomized in a 2:1 ratio to receive SER-109 [1×10^8 spore equivalents (SporQs)] or matching placebo, respectively; and stratified by age (<65 years, ≥ 65 years). Subjects received a single dose of SER-109 or placebo on Day 1. Subjects who had diarrhea, a positive *C. difficile* stool test result, and had responded to 10-21 days of standard of care antibiotic treatment were eligible to enroll.

Reviewer comments: *SERES-004 enrolled 87 adults with rCDI. The primary endpoint was recurrence of CDI by Week 8, evaluated through either a PCR test or a toxin test, among the ITT population. Assumed CDI recurrence rates in the placebo arm was 60% and 30% in the SER-109 arm. SERES-004 failed to meet the efficacy success criterion (lower bound of the 95% CI of the RR ratio (placebo/SER-109) of 1.2). The results from this study were difficult to interpret. In the ITT population, CDI recurrence by Week 8 occurred in 53.3% (16/30) of the placebo recipients and in 44.1% (26/59) of the SER-109 recipients. The corresponding RR (Placebo/SER-109) was 1.22 [95% CI: 0.79, 1.88]. However, results varied substantially by age strata. In subjects under 65 years of age, the CDI recurrence rate was higher in SER-109 recipients (42.9% (12/28)) than placebo recipients (26.7% (4/15)), which was also significantly lower than the assumed rate of 60%. Among subjects 65 years of age and above, CDI recurrence was lower in the SER-109 arm (45.2% (14/31)) than in the placebo arm (80% (12/15)).*

Median duration of follow-up in SER-109 recipients and placebo recipients was 167.0 (range 15, 215) days and 161.0 (8, 221) days, respectively. Most subjects in the SER-109 arm dropped out due to a CDI recurrence (23/59) and all dropouts in the placebo arm were due to CDI recurrence (14/30). There were two SER-109 recipients lost to follow-up, one SER-109 recipient who withdrew consent, and one SER-109 recipient (82 year old male with multiple comorbidities) who dropped out due to AEs, specifically due to chest pain and agitation that occurred in the setting of metastatic lung cancer, which was eventually fatal. This specific subject experienced a total of 14 TEAEs, including 8 AEs graded as severe and 4 SAEs. The safety and tolerability profile of the one-day course of SER-109 was similar to what was described earlier for SERES-012, with most TEAEs belonging to the SOC of Gastrointestinal disorders. Overall, 15 of the 89 (16.9%) subjects had an adverse reaction, that is an AE considered related to investigational, with 11 SER-109 recipients (18.3%; n=60) and 4 placebo recipients (13.8%; m=29). UTIs occurred at similar rates in both arms: two SER-109 recipients (3.3%) and 1 placebo recipient (3.4%) had UTIs, all graded as mild. All subjects were White females in their sixth decade of life and all events resolved. The two SER-109 recipients received nitrofurantoin and the placebo recipient received cranberry extract. All events were considered unrelated to study drug. There were no SAEs of UTI in SERES-004. Two AESIs, which were retrospectively detected, were reported in 2 SER-109 recipients

(3.3%). None were reported among placebo recipients. The reported events were cellulitis of the lower leg and sinusitis (presenting as headache occurring with shortness of breath that led to hospitalization). Neither case had documented cultures. In the opinion of this reviewer, neither case reflects invasive infection. There were 43 SAEs that occurred in 12 subjects, comprised of 9 of the 60 SER-109 recipients and 3 of the 29 placebo recipients. This reviewer agrees that none of the SAEs are likely to have been related to the study drug. There was one unrelated death in a SER-109 recipient on Study Day 138 due to metastatic small cell lung carcinoma. This subject experienced a total of 14 TEAEs, including 4 SAEs, and 8 AEs rated severe.

Notably, the observed recurrence rate in the placebo arm was much lower than the assumed rate, which is based on published literature. The Applicant pointed out that recurrences in subjects from SERES-004 were documented as early as 3 days from receiving the study drug, and 75% of recurrences in both study arms had occurred by Day 20 of Day 56 of the primary endpoint. In other words, what was captured as a recurrence could have been post-infectious diarrhea and the PCR positivity could have reflected colonization. As a result of failure analysis of SERES-004, the diagnostic algorithm for verifying CDI was revised to avoid misclassification of colonization as a recurrence by relying on the more specific toxin assay as opposed to PCR and to require that the diarrhea must still be present at the time of antibiotic initiation. The Applicant also conducted a retrospective analysis of stool samples from SERES-001. (b) (4) metagenomic sequencing of these stool samples showed greater microbiome changes and greatest engraftment associated with higher doses as compared to the dose administered in SERES-004, suggesting that the dose selected for SERES-004 was too low.

Based on the findings of the post hoc analysis of the failure of SERES-004, the dose of SER-109 was increased by approximately 3-fold and treatment duration was extended from 1 day to 3 days for further clinical development.

6.4 Trial #4: **SERES-005**

An Expanded Access for Intermediate-Size Patient Populations and Open-Label Extension of Study SERES-004 to Evaluate SER-109 in Patients with Recurrent *Clostridioides Difficile* Infection (ECOSPOR II)

6.4.1 Objectives (Primary, Secondary, etc.)

Primary efficacy objective: To evaluate CDI recurrence rates up to 8 weeks after treatment in adult subjects who received SER-109.

Secondary efficacy objectives:

- To evaluate the time to CDI recurrence in subjects who received SER-109.
- To evaluate the proportion of subjects experiencing clinical CDI recurrence up to 4, 12, and 24 weeks after treatment.

Safety objective: To evaluate the safety and tolerability of SER-109 in subjects with rCDI.

6.4.2 Design Overview

This was a Phase 2 open-label extension study of the safety, tolerability, and efficacy of SER-109 in subjects ≥ 18 years of age with rCDI. Initial enrollment was limited to subjects who had received a dose of SER-109 or placebo in study SERES-004 and experienced CDI recurrence within 8 weeks, and had achieved clinical resolution to a course of CDI-targeted standard-of-care antibiotic treatment. The study was subsequently amended to expand access to subjects with a history of rCDI, diarrhea, and a positive *C. difficile* test result on a stool sample, and who had responded to 10-21 days of standard-of-care antibiotic treatment (vancomycin or fidaxomicin [excluding pulse-tapered regimens]) for their CDI, and for whom there was no comparable or alternative therapy for treatment. Subjects received a single dose of SER-109 (1 \times 108 SporQs) in 4 capsules on study Day 1. Subjects were followed weekly through the 8-week efficacy period. Safety follow-up lasted through Week 24.

Reviewer comment: *SERES-005 enrolled a total of 72 subjects, with 34 subjects from SERES-004 who had a CDI recurrence within 8 weeks of treatment (Cohort 1; 21 SER-109 recipients and 13 placebo recipients) and 38 de novo subjects, who were enrolled through expanded access (Cohort 2). After 8 weeks of treatment, CDI recurrence in the ITT population was observed in 28/72 (38.9%) subjects (95% CI 27.6, 51.1).*

*This study was terminated early once it was determined, based on top-line data, that SERES-004 did not meet success criteria. Available safety data did not indicate any unusual or new signals. TEAEs were reported in 76.4% of subjects, and at similar rates when considering Cohorts 1 and 2 separately. The most common individual TEAEs by MedDRA PT were diarrhea (27.8%; 20/72), abdominal pain (13.9%; 10/72), and constipation (13.9%; 10/72). The most common type of adverse reactions were Gastrointestinal disorders (8.3%; 6/72), namely constipation, diarrhea, and nausea (2.8%; 2/72), and abdominal pain and vomiting (1.4%; 1/72 each). There were four deaths, which is accompanied by narratives that support investigators' assessments that each was not related to the study drug. An 84-year-old White male who was a placebo recipient in SERES-004) died on Day 68 due to aspiration pneumonia in the context of having a myocardial infarction and cerebrovascular accident. The other three deaths occurred in Cohort 2 (expanded access group). A 76-year-old White female with atrial fibrillation on amiodarone and anticoagulant, adrenal insufficiency on hydrocortisone, and history of multiple myeloma with stem cell transplant) died on Day 120 due to *C. difficile* colitis. The subject contacted the site on Day 118 and reported 4 loose stools that day. Sample was received on Day 119, and husband confirmed continued loose stools along with incontinence. Her stool was positive for *C. difficile* toxin A and B, negative for 027-NAP1-B1. Vancomycin was ordered (but unknown if subject started treatment) and follow-up scheduled for Day 121. However, her husband notified site that subject had passed away on Day 120, but was unable to give details. Death certificate listed CDI as the cause of death. An 81-year-old Hispanic female who was hospitalized for an inflammatory diarrhea, which was *C. difficile* toxin negative) died on Day 24 in the ICU after going into cardiac arrest in the setting of septic shock (blood culture negative, positive finding of colitis on abdominal CT without evidence of perforation, but bacterial translocation was suspected). Blood cultures had no growth. This subject's septic shock was captured as an adverse event of special*

interest, which was not attributed to the study drug. The fourth death was an 82-year-old White male) died on Day 133 due to a cerebrovascular accident.

6.5 Trial #5: **SERES-001**

A Study of Modified Fecal Microbiota Transplant [SER-109] Delivered via Oral Administration for the Treatment of Recurrent *Clostridium Difficile*

6.5.1 Objectives (Primary, Secondary, etc.)

The objective of this trial was to test the hypothesis that SER-109 recapitulates the safety and efficacy of conventional FMT in the setting of rCDI.

6.5.2 Design Overview

This 2-part, Phase 1b/2, open-label trial explores the safety and efficacy of SER-109 in patients with rCDI, defined as 3 or more occurrences of CDI in the previous 12 months, including the current episode. The trial was designed to explore 2 doses and dose regimens of SER-109: Part 1 evaluated oral SER-109 administered over 2 days with the dose derived from approximately ^{(b) (4)} of stool (a geometric mean dose of 1.7×10^9 SporQs in 30 capsules); Part 2 evaluated oral SER-109 administered over 1 day with a dose of 1×10^8 SporQs (A SporQ is a spore equivalent dose, based on the amount of dipicolinic acid [DPA; pyridine-2,6-dicarboxylic acid] contained in an equivalent number of spores).

Reviewer comments: *This open-label non-IND study evaluated one- and two-day regimens of SER-109 in two parts in a total of 30 adults (22-88 years old) with 3 or more episodes of CDI (i.e., two recurrences) who completed antibacterial therapy with oral metronidazole or vancomycin. The study was conducted at 4 academic sites. Clinical response was defined as the absence of CDI during the 8 weeks following study drug. CDI recurrence was defined as >3 UBMs in a 24-hour period, which is different from the case definition used in the studies under IND, which required 3 or more UBMs over 2 consecutive days. SERES-001 allowed for laboratory confirmation of the presence of *C. difficile* in the stool by toxin or PCR testing.*

Fifteen adults in Part 1 received oral SER-109 (mean dose of 1.7×10^9 SporQs, a proprietary dosing unit measured by dipicolinic acid content) administered for 2 consecutive days. Fifteen subjects in Part 2 received a mean dose of 1×10^8 SporQs for one day. Overall response rates in both Part 1 and Part 2 were evaluated as the sum of responses from either first or second treatment, which was offered to subjects who had a CDI recurrence within 8 weeks after treatment.

*The primary efficacy endpoint was response to SER-109 treatment 8 weeks after initiation of therapy. Response was defined as the absence of CDI during the efficacy evaluation period. CDI recurrence was defined as >3 UBMs in a 24-hour period with laboratory confirmation of the presence of *C. difficile* in the stool by toxin or PCR testing. Four of the 30 subjects (13.3%) had a CDI recurrence within 8 weeks after treatment. Two of these subjects with recurrence were from Part 1; they developed diarrhea 7 and 9 days after treatment. In Part 2, 2 subjects developed diarrhea 3 and 5 days after treatment. As part of a post hoc*

analysis, it was determined that 3 of these 4 subjects (2 from Part 1 and 1 from Part 2) who experienced diarrhea and a positive test result for *C. difficile* between 5 and 9 days after receiving the study drug reported that the diarrhea had resolved by the time test results were available. They were categorized as being “clinically cured” because they did not require a “clinically significant” course of antibacterial treatment during the 8 weeks (one of the subjects took one dose of vancomycin) and were PCR test negative at Week 8.

In Part 1, 86.7% (13 of 15) of subjects reported at least 1 AE. The AEs were most commonly under the SOCs of Gastrointestinal disorders (80%, 24/30 subjects), and Infections and infestations (46.7%, 14/30 subjects, mostly comprised of the PT diarrhea infectious and two subjects with cystitis). The most common (defined as ≥ 5 patients) PTs were diarrhea (40%, 12/30 patients), abdominal pain (30%, 9/30 patients), nausea (30%, 9/30 patients), and diarrhea infectious (26.7%, 8/30 patients). Most AEs in both parts of the study were mild in severity (56.7%; Part 1: 53.3% and Part 2: 60.0%). There was one subject in Part 2 with chest pain graded as severe. Five subjects (33.3%) experienced AEs considered related to investigational product.

Two subjects in Part 1 had a total of 5 non-fatal SAEs (84-year-old man with cardiac comorbidities who developed CHF on Day 35, hematuria on Day 41, infectious diarrhea on Day 77 attributed to antibiotic use for a cutaneous cyst, CHF exacerbation on Day 162; 80-year-old man with diabetes and cardiac comorbidities with jaw pain (moderate) on Day 88). This reviewer agrees with the investigator’s assessment that none of these were related to SER-109. In Part 2, all 15 subjects experienced AEs, and 10 subjects (66.7%) had AEs considered related to investigational product. Two subjects had 1 SAE each (83-year-old woman with diabetes mellitus and prior cellulitis with staphylococcal skin infection of the right foot on Day 146; 69-year-old male with history of MI and multiple coronary stents with severe chest pain on Day 54). Based on the pre-existing conditions and timing of onset, this reviewer agrees with the investigator’s assessment that they are unrelated to SER-109. There were no deaths in Part 1 or Part 2.

7. INTEGRATED OVERVIEW OF EFFICACY

Efficacy data were not integrated because SERES-012/-013 evaluated the 3-day regimen of SER-109 being licensed while SERES-004/-005 evaluated the 1-day regimen of SER-109, which did not meet the pre-specified success criteria for efficacy. SERES-012 provided the primary efficacy for this BLA submission. SERES-013 provided descriptive efficacy data that aligned with results from SERES-012.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Unsolicited AEs, AESIs, and SAEs were pooled for subjects from SERES-004/SERES-005 (one-day regimen) and SERES-012/SERES-013 (3-day regimen). The ISS groups included any subject who received at least one dose of SERES-109 (blinded or open-label). In each ISS group, safety data were analyzed by the dosing regimen and the number of doses received. All studies included at least 6 months of safety follow-up from

the last dose. Demographic subgroup analyses were not conducted due to small numbers.

- Review of safety data in the ISS focused on TEAEs that were collected weekly for the first two months and monthly thereafter. Definitions of TEAEs were the same across studies. Criteria for grading the severity and relatedness of AEs were also the same across all studies. AEs were categorized by severity, seriousness, and relatedness by the site investigator.
- AEs were serious if they were life-threatening and/or resulted in death, inpatient hospitalization ≥ 24 hours or prolongation of an existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or congenital anomaly/birth defect.
- AESIs of invasive infection were prospectively monitored in SERES-012/SERES-013 and retrospectively assessed in SERES-004/SERES-005. Specific PTs were not pre-specified as AESIs in the protocols. For the ISS, the Applicant performed a pre-specified retrospective assessment, which is described in [Section 8.4.8](#).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

In total, 490 subjects received SER-109 during the clinical development program. However, the minimum safety database of 300 was fulfilled with 349 subjects who received the 3-day regimen of SER-109 in studies SERES-012 (n=90) and SERES-013 (n=259). Median duration of follow-up in subjects across these two studies was 169.0 days (range: 5 to 232 days).

Table 26. Clinical Studies of SER-109 Submitted in the BLA

| Study Category Clinical Study | Study Design | Total Unique Subjects Exposed to SER-109 |
|----------------------------------|---|---|
| Target Dose Studies | -- | -- |
| SERES-012 (ECOSPOR III) | 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 <i>C. difficile</i> infection in adults who have received antibacterial drug treatment for rCDI | 90 |
| SERES-013 (ECOSPOR IV) | Phase 3 single arm, open-label extension of study SERES-012 and open-label program evaluating SER-109 in adult subjects with rCDI | 259 ^a |

| Study Category Clinical Study | Study Design | Total Unique Subjects Exposed to SER-109 |
|----------------------------------|--|---|
| Non-Target Dose Studies | -- | -- |
| SERES-004 (ECOSPOR) | Randomized, double-blind, placebo-controlled, parallel-group Phase 2 study in subjects with rCDI to evaluate the safety, tolerability, and efficacy of SER-109 | 60 ^b |
| SERES-005 (ECOSPOR II) | Phase 2 single arm, expanded access study and open-label extension of study of SERES-004 evaluating SER-109 in adult subjects with rCDI | 51 ^c |
| SERES-001 ^d | Two-part, single arm, open label Phase 1b/2 study in subjects with rCDI to evaluate the efficacy and safety of SER-109 | 30 |

Source: STN 125757/1, Integrated Summary of Safety, p. 21.

Abbreviations: ITT=intent-to-treat; rCDI=recurrent *Clostridioides difficile* infection

Notes:

- a. Includes 25 subjects who received placebo in SERES-012 (Cohort 1 [rollover subjects]) and 234 subjects who enrolled in the open-label cohort (Cohort 2 [de novo subjects]) and received SER-109 in SERES-013. SER-109 recipients from SERES-012 was not counted.
- b. One subject was randomized to the placebo group but received a full dose of SER-109. This subject was analyzed in the placebo group in the ITT Population (efficacy) and in the SER-109 group in the Safety Population.
- c. Includes 13 subjects who received placebo in SERES-004 and 38 subjects who enrolled under expanded access and received SER-109 in SERES-005.
- d. Not included in the ISS

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 349 adults with rCDI were enrolled to receive the 3-day regimen of SER-109 in SERES-012 or SERES-013. Mean age was 64.2 years and median age was 66.0 (range: 21-100 years). Representation across the two age subgroups were balanced, with 47.6% under 65 years of age. There were more females (68.8%; n=240) than males (31.2%; n=109), and most subjects were White (92.3%). A small number of subjects were Black (5.2%). Most subjects had a total of 3 CDI episodes (43.0%), which included the CDI at study entry, followed by 4 or more CDI episodes (34.7%), and 2 or more CDI episodes (22.1%). Subjects with the least number of total CDI episodes (n=77) were from SERES-013. Vancomycin was used more frequently than fidaxomicin to treat the study-qualifying CDI episode (72.2% versus 27.8%). The majority of subjects were FMT-naïve (96.8%). Of the 349 subjects, 51% had at least one of the following comorbidities:

- Cardiac disease: 109 (31.2%)
- Immunocompromised/immunosuppressed: 74 (21.2%)
- Diabetes: 66 (18.9%)
- Renal impairment/failure: 46 (13.2%)

A total of 111 adults with rCDI received the 1-day regimen of SER-109 in SERES-004 or SERES-005. Mean and median age was 65.6 years and 68.0 years, respectively. Individuals ≥65 years old comprised 58.6% of the population. There were more females (64.0%) than males and most subjects were White (92.8%) and non-Hispanic (94.6%). With respect to the total number of CDI episodes, including the episode at study entry, 45.9% had 3, and 54.1% had 4 or more CDI episodes. Individuals with their first CDI recurrence were not eligible for SERES-004 or SERES-005. Most received vancomycin (79.3%). The rates of the abovementioned comorbidities were similar to those for SERES-012/-013, with cardiac disease in 35.1%, immunocompromise or

immunosuppression in 27.0%, diabetes in 19.8% and renal impairment in 16.2%. The BI/NAP1/027 strain of *C. difficile* was detected in 7.2% of subjects at baseline. However, strain status was listed as “missing” for 66.7% of subjects.

Reviewer comment: *Subjects who received SER-109 across the 4 studies were included in this ISS. Over 50% were 65 years of age and older. Subjects classified as immunocompromised/immunosuppressed comprised a heterogeneous group of individuals with solid or hematologic malignancies, autoimmune conditions (e.g., rheumatoid arthritis), transplant recipients and those on immunosuppressants. This heterogeneity, combined with the relatively small numbers of subjects limits the ability to make generalizations about the safety and efficacy of SER-109 in immunocompromised compared to immunocompetent individuals. However, it is noteworthy that subgroup analyses of safety and efficacy with respect to age subgroup and immunosuppression status did not reveal any concerning disparities in rates of SAEs compared to the total population.*

8.2.3 Categorization of Adverse Events

Adverse event coding was updated to MedDRA v24.1 for these studies using the following approach:

- 1) For individual studies MedDRA Lowest Level Terms (LLT) were merged from the original version used in the study with version 24.1. Following the merge:
 - a. If LLTs matched, then other MedDRA terms in the hierarchy were updated.
 - b. If a match to the older LLT was not found, manual coding was employed.
- 2) Coding differences across studies were manually reviewed by a MedDRA coder to reconcile any differences.
- 3) Final coding was reviewed and approved by a medical reviewer.

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

Due to differences in safety monitoring procedures, namely the collection of solicited AEs in only SERES-012, pooling was limited to unsolicited AEs, AESIs, and SAEs obtained weekly following treatment. We requested at the pre-BLA stage that the safety data from all studies in the clinical development program should not be presented in one pool because of differences in dosing regimen and in safety data collection procedures. However, SAEs, AESIs, and deaths are summarized collectively in the following section because of the lower frequencies and seriousness of these events.

8.4 Safety Results

In SERES-012, TEAEs reported in a higher proportion of SER-109 recipients than placebo recipients were abdominal distension (54.4% vs 53.3%), constipation (31.1% vs 23.9%), diarrhea (24.4% vs 21.7%), and UTI (8.9% vs 1.1%). In the SERES-012/SERES-013 integrated dataset, 63.3% of subjects experienced at least 1 TEAE, most commonly flatulence (23.8%), diarrhea (23.2%), fatigue (18.6%), and abdominal pain (18.3%). The incidence of each of these events was lower in the integrated dataset compared with SERES-012 due to the absence of solicited AE reporting in SERES-013. In the SERES-004/SERES-005 integrated dataset, 80.2% of SER-109 recipients experienced at least 1 TEAE, most commonly diarrhea (30.6%) and abdominal pain (18.9%). [Table 27](#) summarizes safety outcomes in the ISS Population for the 3-day

regimen of SER-109 (SERES-012/-013) and the 1-day regimen of SER-109 (SERES-004/-005).

Table 27. Safety Outcomes Data in SERES-012/SERES-013 and SERES-004/SERES-005

| TEAE Category | SERES-012 SER-109 (N=90) n (%) | SERES-012 Placebo (N=92) n (%) | SERES-013 SER-109 (N=263) n (%) | 3-day regimen SERES-012/-013 SER-109 (N=349) n (%) | 1-day regimen SERES-004/-005 SER-109 (N=111) N (%) |
|--|---|---|--|--|--|
| TEAEs | 84 (93.3) | 84 (91.3) | 141 (53.6) | 221 (63.3) | 89 (80.2) |
| Subjects with at least 1 unsolicited TEAEs | 61 (67.8) | 61 (66.3) | 141 (53.6) | 199 (57.0) | 89 (80.2) |
| Subjects with severe TEAEs | 25 (27.8) | 30 (32.6) | 26 (9.9) | 51 (14.6) | 13 (11.7) |
| Subjects with potentially life threatening TEAEs | 2 (2.2) | 0 | 2 (0.8) | 4 (1.1) | NA |
| TEAEs leading to study withdrawal | 1 (1.1) | 2 (2.2) | 0 | 1 (0.3) | 5 (4.5) |
| TEAEs leading to death ^a | 3 (3.3) | 0 | 8 (3.0) | 11 (3.2) | 5 (4.5) |
| TEAE relatedness | -- | -- | -- | -- | -- |
| Related to study drug | 46 (51.1) | 48 (52.2) | 32 (12.2) | 77 (22.1) | 18 (16.2) |
| Related to <i>C. difficile</i> infection | 11 (12.2) | 31 (33.7) | 16 (6.1) | 27 (7.7) | NA |
| Related to a pre-existing condition | 28 (31.1) | 32 (34.8) | 38 (14.4) | 65 (18.6) | NA |
| AESIs^b | 9 (10.0) | 3 (3.3) | 19 (7.2) | 28 (8.0) | 8 (7.2) |
| Related to study drug | 0 | 0 | 0 | 0 | 0 |
| Related to <i>C. difficile</i> infection | 0 | 0 | 0 | 0 | NA |
| Related to a pre-existing condition | 1 (1.1) | 2 (2.2) | 6 (2.3) | 7 (2.0) | NA |
| Serious TEAEs | 15 (16.7) | 19 (20.7) | 33 (12.5) | 48 (13.8) | 19 (17.1) |
| Related to study drug | 0 | 0 | 0 | 0 | 0 |
| Related to <i>C. difficile</i> infection | 2 (2.2) | 6 (6.5) | 8 (3.0) | 10 (2.9) | NA |
| Related to a pre-existing condition | 7 (7.8) | 11 (12.0) | 14 (5.3) | 21 (6.0) | NA |
| Serious TEAEs leading to study withdrawal | 1 (1.1) | 1 (1.1) | 0 | 1 (0.3) | 5 (4.5) |
| Serious TEAEs leading to death ^a | 3 (3.3) | 0 (0.0) | 8 (3.0) | 11 (3.2) | 5 (4.5) |

Source: STN 127575/62; 1.11.3 Clinical Information Amendment, pg. 5, Table 1

Abbreviations: AESI=adverse event of special interest; NA=not applicable, TEAE=treatment-emergent adverse event

Notes: AEs include solicited and unsolicited events from SERES-012 unless noted; all adverse events reported on other studies (SERES-013, SERES-004, SERES-005) were unsolicited. A subject with multiple occurrences within a specified category is only counted once. Data fields "potentially life threatening TEAEs", "Related to *C. difficile* infection", "Worsening of pre-existing condition" were captured for SERES-012 and SERES-013 studies only; therefore, these fields are labeled "NA" for SERES-004 and SERES-005.

a. For the categories "TEAEs leading to death" and "Serious TEAEs leading to death", adverse events with outcome "fatal" were included.

b. Includes AESIs as defined by ISS specifications.

8.4.1 Deaths

A total of 16 deaths (10 males and 6 females) occurred across the 4 studies included in this ISS. In SERES-012, 3 of 90 SER-109 recipients (3.3%) died compared to 0 of 92 placebo recipients. In SERES-013, 8 of 263 SER-109 recipients (3.0%) died. In SERES-004, 1 of 60 SER-109 recipients (1.7%) died compared with 0 of 29 placebo recipients. In SERES-005, 4 of 72 SER-109 recipients (5.6%) died. No deaths occurred in SERES-001, which was not included in the ISS. [Table 28](#) presents demographic features, timing of death relative to study drug, and relevant AEs prior to death.

Table 28. Deaths in SER-109 Recipients in Clinical Studies SERES-012, -013, -004, and -005

| Study | Age (yrs) | Sex | Time of Death ^a (Study Day) | TEAEs Leading to Death |
|-----------|-----------|-----|--|--|
| SERES-012 | 87 | F | Day 12 | Fall, Subdural hematoma |
| SERES-012 | 66 | M | Day 60 | Atrial fibrillation, Sepsis |
| SERES-012 | 66 | M | Day 164 | Progression of glioblastoma |
| SERES-013 | 54 | M | Day 5 | Congestive cardiomyopathy (fatal arrhythmia suspected) |
| SERES-013 | 64 | M | Day 28 | Coronavirus infection, Intestinal perforation |
| SERES-013 | 79 | F | Day 39 | <i>C. difficile</i> infection |
| SERES-013 | 93 | F | Day 44 | Natural causes |
| SERES-013 | 72 | M | Day 55 | Fournier's gangrene |
| SERES-013 | 84 | F | Day 115 | Cardiac failure chronic, Coronary artery disease, Duodenal ulcer hemorrhage, Gastric ulcer hemorrhage, End stage renal disease |
| SERES-013 | 68 | M | Day 122 | Pneumonia aspiration, Urosepsis |
| SERES-013 | 65 | M | Day 132 | Pancreatic carcinoma |
| SERES-004 | 81 | M | Day 138 | Non-small cell lung cancer metastatic |
| SERES-005 | 81 | F | Day 24 | Sepsis |
| SERES-005 | 84 | M | Day 96 | Myocardial infarction, aspiration pneumonia, Cerebrovascular accident |
| SERES-005 | 76 | F | Day 120 | <i>C. difficile</i> colitis |
| SERES-005 | 82 | F | Day 133 | Cerebrovascular accident |

Source: Listing 3.2, ISS Table 45: Listing of Deaths in Target Dose Studies SERES-012 and SERES-013; ISS Table 46: Listing of Deaths in Supportive Studies SERES-004 and SERES-005 (Non-Target Dose)
Abbreviations: ID=identification; yrs=years; TEAE=treatment emergent adverse events
Notes: a. In relationship to study drug initiation

Of the 8 deaths across the 4 studies that occurred within 8 weeks after treatment, 5 had infectious TEAEs, as indicated in the last column of Table 28. Four subjects had rCDI at the time of death, ranging between Days 28 and 120. Relevant details are provided below:

- A 64-year-old Black NH male with a complex medical background of HIV, peripheral artery disease, coronary artery disease, systolic and diastolic heart failure, abdominal aneurysm with surgical repair, end stage renal disease on dialysis and on anticoagulant therapy presented to an emergency department 3 days after completing SER-109 with chest pain, shortness of breath, bilateral leg pain in the setting of missed dialysis for 1 week. He was found to be in acute decompensated heart failure and was started on daily dialysis. Due to hypoxia, he was placed on bilevel positive air pressure (BiPAP) and transferred to intensive care. Hospital course was also complicated by thrombocytopenia, for which he received intravenous immunoglobulins on the same day. He was also started on dexamethasone 40 mg. His heart failure was stabilized and he was discharged on Day 16. On Day 22, he presented to the emergency department with cramping abdominal pain, bloody diarrhea, hematemesis, hematochezia, epistaxis, and chest pain. Chest radiograph showed a possible infiltrate on the left. Nasopharyngeal swab positive for COVID-19, for which he was started on remdesivir and solumedrol. CT of the abdomen and pelvis showed small bowel thickening and diffuse mesenteric edema. Stool was also positive for *C. difficile* toxin A/B; he was started on fidaxomicin and transitioned to vancomycin the following day. On Day 28, he reported diffuse abdominal pain and imaging showed intestinal perforation, which was thought to be in the small bowel and unrelated to his rCDI. He was started on broad spectrum antibiotics and infectious disease eventually placed on eravacycline for his complex intra-abdominal infection. Cardiology was consulted and he was not considered a surgical candidate. He was made do not resuscitate (DNR) with comfort

measures only, and he expired on the same day (Day 28). No autopsy was performed. Death was considered due to COVID-19 infection and intestinal perforation (suspected to be small bowel, possibly ischemic, rather than infectious). Blood culture from that day eventually grew *Klebsiella oxytoca* and diarrhea was ongoing at the time of death.

- A 79 yo White female was hospitalized for a UTI diagnosed on Day 11 (also incontinent of stool and confused at the time). Urine culture grew *Citrobacter freundii*. In the setting of broad-spectrum antibiotics for her UTI (ceftriaxone and meropenem), the loose stools resolved by Day 14. She remained hospitalized until Day 22 for medical optimization of CHF and resolution of confusion. Repeat urine culture grew *Candida albicans*, which was not treated due to lack of symptoms. On Day 31, subject was readmitted for confusion and increasing weakness. Daughter reported loose stools (onset not specified). Urine, stool and blood were cultured. Urine grew *Enterococcus faecium* and GI PCR panel was positive for toxin A and B. Blood culture was negative. Vancomycin 125 mg po was started on Day 32. There was no mention of the treatment for her current UTI. Her CHF worsened on Day 37. She was placed on 5L oxygen and vancomycin dose was increased to 250 mg on Day 38. Later that day she was found to be unresponsive in her hospital bed.
- An 81 yo Hispanic female was hospitalized on Day 8 for inflammatory diarrhea, stool PCR negative for *C. difficile* toxin A/B, stool culture showing many white blood cells and positive for occult blood. She was reported to have had her CDI episode at study entry with metronidazole rather than vancomycin. Blood culture was negative. On Day 9 (hospital discharge), she was found to have hematuria. Colonoscopy as an outpatient was remarkable only for a small area of erythema in the mucosa of the descending colon. Biopsies were taken but results could not be obtained. By Day 17 the inflammatory diarrhea was considered resolved. On Day 24, she presented with sepsis, but stool testing was not done because of the subject's critical clinical status. Sepsis progressed to multi-organ failure and death.
- A 76 yo White female contacted the study site on Day 118 and reported 4 loose stools that day. Her husband dropped off a stool sample on Day 119 and confirmed continued loose stools along with incontinence. Her stool was positive for *C. difficile* toxin A and B, negative for 027-NAP1-B1. Vancomycin was ordered (but unknown if subject started treatment) and follow-up scheduled for Day 121. However, her husband notified site that subject had passed away on Day 120 but was unable to give additional details on her passing. Her death certificate listed CDI as the cause of death.

Refer to Sections [6.1.12.3](#) and [6.2.12.3](#) for narratives of deaths for the other subjects.

Reviewer comment: *Each of the sixteen death narratives were reviewed and the clinical reviewer agrees with the investigators' assessments that they were likely unrelated to the study drug. Twelve of the 16 deaths occurred in the open-label study. The lack of a comparator arm and the medical complexity of the study population complicate the assessment of causality, but the available data (i.e., narratives and test results) indicate that mortality is more likely due to*

comorbid conditions and acute events associated with underlying risk factors than the study drug.

With respect to the subjects who had CDI recurrence at the time of death, there were concurrent illnesses and broad-spectrum antibiotic exposure that likely triggered the rCDI. One subject had immunocompromise (HIV), peripheral artery disease and acute SARS-CoV2 infection. The intestinal perforation was reported to be in the small bowel, which is atypical for CDI, and thought to be ischemic. Another subject had CDI recurrence on Day 31 but received broad spectrum antibiotics for UTI starting on Day 11. In summary, the mortality rate observed in this product development program is within an expected rate of mortality in this patient population of rCDI.

8.4.2 Nonfatal Serious Adverse Events

Across SERES-012 and SERES-013, 13.8% (48/349) of SER-109 recipients and 20.7% (19/92) of placebo recipients reported a SAE within 6 months after the first dose of investigational product. The most frequently reported SAE in SER-109 recipients was UTI (3.3%) while in placebo recipients it was *C. difficile* colitis (7.6%). None of these events were considered related to the study drug. Across SERES-004 and SERES-005, 17.1% (19/111) of SER 109 recipients and 10.3% (3/29) of placebo recipients reported an SAE. The most frequently reported SAE in SERES-004/-005 was diarrhea.

8.4.3 Study Dropouts/Discontinuations

The most common reason for subjects to drop out of the randomized study was CDI recurrence and eligibility to enroll in the associated open-label study. Across SERES-012 and SERES-013, three subjects (2 placebo recipients from SERES-012 and 1 SER-109 recipient from SERES-013) experienced TEAEs leading to study discontinuation. All were due to pre-existing conditions, namely progressive glioblastoma (fatal), exacerbation of pre-existing CHF and severe pulmonary hypertension, and acute respiratory failure in setting of COPD and recurrent pleural effusion, respectively. Across SERES-004 and SERES-005, five subjects (1 placebo recipient from SERES-004 and 4 SER-109 recipients from SERES-005) dropped out due to TEAEs, all of which were fatal SAEs of myocardial infarction/aspiration pneumonia/CVA, metastatic non-small cell lung cancer, sepsis (negative cultures) in the setting of inflammatory diarrhea (negative *C. difficile* PCR), cerebrovascular accident (CVA), and *C. difficile* colitis, respectively. All TEAEs were considered unrelated to study treatment by the investigator.

Reviewer comment: *This reviewer agrees with the investigators' assessments that most of the aforementioned TEAEs were unrelated to the study drug because they were attributable to pre-existing serious medical conditions or acute events occurring due to comorbidities or potentially related to medical interventions.*

8.4.4 Common Adverse Events

Solicited AEs were only collected in SERES-012 (see [Section 6.1.12.2](#)) while unsolicited AEs were collected weekly (Week 8 after treatment) and monthly (out to Month 6 after treatment). The most commonly reported AEs were in the SOC *Gastrointestinal disorders*, with the most common PTs being diarrhea, flatulence, nausea, abdominal

distention, and abdominal pain. Rates of subjects reporting these PTs, as shown in [Table 29](#), were comparable across the SER-109 and placebo arms, and mostly similar to those reported by subjects receiving open-label treatment in SERES-013. The rate of reporting of unsolicited AEs was highest during the first week after completion of the 3-day regimen. For a more granular presentation of the unsolicited AEs over time, please refer to tables in Sections [6.1.12.2](#) and [6.2.12.2](#).

Table 29. Unsolicited 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 (%) | Placebo (N=92) n (%) | SERES-013 SER-109 (N=263 ^a) n (%) | Overall SER-109 Exposure ^a (N=349 ^b) n (%) |
|-----------------------------------|--------------------------------|----------------------|---|---|
| Subjects with at least one TEAE | 61 (67.8) | 61 (66.3) | 141 (53.6) | 199 (57.0) |
| Gastrointestinal disorders | 37 (41.1) | 40 (43.5) | 104 (39.5) | 139 (39.8) |
| Diarrhea | 22 (24.4) | 20 (21.7) | 60 (22.8) | 81 (23.2) |
| Flatulence | 5 (5.6) | 6 (6.5) | 20 (7.6) | 25 (7.2) |
| Nausea | 5 (5.6) | 3 (3.3) | 20 (7.6) | 25 (7.2) |
| Abdominal pain | 2 (2.2) | 4 (4.3) | 18 (6.8) | 21 (6.0) |
| Constipation | 5 (5.6) | 4 (4.3) | 7 (2.7) | 12 (3.4) |
| Infections and infestations | 21 (23.3) | 17 (18.5) | 38 (14.4) | 60 (17.2) |
| Urinary tract infection | 8 (8.9) | 1 (1.1) | 13 (4.9) | 21 (6.0) |
| <i>C. difficile</i> colitis | 1 (1.1) | 8 (8.7) | 2 (0.8) | 4 (1.1) |

Source: SER-109, 1.11.3 Clinical Information Amendment, Table 19a, pg. 4 Seq0051, 1.11.3, Table 14.3.1.2.1 ISS, Table 14.3.1.2.1 revised, Table 14.3.1.3.1 b1, Table 14.3.1.3.1 b2

Abbreviations: AE=adverse event; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Notes: Only SOCs with individual PTs reported in at least 5% of subjects in any treatment group are included in the table. Percentages are based on the number of subjects in the Safety Population in each treatment group. For each level of summarization, a subject contributes only once to the count for a given TEAE on the SOC level and on the PT level within SOC. SOC and PT are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, v20.0 (March 2017). Solicited adverse events were those of 'Abdominal pain or cramping' (PTs Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness); 'Abdominal distension or bloating' (PT 'Abdominal distension'); 'Constipation' (PT 'Constipation'); 'Gas or flatulence' (PT 'Flatulence'); 'Nausea' (PT 'Nausea'); 'Vomiting' (PT 'Vomiting'); 'Chills or shivering' (PT 'Chills'); 'Fatigue' (PT 'Fatigue'); 'Anorexia or loss of appetite' (PT 'Decreased appetite'); 'Fever' (PT Fever, Pyrexia) and reported by the subject when solicited via diary (during Days 4-10 in SERES-012). All other adverse events were considered unsolicited.

- Includes subjects who received one (N=345) or two (N=4) SER-109 treatment regimens in SERES-012 and SERES-013.
- Excludes the 4 SER-109 recipients from SERES-012 and represents number of unique subjects who received SER-109 (once).

Adverse Reactions

[Table 30](#) presents unsolicited TEAEs that were considered related or possibly related to the study drug in the studies of the 3-day regimen of SER-109.

Table 30. Unsolicited Related or Possibly Related TEAEs Reported in at Least 5% of Subjects in Any Treatment Group, SERES-012 and SERES-013

| System Organ Class Preferred Term | SERES-012 SER-109 (N=90) n (%) | Placebo (N=92) n (%) | SERES-013 SER-109 (N=263) n (%) | Overall SER-109 Exposure ^a (N=349) n (%) |
|--|--------------------------------|----------------------|---------------------------------|---|
| Subjects with at least 1 treatment-related ^b TEAE | 19 (21.1) | 13 (14.1) | 32 (12.2) | 50 (14.3) |
| Gastrointestinal disorders | 18 (20.0) | 10 (10.9) | 29 (11.0) | 46 (13.2) |
| Diarrhea | 9 (10.0) | 4 (4.3) | 9 (3.4) | 18 (5.2) |

Source: SER-109, 1.11.3 Clinical Information Amendment, Table 27a, pg. 5, Table 14.3.1.2.1 ISS a, Table 14.3.1.2.1 a, Table 14.3.1.3.1 bb1, Table 14.3.1.3.1 bb2

Abbreviations: PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Note: Only SOCs with related PTs reported in at least 5% of subjects in any treatment group are included in the table. Percentages are based on the number of subjects in the Safety Population in each treatment group. For each level of summarization, a subject contributes only once to the count for a given TEAE on the SOC level and on the PT level within SOC. SOC and PT are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, v20.0 (March 2017). Solicited adverse events were those of 'Abdominal pain or cramping' (PTs Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness); 'Abdominal distension or bloating' (PT 'Abdominal distension'); 'Constipation' (PT 'Constipation'); 'Gas or flatulence' (PT 'Flatulence'); 'Nausea' (PT 'Nausea'); 'Vomiting' (PT 'Vomiting'); 'Chills or shivering' (PT 'Chills'); 'Fatigue' (PT 'Fatigue'); 'Anorexia or loss of appetite' (PT 'Decreased appetite'); 'Fever' (PT Fever, Pyrexia) and reported by the subject when solicited via diary (during Days 4-10 in SERES-012). All other adverse events were considered unsolicited.

a. Includes subjects who received one (N=345) or two (N=4) SER-109 treatment regimens in SERES-012 and SERES- 013.

b. Includes TEAEs that were considered to be related or possibly related to study treatment according to the investigator.

Similar trends in adverse reactions were observed in both SERES-004 and SERES-005, studies of a 1-day regimen of SER-109. Adverse reactions were reported at a higher frequency among SER-109 recipients from SERES-004 and SERES-005 (18.3%; n=11 and 16.2%; n=18, respectively) than among placebo recipients from SERES-004 (13.8%; n=4). The most common PTs were in the SOC *Gastrointestinal disorders*, namely abdominal pain (6 [10.0%] SER-109 recipients versus 1 [3.4%] placebo recipient) as well as diarrhea (3 [5.0%] SER-109 recipients versus 1 [3.4%] placebo recipient).

8.4.5 Clinical Test Results

Blood samples were collected at screening and baseline and abnormalities detected at later time points were graded for general surveillance. In SERES-012, the proportions of subjects with treatment-emergent laboratory abnormalities were similar between SER-109 recipients (7.8%) and placebo (7.6%). The most common lab abnormalities in the SERES-012/SERES-013 integrated dataset included decreased neutrophil count (6 subjects; 1.7%) and hypoglycemia (3 subjects; 0.9%). In SERES-004, treatment-emergent abnormal laboratory values were only observed among SER-109 recipients (5 subjects; 8.3%). In the SERES-004/SERES-005 integrated dataset, 8 SER-109 recipients (7.2%) had treatment-emergent abnormal laboratory values. The most common abnormalities were hypokalemia (3 subjects; 2.7%) and hyperglycemia (2 subjects; 1.8%).

8.4.6 Systemic Adverse Events

There was one subject (44-year-old White female enrolled in SERES-013) who experienced a mild systemic reaction consistent with an IgE-mediated process. This subject experienced mild facial flushing approximately 30 minutes after the first dose. There were no other cutaneous or respiratory findings or symptoms. Flushing resolved over approximately 15 minutes without any intervention. She also had similar symptoms

along with subjective throat and jaw tightness after the second and third dose. Vitals were within normal limits. The subject self-medicated with diphenhydramine only.

8.4.7 Local Reactogenicity

SER-109 is taken orally. There were no cases of objective angioedema of the oropharynx following SER-109. There was one subject from SERES-013 who had vomiting shortly after her first dose, but this was determined to be related to gastric volvulus rather than an IgE-mediated reaction.

8.4.8 Adverse Events of Special Interest

Invasive infections were prospectively identified in SERES-012 and SERES-013 and retrospectively summarized for SERES-004 and SERES-005. In studies SERES-012 and SERES-013, different types of invasive infection events (i.e., PTs) were designated as AESI by various investigators. To consistently account for all AESIs, the Applicant performed a retrospective AESI analysis for the integrated safety reporting in the ISS and each study individually.

In the ISS for SERES-012 and SERES-013, an expanded retrospective definition of AESI was applied. Events were designated as AESIs for each individual study SERES-012, SERES-013, as well as SERES-012/-013 integrated dataset. The algorithm used to define AESIs in the ISS was as follows:

- Investigator reporting AESI in respective study eCRF, or
- PTs including one of the following words: Abscess, Bacteremia, Cellulitis, Endocarditis, Meningitis, Osteomyelitis, Sepsis, Sinusitis, Urosepsis, Cholangitis, Peritonitis; or
- Exact match to PTs: Diabetic foot, Necrotizing fasciitis, Septic shock, Infected skin ulcer, Fournier's gangrene

In the integrated set SERES-012/-013, a total of 28 (8.0%) SER-109 recipients had AESIs. The most common AESI by PTs were cellulitis (n=7) and sinusitis (n=5). When considering all MedDRA PTs that included "bacteremia" or "sepsis", there were 7 occurring in 7 subjects. One case was culture-negative, while the others had blood or urine cultures that grew *Escherichia coli* (n=3), *Pseudomonas aeruginosa*, *Serratia marcescens*, *Abiotrophia defectiva*, *Proteus mirabilis*. None of these AESIs were considered related or possibly related to SER-109. They were attributed to subject's intercurrent medical illnesses or pre-existing conditions (e.g., prolonged ventilator-associated pneumonia in the ICU with acute coronavirus infection, chronic indwelling foley, hemodialysis catheter, therapeutic immunosuppression). Furthermore, the organisms isolated from blood cultures were aerobes and non-spore formers. In the SERES-004/SERES-005 integrated database, a total of 8 subjects (7.2%; 8/111) had AESIs, namely cellulitis (4.5%; n=5), sinusitis (1.8%; n=2), and sepsis (1.8%; n=2). With respect to sepsis, 1 subject had numerous intercurrent infections: rCDI, recurrent cellulitis, UTI, and pneumonia. The other subject's sepsis was attributed to diarrhea, colitis, but available cultures (blood) had no growth.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

There were 4 subjects who received two courses of the 3-day regimen of SER-109 (first course in SERES-012, second course in SERES-013). Data are insufficient to draw any conclusions about dose-dependent AEs.

8.5.2 Time Dependency for Adverse Events

AEs were most frequently reported within the first week after treatment. In an analysis of AEs occurring within 8 weeks after blinded treatment, the most common adverse reactions (defined as AEs assessed as definitely, possibly, or probably related to SER-109 by the investigator) reported by $\geq 5\%$ of SER-109 recipients and at a rate greater than that reported by placebo recipients included: abdominal distension (31.1% of SER-109 recipients and 29.3% of placebo recipients), fatigue (22.2% and 21.7%), constipation (14.4% and 10.9%), chills (11.1% and 8.7%), and diarrhea (10.0% and 4.3%). Most adverse reactions occurred within the first week after treatment. Rates of subjects at least one adverse reaction declined from 48.9% and 51.1% during the first week after completing treatment in SER-109 and placebo arms, respectively, to 6.7% and 3.4% during the second week after treatment. Rates plateaued at 6.7% and 5.7% during the third week through eighth week after treatment, and none in both arms out to 6 months of follow-up. The severity profile of the solicited adverse reactions (collected in SERES-012 only) and unsolicited adverse reactions were similar among SER-109 and placebo recipients.

In the SERES-012/SERES-013 integrated dataset, 8.0% of SER-109 recipients had at least 1 AESI. AESIs observed in more than 1 subject were cellulitis (2.0%), sinusitis (1.4%), bacteremia (0.6%), peritonitis (0.6%), tooth abscess (0.6%), and urosepsis (0.6%). None of the AESIs were considered related to study drug.

AESIs were also analyzed by calculating adjusted cumulative proportions, including sample size weighting by study, for multiple randomized, controlled studies (SERES-012 and SERES-004) and multiple integrated datasets (SERES-012/SERES-013 and SERES-004/SERES-005). In this analysis, AESIs were more frequent in the SER-109 recipients from both SERES-012 and SERES-004 (8.0%) compared with the placebo recipients (2.3%) in SERES-012 and SERES-004.

SAEs observed in 67 subjects in the 4 studies occurred between 5 and 166 days after treatment. In the SERES-012/013 set, 48 subjects (13.8%) had 1 or more SAEs, which was lower than the 20.7% SAE rate observed among placebo recipients (19/92). In the SERES-004/-005, there were 19 subjects (17.1%) with 1 or more SAEs. There were 17 deaths among the 460 SER-109 recipients, which occurred between 5 and 164 days after treatment. There were no deaths among placebo recipients in SERES-012 and SERES-004. Of the 11 deaths in SERES-012/-013, 3 occurred in the placebo-controlled SERES-012 and 8 occurred in the open-label SERES-013. Six deaths occurred during the first 8 weeks after treatment and 5 deaths occurred after 8 weeks. In SERES-004/-005, 4 of the 5 deaths occurred in the open-label study SERES-005. One death occurred during the first 8 weeks and 4 occurred after 8 weeks. None of the SAEs were attributed to the study drug by investigators.

8.5.3 Product-Demographic Interactions

[Table 31](#) summarizes TEAEs by baseline demographic variables reported in SERES-012/-013.

Age strata

- SERES-012/-013:
 - Similar proportions of subjects <65 years old (62.0%, n=166) and ≥65 years old (64.5%, n=183) had at least 1 TEAE. The most frequently reported TEAEs in subjects <65 years old were flatulence (25.9%), diarrhea (23.5%), abdominal pain (21.1%), and abdominal distension (18.7%). Similarly, in subjects ≥65 years old, diarrhea (23.0%), flatulence (21.9%), and fatigue (19.3%) were most frequently reported.
 - SAEs occurred in approximately 2-fold more subjects ≥ 65 years old (18.6%; 34/183) than in subjects < 65 years old (8.4%; 14/166). The most common SAE (reported in more than 1 subject) in the older age strata was UTI (n=5) and acute cardiac failure, C. difficile colitis, and syncope (each occurring in 2 subjects) in the younger strata.

Sex

- SERES-012/-013
 - 68.8% of female subjects and 60.8% of male subjects reported ≥1 TEAE.
 - The most frequently reported TEAEs in female subjects were flatulence (23.8%), diarrhea (22.5%), abdominal pain (19.6%), abdominal distension (17.9%), and fatigue (17.9%). Most of the same TEAEs were reported in similar rates of male subjects, namely diarrhea (24.8%), flatulence (23.9%), and fatigue (20.2%).
 - SAEs were reported in a higher proportion of male subjects (22.9%) compared with female subjects (9.6%).

Table 31. Treatment-Emergent Adverse Events, Integrated Data from SERES-012 and -013, Safety Population

| ISS Dataset / Demographic Subgroups | n (%) subjects with TEAEs | n (%) subjects with SAEs |
|-------------------------------------|---------------------------|--------------------------|
| All (N=349) | | |
| SERES-012/-013 | -- | -- |
| Age strata | -- | -- |
| <65 years old (N= 166) | 103 (62.0) | 14 (8.4) |
| ≥ 65 years old (N=183) | 118 (64.5) | 34 (18.6) |
| Sex | -- | -- |
| Female (N=240) | 146 (68.8) | 23 (9.6) |
| Male (N=109) | 75 (60.8) | 25 (22.9) |
| Number of CDI Recurrences | -- | -- |
| 1 (N=77) | 34 (44.2) | 11 (14.3) |
| 2 (N=150) | 105 (70.0) | 21 (14.0) |
| ≥ 3 (N=121) | 81 (66.9) | 16 (13.2) |
| Comorbidities | -- | -- |
| Cardiac Disease (N=109) | 82 (75.2) | 29 (26.6) |
| Immunocompromised (74) | 57 (77.0) | 15 (20.3) |
| Diabetes (N=66) | 46 (69.7) | 13 (19.7) |
| Renal impairment (N=46) | 37 (80.4) | 16 (34.8) |

Source: FDA-generated table

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

These were not evaluated in the context of this BLA review because they are not applicable to the administration of this class of products.

8.6 Safety Conclusions

The ISS did not identify any specific, unexpected, or new safety signals ([Table 32](#), below).

- The proportions of subjects with unsolicited TEAEs with both the 3-day and 1-day regimen of SER-109 relative to the corresponding placebo group were similar.
- The majority of TEAEs were mild or moderate, and the rates of severe TEAEs were similar between SER-109 (27.8%) and placebo (32.6%) for the 3-day regimen. For the 1-day regimen, 6 of the 60 SER-109 recipients (10%) had at least one severe TEAE while no severe TEAEs occurred among the 29 placebo recipients. The overall rates of severe TEAEs in the integrated sets were 14.6% and 11.7% for the 3-day and 1-day regimens, respectively.
- In SERES-012, there was an imbalance of UTIs in SER-109 recipients relative to placebo recipients. However, data from SERES-013 and SERES-004/-005 and epidemiologic data indicate that this is largely driven by the lower-than-expected rate of UTI in the placebo arm. Available culture data do not suggest any causal link between the UTIs to SER-109.
- AESIs reported across the integrated datasets did not reveal clustering of PTs or temporal patterns. The most frequently reported was sinusitis. None were attributed to the study drug or to CDI. Available culture data did not identify spore-forming organisms associated with the infections.
- Review of the narratives for serious/fatal TEAEs did not raise concern for causality and there were no patterns identified suggestive of a specific safety concern.

Table 32. Integrated Summary of Safety, Seres-012, -013, -004 and 005, Safety Population

| Event Type | SERES-012 SER-109 N=90 n (%) | SERES-012 Placebo N=92 n (%) | SERES-013 SER-109 N=263 n (%) | SERES-012/-013 SER-109 N=349 n (%) | SERES-004/-005 SER-109 N=111 n (%) |
|--|---------------------------------------|---------------------------------------|--|---|---|
| TEAEs | 84 (93.3) | 84 (91.3) | 141 (53.6) | 221 (63.3) | 89 (80.2) |
| Subjects with ≥ 1 unsolicited TEAEs | 61 (67.8) | 61 (66.3) | 141 (53.6) | 199 (57.0) | 89 (80.2) |
| Subjects with severe TEAEs | 25 (27.8) | 30 (32.6) | 26 (9.9) | 51 (14.6) | 13 (11.7) |
| Subjects with potentially life threatening TEAEs | 2 (2.2) | 0 | 2 (0.8) | 4 (1.1) | NA |
| TEAEs leading to study withdrawal | 1 (1.1) | 2 (2.2) | 0 | 1 (0.3) | 5 (4.5) |
| TEAEs leading to death ¹ | 3 (3.3) | 0 | 8 (3.0) | 11 (3.2) | 5 (4.5) |
| TEAE relatedness | | | | | |
| Related to study drug | 46 (51.1) | 48 (52.2) | 32 (12.2) | 77 (22.1) | 18 (16.2) |
| Related to CDI | 11 (12.2) | 31 (33.7) | 16 (6.1) | 27 (7.7) | NA |
| Worsening of pre-existing condition | 28 (31.1) | 32 (34.8) | 38 (14.4) | 65 (18.6) | NA |
| AESIs | 9 (10.0) | 3 (3.3) | 19 (7.2) | 28 (8.0) | 8 (7.2) |
| Related to study drug | 0 | 0 | 0 | 0 | 0 |
| Related to CDI | 0 | 0 | 0 | 0 | NA |
| Worsening of pre-existing condition | 1 (1.1) | 2 (2.2) | 6 (2.3) | 7 (2.0) | NA |
| Serious TEAEs | 15 (16.7) | 19 (20.7) | 33 (12.5) | 48 (13.8) | 19 (17.1) |
| Related to study drug | 0 | 0 | 0 | 0 | 0 |
| Related to CDI | 2 (2.2) | 6 (6.5) | 8 (3.0) | 10 (2.9) | NA |
| Worsening of pre-existing condition | 7 (7.8) | 11 (12.0) | 14 (5.3) | 21 (6.0) | NA |
| Serious TEAEs leading to study withdrawal | 1 (1.1) | 1 (1.1) | 0 | 1 (0.3) | 5 (4.5) |
| Serious TEAEs leading to death ^a | 3 (3.3) | 0 | 8 (3.0) | 11 (3.2) | 5 (4.5) |

Source: adapted from Seres ISS, Tables 17, 18, 52, and 53

a. Includes categories "TEAEs leading to death", "serious TEAEs leading to death" and adverse events with outcome "fatal"

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There was one subject who had an ectopic pregnancy (her ninth occurrence). She was medically treated with methotrexate with no complications.

9.1.2 Use During Lactation

SER-109 was not evaluated in lactating females.

9.1.3 Pediatric Use and PREA Considerations

SER-109 received orphan designation (pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the indication of treatment of rCDI. As an orphan designated product, SER-109 is exempt from PREA requirements.

9.1.4 Immunocompromised Patients

Of the 349 adults who received the 3-day regimen of SER-109, 21.2% (n=74) were immunocompromised (heterogeneous subgroup comprised of individuals with malignancies, autoimmune disorders, on immunosuppressants). Data from SERES-012

and SERES-013 are insufficient to determine if safety or effectiveness in immunocompromised populations are different than in the overall study population.

9.1.5 Geriatric Use

Of the 349 adults who received the 3-day regimen of SER-109, 52.4% were 65 years of age and over (n=183), and 28.1% were 75 years of age and over (n=98). Data from SERES-012 and SERES-013 are not sufficient to determine if adults 65 years of age and older respond differently than younger adults.

10. CONCLUSIONS

This BLA includes data from five clinical studies: one open-label dose-ranging Phase 1 trial conducted outside of an IND (SERES-001), two Phase 2 trials of a one-day regimen of SER-109 (SERES-004 and open-label SERES-005) and two Phase 3 trials of the 3-day regimen of SER-109 (SERES-012 and open-label SERES-013). The primary efficacy endpoint for the Phase 2 and 3 trials was RR of CDI recurrence in SER-109 recipients compared to placebo recipients. The primary data that support the safety and effectiveness of SER-109 at the dosage regimen for licensure (oral daily doses of 3×10^7 SCFU administered as 4 capsules on 3 consecutive days) are from SERES-012 and SERES-013. Supportive safety data are from the SERES-004 and SERES-005, which evaluated an oral dose of 1×10^7 SCFU administered as 4 capsules over 1 day. SERES-001 was not included in the ISS due to differences in dosage, study eligibility criteria, safety monitoring procedures, and case definition for CDI recurrence (see [Section 6.5.2](#) for details). Each study included 24 weeks of follow-up after administration of study drug. Subjects in SERES-004 and SERES-012 who experienced a recurrence of CDI prior to Week 8 were eligible to enroll in SERES-005 and SERES-013, respectively.

FDA agreed that demonstration of efficacy in one trial (SERES-012) could support licensure of SER-109 provided that the data achieved the pre-specified success criterion, which was an upper bound of the 95% CI of the RR ratio ≤ 0.833 . SERES-012 achieved this: the point estimate of the RR was 0.32 and the upper bound of the 95% CI was 0.58.

This BLA includes safety data from 349 unique subjects who received the 3-day regimen of SER-109, which fulfilled the agreed upon minimum safety database of 300. Safety data from 111 unique subjects who received a 1-day regimen of SER-109 (in SERES-004 and SERES-005) were considered as supportive evidence. The majority of the safety database came from open-label extension study, SERES-013 (n=259). When SERES-012 was initiated in 2017, a total of 320 subjects were planned for enrollment. Thus, approximately 50% of the safety database would consist of subjects who received SER-109 in the context of a placebo-controlled trial. Due to slow enrollment, the Applicant proposed to reduce the study size (amendments 59 and 60 to IND 16262, May 2018). Slow enrollment was attributed to numerous factors, particularly the availability of FMT provided by commercial stool banks under the FDA's "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies" (2013), public perception of FMT as safe and effective, and medical guidelines, including the IDSA, which endorsed the use of FMT in persons with their second CDI recurrence as part of the practice of medicine. As these factors were outside of the Applicant's control, FDA agreed that the sample size could be reduced but that the

success criterion for a single study supporting licensure would remain the same. The Applicant agreed and aimed to enroll 190 subjects. However, due to the COVID-19 pandemic, enrollment was closed early for SERES-012, which had enrolled 182 subjects.

In SERES-012, the most common adverse reactions (defined as AEs [inclusive of solicited and unsolicited] assessed as definitely, possibly, or probably related to SER-109 by the investigator) reported by $\geq 5\%$ SER-109 recipients within 8 weeks of completing treatment, and at a rate greater than that reported by placebo recipients, included abdominal distension (31.1%), constipation (16.7%), chills (11.1%) and diarrhea (10.0%). Most adverse reactions were mild or moderate in severity. Severe adverse reactions were reported in 9 (10.0%) SER-109 recipients and 11 (12.0%) placebo recipients and mostly resolved within days. None were life-threatening. Most adverse reactions occurred within Study Days 4-10. After this, the proportion of subjects with adverse reactions declined through follow-up, which was weekly for the first 8 weeks and monthly thereafter for 6 months after treatment.

Across SERES-012 and SERES-013, 99.1% (346/349) received all scheduled doses and capsules of SER-109. Of the 349 unique subjects, 4 received 2 courses of SER-109: first course in SERES-012 and the second in SERES-013 due to CDI recurrence within 8 weeks of completing the first course. Safety data from SERES-012 and SERES-013 and the Phase 2 studies SERES-004 and SERES-005 were analyzed in an ISS. The majority of subjects across the paired studies of the 3-day and 1-day regimens, respectively, were White (92.3% and 92.8%, respectively), female (68.8% and 64.0%), and not Hispanic or Latino (92.6% and 94.6%). The ages of subjects ranged from 18 to 100 years. In the SERES-012/-013 and SERES-004/-005 datasets, median ages were 66.0 and 68.0 years, respectively, and mean ages were 64.2 and 65.6 years, respectively. All subjects had at least 2 CDI episodes with at least one recurrence at the time of study entry. In SERES-012/013 and SERES-004/005, respectively, 77.7% and 100.0%, reported at least 3 CDI episodes including the one at study entry. Demographic variables and incidence of comorbidities, namely cardiac disease, diabetes, immunocompromise or immunosuppression and renal impairment, were similar across SER-109 and placebo recipients.

In the ISS, a total of 460 subjects were exposed to SER-109; 349 received the 3-day regimen and 111 received the 1-day regimen. Solicited AEs were collected in SERES-012 only and are discussed in [Section 6.1.12.2](#). To facilitate comparison across studies, unsolicited TEAEs were compared across the study pairs. The proportion of subjects with at least one unsolicited TEAE was 57.0% (199/349) for the 3-day regimen (SERES-012/-013) and 80.2% (89/111) in the 1-day regimen (SERES-004/-005), compared to 66.3% (61/92) and 69.0% (20/29) in the corresponding placebo groups in SERES-012 and SERES-004, respectively.

In SERES-012/-013, the most frequently reported unsolicited TEAEs from Day 3 through Day 10 were diarrhea (23.2%), flatulence (7.2%) and nausea (7.2%). Most of the events were mild (50%; n=80) or moderate (35%; n=56) in severity. In SERES-004/-005, the most frequently reported unsolicited TEAEs were diarrhea and abdominal pain. Most of the events were mild (35.1%; n=39) or moderate (33.3%; n=37).

Across SERES-012 and SERES-013, 13.8% (48/349) of SER-109 recipients and 20.7% (19/92) of SERES-012 placebo recipients reported at least one SAE within 6 months

after the first dose of investigational product. Across SERES-004 and SERES-005, 17.1% (19/111) of SER-109 recipients and 10.3% (3/29) of SERES-004 placebo recipients reported at least 1 SAE within 6 months. None of the SAEs across the 4 studies were considered related to the investigational product.

There were 11 subjects with fatal TEAEs among the 349 SER-109 recipients in SERES-012/-013 (3.2%) and 5 SER-109 recipients with fatal TEAEs in SERES-004/-005 (4.5%) compared to 0% in the corresponding placebo groups. Deaths occurred only in SER-109 recipients, but the variable temporal relationships (range in time of death from Day 5 to Day 164) and the narratives indicate that they were related to (acute events attributable to) pre-existing conditions. Based on the review of the individual narratives and MedWatch summaries, FDA agreed that all the deaths were due to chronic medical condition(s) or acute events reflecting individual subjects' comorbidities and considered unrelated to SER-109. Most deaths occurred in the uncontrolled studies, and the mortality rates were within an expected rate in this patient population.

The safety review revealed imbalances in GI TEAEs, UTIs, and fatalities between the SER-109 groups and corresponding placebo groups. The majority of adverse reactions (TEAEs considered related to SER-109) were mild or moderate diarrhea. The imbalance in UTIs was likely due to confounding factors (i.e., more females in the SER-109 arm compared to the placebo arm, relatively small sample sizes). Furthermore, the incidence of UTI in the placebo arm was lower than expected for the population and available culture data demonstrated common uropathogens and none were spore-formers.

The primary efficacy study, SERES-012, demonstrated the effectiveness of SER-109 in reducing the risk of recurrence of CDI, with 0.32 as the point estimate of the RR of rCDI with SER-109 compared to placebo. The success criterion of upper bound of the 95% CI of RR ≤ 0.833 was met. Although there were imbalances in UTIs and fatal and non-fatal SAEs among SER-109 recipients compared to placebo recipients, none were considered related to SER-109. FDA agrees with this assessment based on independent review of the narratives and related documents. Therefore, postmarketing safety assessment would be sufficiently addressed by routine pharmacovigilance, as discussed in [Section 4.6](#). The overall risk-benefit profile of SER-109, which will be discussed in greater detail in [Section 11](#), is acceptable for approval.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 33. Risk-Benefit Considerations for SER-109

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|------------------------------|---|---|
| Analysis of Condition | <ul style="list-style-type: none"> • <i>Clostridioides difficile</i> (formerly <i>Clostridium difficile</i>), also known as <i>C. difficile</i> (CDI), is serious condition that results in significant morbidity and mortality. In the United States, CDI is associated with 15,000 to 30,000 deaths annually, with acute inpatient costs exceeding \$4.8 billion. • The most common signs and symptoms of CDI are watery diarrhea >3 times a day for more than 1 day and mild abdominal cramping and tenderness. • Severe infection can be associated with significant colitis leading to colectomy and death. • CDI complications include dehydration, hypotension, and kidney failure from significant loss of fluids and electrolytes due to severe diarrhea. Although rare, toxic megacolon can occur, resulting in colonic rupture, septicemia, and death. • Recurrent CDI (rCDI) is defined as an episode of CDI occurring within 8 weeks of a previous episode and associated with increased risks of mortality and significant morbidities. • Approximately 25%-35% of patients develop rCDI disease after the initial episode. • Approximately 40%-60% of patients experience additional recurrent episodes after the first CDI recurrence, creating a subpopulation of subjects with an infection that does not respond to standard therapies. • Quality-of-life scores in patients with rCDI are lower compared to patients with a first episode of CDI, and consistently decrease with increasing numbers of CDI episodes. | <ul style="list-style-type: none"> • rCDI is a serious condition that is associated with significant healthcare costs and decreased quality of life for affected individuals. |
| Unmet Medical Need | <ul style="list-style-type: none"> • Antibiotics are first line therapy; these are generally effective for treating acute infection, but can further disrupt the gut bacteria and limit recovery of the gut microbiome following CDI. • Bezlotoxumab, a human monoclonal antibody against CDI toxin B was approved to reduce recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and at high risk for CDI recurrence. Bezlotoxumab must be administered with antibiotics and carries a warning related to heart failure. | <ul style="list-style-type: none"> • There are two FDA-approved products indicated to reduce recurrence of CDI. Both require administration in healthcare settings. SER-109 is the first oral product that can be administered in an outpatient setting and can be used following completion of standard-of-care antibacterial treatment for CDI to prevent additional rCDI. In addition, SER-109 is the product of manufacturing processes that includes ethanol inactivation and filtration of the raw material of |

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|--------------------------------|---|--|
| | <ul style="list-style-type: none"> Rebyota, a fecal microbiota enema suspension prepared from human stool, was approved in 2022 for the prevention of recurrence of CDI in adults (age ≥18 years) following antibiotic treatment for rCDI. | <p>human stool which likely provides advantages with respect to risk of transmission of infectious agents.</p> |
| <p>Clinical Benefit</p> | <ul style="list-style-type: none"> All 5 studies of SER-109 conducted in individuals 18 years and older defined recurrence of CDI as any confirmed infection occurring within 8 weeks of completing treatment. This aligns with both CDC and clinical treatment guidelines. In all studies, SER-109 was administered 48-96 hours after completion of antibacterial treatment for the episode of rCDI at study entry. The primary evidence of effectiveness of the 3-day regimen of SER-109 was provided by randomized, double-blinded, placebo-controlled multi-center Phase 3 study SERES-012. For this BLA to be supported by a single efficacy study, SERES-012 was required to achieve a pre-specified margin of success with respect to CDI recurrence rates in SER-109 recipients compared to placebo. The success criterion was for the upper bound of the 95% confidence interval (CI) around relative risk (RR) of CDI recurrence 8 weeks after treatment to be ≤0.833. This criterion was met: The upper bound of the 95% CI of the RR of 0.32 was 0.58, which is < 0.833. Efficacy data from the prospective open-label study of the 3-day regimen of SER-109, SERES-013, while limited by the lack of a control arm, support the benefit of SER-109 in preventing rCDI. | <ul style="list-style-type: none"> SERES-012 and SERES-013 provide evidence that a 3-day regimen of SER-109 is effective in preventing rCDI in individuals 18 years of age and older following completion of antibacterial treatment for rCDI. |
| <p>Risk</p> | <ul style="list-style-type: none"> In the main efficacy study, SERES-012, the most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to the study drug by the investigator) reported by ≥5% of SER-109 recipients at a rate greater than that reported by placebo recipients were abdominal distension (31.1% of SER-109 recipients and 29.3% of placebo recipients), constipation (16.7% and 10.9%), chills (11.1% and 8.7%), and diarrhea (10.0% and 4.3%). Rates of subjects with at least one adverse reaction declined from 48.9% and 51.1% during the first week after completing treatment in SER-109 and placebo arms, respectively, to 6.7% and 3.4% during the second week after treatment. Rates plateaued at 6.7% and 5.7% during the third week through eighth week after treatment, and none in both arms out to 6 months of follow-up. Invasive infection was prospectively monitored in SERES-012 and SERES-013. Pathogen transmission was not observed in the safety population in these two studies, which evaluated the 3-day regimen of SER-109. Serious adverse events within 6 months of the 3-day regimen of SER-109 were reported in 13.8% SER-109 recipients (48/349) and in 20.7% (19/92) of SERES-012 placebo recipients. For the 1-day regimen, 17.1% (19/111) of SER-109 recipients and 10.3% (3/29) of SERES-004 placebo recipients. | <ul style="list-style-type: none"> Most adverse reactions associated with SER-109 were gastrointestinal in nature (e.g., flatulence, abdominal distention, diarrhea), transient, and occurred within a week after treatment. Although there was an imbalance in UTIs occurring more frequently among SER-109 recipients, the clinical data and available microbiologic data from affected subjects do not support a causal relationship with SER-109. Prospective monitoring for invasive infections in SERES-012/-013 did not reveal any concerning patterns concerning for pathogenic potential of SER-109. Most adverse events that were classified as serious (SAEs) were most likely associated with underlying comorbid illness, acute events associated with underlying comorbidities, or rCDI. |

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|------------------------|--|---|
| | <ul style="list-style-type: none">• Sixteen deaths occurred in recipients of SER-109. | <ul style="list-style-type: none">• FDA agreed with study investigators that all 16 deaths were due to chronic medical condition(s) or acute events reflecting individual subjects' comorbidities. FDA considered all 16 deaths unrelated to SER-109. |
| Risk Management | <ul style="list-style-type: none">• Ongoing donor and stool screening and testing to mitigate the potential risk of transmission of pathogens through SER-109.• The ethanol inactivation of product manufacturing has been demonstrated to provide additional pathogen killing activity, evidenced by spiking experiments with prototype pathogens. | <ul style="list-style-type: none">• If SER-109 were approved for adults with CDI recurrence to prevent additional recurrence, routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks. |

11.2 Risk-Benefit Summary and Assessment

Recurrent CDI is a serious condition that is associated with significant healthcare costs and decreased quality of life for affected individuals. There are two currently approved products for prevention of rCDI: ZINPLAVA™ (bezlotoxumab), a monoclonal antibody against *C. difficile* toxin B for intravenous use, and REBYOTA™, a fecal microbiota suspension for rectal use. Both are indicated for use in persons 18 years of age or older who are receiving antibacterial drug treatment for rCDI or have completed antibacterial treatment for rCDI, respectively, and are at risk of CDI recurrence. Availability of additional safe and effective options, particularly one that can be taken orally and in an outpatient setting, would be beneficial and meet an unmet need. SER-109 is intended to be used as a preventive agent against rCDI and would be an option with a more comfortable route of administration (oral rather than intravenous or intrarectal) that does not require being in a healthcare setting. The manufacturing process for deriving the fecal microbiota spores includes ethanol-based inactivation of adventitious agents which may lessen the risk of transmission of infectious agents.

Data submitted to the BLA demonstrate that SER-109 is effective in preventing recurrence of CDI in individuals 18 years of age and older following the completion of antibacterial treatment for recurrent CDI. Available data as summarized in the Risk-Benefit Analysis table in the preceding section and Sections 6 and 8 support the effectiveness and safety of SER-109 when administered 48 to 96 hours after completion of antibacterial treatment for an episode of rCDI and preceded by a bowel cleanse.

11.3 Discussion of Regulatory Options

The data support traditional approval of SER-109 to prevent recurrence of CDI in individuals 18 years of age and older, following antibacterial treatment for recurrent CDI. Therefore, options other than approval were not considered. Available data, primarily from SERES-012 and SERES-013, support the safety and effectiveness of SER-109 for the intended indication, with a favorable benefit-risk profile for the intended patient population who is experiencing a serious condition for which the FDA-approved treatment options require administration in a healthcare setting.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of SER-109 for the reduction of recurrence of CDI in individuals 18 years of age and older, following antibacterial treatment for rCDI.

11.5 Labeling Review and Recommendations

Labeling negotiations resulted in the following revisions to the draft product label submitted in this BLA:

- The approved trade name for SER-109, VOWST (fecal microbiota spores, live-brpk) was added to the package insert.
- Section 1 [Indications and Usage] was revised to explicitly state that SER-109 is to be taken after completion of antibacterial treatment of the CDI recurrence that qualifies an individual for use: “to prevent the recurrence of CDI in individuals 18 years of age and older **following antibacterial treatment for rCDI.**” Limitation of use regarding SER-109 (i.e., not treatment for CDI) was inserted.

- Section 2 [Dosage and Administration] was revised to improve the readability instructions for use, starting with bowel cleanse followed by dosing for three consecutive days.
- Section 5 [Warnings and Precautions] was incorporated to inform the prescriber of the potential risk for transmissible infectious agents and potential presence of food allergens in SER-109.
- Section 6 [Adverse Reactions] was limited to adverse reactions rather than all reported TEAEs, including those with imbalances across treatment arms (namely UTIs) due to narratives and culture data supporting unrelatedness to SER-109. Safety data from SERES-012 (Study 1) and SERES-013 (Study 2) were presented separately to reflect the differences in study design (placebo-controlled versus open-label). ~~and~~
- Section 8 [Use in Specific Populations] was revised to indicate that data from 183 individuals 65 years of age and over are not sufficient to determine if older adults respond differently than younger adults.
- Section 11 [Description] was revised to explicitly state that the source material for SER-109 is human stool and to describe the manufacturing process as filtration steps versus “purification.”
- Section 12 [Clinical Pharmacology] states that the mechanism of action of SER-109 has not been established.
- Section 14 [Clinical Studies] was revised to include only primary and secondary efficacy data based on agreed-upon endpoints and to include CDI recurrence rates at all collected points (secondary objectives), beyond the time frame for primary efficacy analysis at Week 8.

11.6 Recommendations on Postmarketing Actions

The pre-licensure safety database, consisting of 349 individuals 18 years of age and older who received the 3-day regimen of SER-109 and 111 individuals 18 years of age and older who received the 1-day regimen of SER-109, did not reveal any safety signals warranting assessment beyond standard pharmacovigilance. Therefore, FDA is not requiring any post-marketing safety studies. The Applicant will be conducting a voluntary postmarketing study to further characterize the safety profile of SER-109. This surveillance study of approximately 750 individuals with rCDI will be conducted using data from large US healthcare database(s) following feasibility assessment. The primary objective is to characterize the safety of SER-109 in patients with rCDI, including the rates of UTIs and other medically important infections.