

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From: Jonathan D. Reich, MD
Medical Officer Pharmacovigilance Branch 2 (PB2),
Division of Pharmacovigilance (DPV), Office of
Biostatistics and Pharmacovigilance (OBPV), CBER,
FDA

To: Christina Houck
Chair, OVR

Through: Christopher Jason, MD
Branch Chief, PB2

Meghna Alimchandani, MD,
Deputy Director
DPV, OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan for Seres FMT
therapy for chronic infection with C. Difficile.

Applicant: Seres Therapeutics

Product: VOWST, **SER-109**, Purified Suspension Encapsulated
fecal microbiota spores

Application Type/Number: 125757/0. Original BLA

Indication: Prevention of recurrence of Clostridioides Difficile
infection (CDI) in adults with chronic CDI

1 Objective

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP), submitted under 125757/0, based on the safety profile of SER-109 (VOWST), and determine the adequacy of the applicant's plans for postmarketing safety monitoring for SER-109.

2 Product Information

2.1 Clinical Background

Recurrent *Clostridioides difficile* infection (CDI) is a rare, serious and life-threatening disease. A Center for Disease Control (CDC) estimate of the morbidity of health care-associated or community-onset CDI found it led to 223,900 hospitalizations in the US in 2017. The 30-day mortality rate associated with recurrent CDI is high, estimated at between 7 and 10% of hospitalizations.¹

C. difficile can cause a wide range of clinical manifestations from mild diarrhea to life-threatening colitis. From the patient perspective, it contributes to a high disease burden, and reduced quality of life (QoL), functioning, and productivity. Recurrent CDI (rCDI) is characterized by abatement of symptoms while on appropriate antibiotic therapy, followed by recurrence of diarrhea and other symptoms after antibiotics have been completed. Recurrent CDI is a rare, serious and life-threatening disease, and in severe cases can lead to death. The current treatment of recurrent CDI is with vancomycin or fidaxomicin, which kill vegetative *C. difficile*, but has no effect on the spore form leading to continued recurrences. On November 30, 2022, FDA approved Rebyota, the first fecal microbiota product, for the prevention of recurrence of CDI in individuals 18 years of age and older, providing an additional approved option to prevent recurrent CDI.¹ Rebyota is for use after an individual has completed antibiotic treatment for recurrent CDI. Rebyota is administered rectally as a single dose. Rebyota is prepared from stool donated by qualified individuals. Currently, there remains a key public health need for an effective, safe and convenient treatment for patients with rCDI.

2.2 Product Description

SER-109 is a microbiome therapeutic developed to prevent the recurrence of *Clostridioides difficile* infection (CDI) in adults with recurrent CDI (rCDI). SER-109 is an ecology of bacteria in spore form, purified from stool donations obtained from qualified healthy donors. (b) (4) stool donations from a single donor are (b) (4) to produce a batch. Ethanolic exposure ensures selection of the target bacterial spores while purification operations separate the resulting spore population from the starting raw materials. SER-109 is ultimately formulated in 92 ± 4% w/w glycerol in saline and encapsulated for oral administration to patients.

¹ FDA Approves First Fecal Microbiota Product (November 30, 2022) available at <https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product>

The applicant is claiming that SER-109 is a first in its class targeted therapy. The product differs from Fecal Microbiota Transplant (FMT) therapy in that this therapy is a purified spore of the Firmicutes bacteria class. Unlike FMT, oral administration of SER-109 does not have procedural related risks of fecal enemas or invasive endoscopy and reduces the subsequent burden for patients and to the healthcare system. Because it is an oral therapy and stable at room temperature, the applicant alleges it demonstrates improved compliance and reduces clinic visits.

2.3 Proposed Indication

The proposed indication for SER-109 is to prevent the recurrence of CDI in adults with rCDI. SER-109 received Orphan Drug Designation for this rare disease. The commercial dose and regimen for SER-109 for rCDI is 4 capsules taken orally once daily for 3 consecutive days.

2.4 Pertinent Regulatory History

SER-109 has both Breakthrough Therapy Designation and Orphan Drug Designation. SER-109 capsules are not currently marketed in any country or region.

2.5 Known Safety Information for this Class of Product

Because this therapy is proposed as a first in its class product there is no other safety information besides the clinical studies which are submitted to support this application.

3 Documents Reviewed

The following documents were reviewed in support of this application:

Table 1: Documents Reviewed

Source	STN Number	Description
Applicant	125757/0	Integrated Safety Summary
Applicant	125757/0/2	Risk Management Plan
Applicant	125757/0/37	Response to IR, PAS protocol, updated PVP
Applicant	125757/0/58	Response to IR,

4 Clinical Studies Submitted in Support of this Application

4.1 Clinical Trial Overview

The applicant submitted data from 5 trials that comprise the analyzed safety population: 3 trials in phase 1 or phase 2 and 2 trials in phase 3. They are listed in Table 2 below. The applicant categorized the studies as “Targeted” or “Non Targeted” based on the dose of SER-109. Subjects in the Targeted studies received the proposed dose while those in nontargeted studies received lower doses.

Note: The studies are reviewed as part of an integrated safety set except SERES-001 which is reviewed individually because it is a first in human study.

Table 2: Clinical Trial Overview

Trial	N	Description
<i>SERES-001</i>	26 (13/13)	Two-part, single arm, open label Phase 1b/2 study, 2 groups received different doses over 1 day and 2 days
<i>SERES-004</i>	48 (32 treatment, 16 placebo)	Randomized, double-blind, placebo-controlled, parallel-group Phase 2 study in patients with rCDI to evaluate safety, single dose, SAEs followed through 24 weeks (SERES 005-expanded access includes same patients)
<i>SERES-005</i>	72	Single arm, expanded access study, open-label study. Single dose administered to adults with rCDI
SERES-012	182	Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of SER-109 vs. placebo to reduce recurrence of CDI
SERES-013	263	Single arm, open label extension of SERES-012 and open-label program evaluating SER-109 in adult subjects with rCDI.

Italics-Non-targeted studies

Bold-Targeted Studies

4.2 Safety Analysis

The applicant conducted an integrated review of safety and developed a safety dataset for adults (≥age 18) comprised of 462 subjects who received SER-109 and 121 subjects who received placebo.

4.2.1 Patient Withdrawals

Untargeted dose group comprised 113 treated patients and 29 received placebo. In SERES-001, 2 patients in each group withdrew. In SERES-004, the withdrawn patients are not included in the table above (27 treated, 14 placebo). In SERES-005, 32 patients withdrew from the study (15 treated and 17 placebo).

Target dose group comprised 349 treated patients of whom 345 received one dose of SER-109, 4 patients received two doses, 92 received placebo, and 4 were lost to follow-

up. The non-target group consisted of 111 patients of which 90 received one dose and 21 received two doses, 29 received placebo, and 6 were lost to follow-up.

4.2.2 Adverse Events/Collection Protocol

In SERES-012 and SERES-013, all AEs were collected through Week 8 (reports of non-serious and non-AESI events received after Week 8 were excluded from the individual study analyses). SAEs and AESIs (serious and non-serious) were collected through Week 24. In SERES-004 and SERES-005, all AEs were collected through Week 12 (reports of non-serious events received after Week 12 were excluded from the individual study analyses). SAEs were collected through Week 24. AE collection in each study began from the time of study drug dosing.

4.2.3 Diarrhea

The main adverse event of both CDI and the therapy is diarrhea. As a result, the protocol contains a grading system for diarrhea. Unformed bowel movements were recorded daily in an electronic diary.

Mild: 3-4 unformed bowel movements per day

Moderate: 5-6 unformed bowel movements per day

Severe: >6 unformed bowel movements per day

4.2.4 Treatment Emergent Adverse Events (TEAE) analysis

TEAEs were summarized by time of onset for each analysis dataset using the following intervals: at any time; 1-58 days; 1-10 days; 11-14 days; 15-58 days; and ≥ 59 days following study drug initiation. TEAEs were evaluated for overall numbers, relationship with drug, and those which resulted in discontinuation of the study.

4.2.5 Subgroup Analysis

The data was analyzed according to the following variables: age, race, sex, number of previous episodes of CDI, and concomitant diseases including renal impairment, diabetes, cardiac disease, hepatic failure, previous use of antibiotics, and immunocompromise/immunosuppression.

4.3 Safety Results

4.3.1 Targeted Dose Study Results:

For safety result analysis, the results of SERES-012 and SERES-013 are combined because these two studies were target dose studies. There were 90 treated patients in SERES-012 and 90 placebo patients. A comparison of the two groups does not demonstrate a statistical difference. Results were evaluated in 8 categories: (see Amendment 2, page 121 for SERES-13 and page 151 for SERES-12)

- 1) Total TEAEs
- 2) Subjects with at least one Treatment Emergent Adverse Events of Special Interest (AESI),
- 3) Subjects with at least 1 drug related TEAE,
- 4) Subjects with a serious TEAE,
- 5) Subjects with a severe TEAE,
- 6) Subjects with treatment emergent invasive infection,
- 7) Subjects with TEAE leading to subject withdrawal,
- 8) TEAEs leading to death.

The numbers and percentages of patients in the treated group and placebo groups were roughly the same. No statistical differences were noted.

4.3.2 Untargeted Dose Study Results

SERES-004 was a double-blind study in which there were 60 patients who received SER-109 and 29 patients who received placebo. Comparison was made for the same 9 categories listed above and there were no significant differences between the rates of TEAEs in the two groups.

4.3.3 Common Adverse Events

4.3.3.1 Common Adverse Events in Targeted Dose Studies (Seres-012 and Seres-013)

The most common organ system affected was the gastrointestinal system. The treated group reported that 87.8% of the participants had an adverse event related to the GI tract compared to 87.0% of the placebo group, the most common being flatulence. Other GI complaints experienced by more than half of the participants were abdominal pain and abdominal distension.

Table 3: 10 most common treatment emergent adverse event (TEAE) rates in treated and placebo subjects in targeted studies combined (SERES-012 and SERES-013)

AE	Treated (%) N=353	Placebo (%) N=92	Comment
Patients with any AE	225 (64%)	84 (91%)	
Most Common GI complaints			
Flatulence	83 (24%)	70 (76%)	Placebo higher %
Abdominal Distension	60 (17%)	49 (53%)	Placebo higher %
Abdominal Pain	65 (18%)	56 (61%)	Placebo higher %
Non-GI complaints			
Fatigue	65 (18%)	58 (63%)	Placebo higher %

Urinary Tract Infection	21 (6%)	1 (1%)	Treated % significantly higher
Chills	23 (7%)	22 (24%)	
Other GI complaints			
Constipation	35 (10%)	22 (24%)	Consistent with other GI complaints
Diarrhea	82 (23%)	20 (22%)	Expected due to pre-existing CDI
Nausea	36 (10%)	30 (33%)	

Another less common adverse event, rCDI affected significantly more placebo patients than treated patients (4 treated patients and 8 placebo patients).

Reviewer Comment: In general, the reporting of TEAEs in these two studies is reassuring. The placebo group had a higher percentage of patients reporting at least one TEAE and for every specific TEAE except one, UTIs, the placebo group experienced a higher rate. The higher incidence of UTIs is noted and the applicant plans to monitor with an active surveillance postmarketing safety study.

4.3.4 All Reported Adverse Events in Untargeted Dose (Supportive) Studies (Seres-004 and Seres-005)

As in the targeted studies flatulence, abdominal pain, and abdominal distension were common in these studies but the adverse event rates were much lower.

Table 4: TEAE rates in supportive/non-dose targeted studies (SERES-004 and SERES-005)

AE	Treated (%) N=111	Placebo (%) N=29	Comment
Patients with any AE	62 (56%)	13 (45%)	
GI Side effects			
Flatulence	11 (10%)	1 (3%)	Higher Rate in Treated
Diarrhea	34 (31%)	4 (14%)	
Nausea	14 (13%)	3 (10%)	
Constipation	31 (28%)	1 (3%)	Higher rate in treated, consistent with flatulence above
Nausea	22 (20%)	3 (10%)	Higher rate in treated patients
Vomiting	4 (4%)	1 (3%)	
Other organ systems			

Urinary Tract Infections	9 (8%)	1 (3%)	Consistent with targeted study results
Back Pain	7 (6%)	0 (0%)	Consistent with constipation

Reviewer Comment: Unlike the targeted studies the treated patients had higher rates of gastrointestinal adverse events than the placebo patients. Because both placebo and treated patients have CDI, the presence of GI symptoms is expected and it is difficult to assign a reason for GI side effects to be higher in placebo patients in targeted studies and higher in treated patients in untargeted studies. The only AE consistently more common in treated patients is urinary tract infections.

4.4 Deaths

4.4.1.1 Deaths in Targeted Studies

SERES-012 had 3 deaths reported. There was a case of glioblastoma, a case of atrial fibrillation and sepsis, and a fall which resulted in a subdural hematoma. None of these deaths were adjudicated to be related to the investigational therapy by the reporter.

SERES-013 had 8 deaths reported. There was a case of gangrene, 2 deaths from heart failure, one from C. Difficile infection, one from unspecified natural causes, one from pneumonia, and one from pancreatic cancer.

Reviewer Comment: A review of the patient death reports indicates all patients were sick prior to therapy and it's unlikely the therapy contributed to any of these deaths.

4.4.1.2 Deaths in Nontarget Studies

SERES-004 had one death from non-small cell metastatic cancer of the lung which was adjudicated to be unrelated to the therapy.

SERES-005 had 4 deaths. One was from the pre-existing rCDI, two were from CVA, and one was from sepsis. The septic patient had serious pre-existing conditions including serious heart disease, Parkinson's Disease, and type II diabetes.

4.4.1.3 Description of Death Cases

Of the 16 total deaths in all 4 studies, 12 were adjudicated to be due to pre-existing conditions including malignancies, rCDI, and heart disease.

- 1) SERES-004: Case (b) (6) : death due to small cell carcinoma of the lung.
- 2) SERES-012: Case (b) (6) : subdural hematoma after a fall
- 3) Case (b) (6) : pre-existing arrhythmia and kidney failure.
- 4) Case (b) (6) : secondary to a glioblastoma
- 5) SERES-013: Case (b) (6) : pancreatic cancer
- 6) Case (b) (6) : pre-existing cardiomyopathy
- 7) Case (b) (6) : Coronavirus infection, intestinal perforation

- 8) Case (b) (6) : 93-year-old, "natural causes"
- 9) Case (b) (6) : recurrent CDI
- 10) Case (b) (6) : Urosepsis
- 11) Case (b) (6) : necrotizing fasciitis
- 12) Case (b) (6) : end stage heart failure, kidney failure
- 13) SERES-005: Case (b) (6) : pseudomonas sepsis, coronary artery disease, NSTEMI, chronic renal disease
- 14) Case (b) (6) : rCDI, autopsy did not identify a specific cause of death
- 15) Case (b) (6) : DVT
- 16) Case (b) (6) : hematuria, renal failure, multi-system organ failure

Reviewer Comment: Narratives of deaths were reviewed and none of the reported deaths are attributed to the investigational therapy, SER-109. Underlying conditions and alternative etiologies contributed to the deaths.

4.5 Serious Adverse Events

4.5.1 Serious Adverse Events in Targeted Studies

The targeted studies are SERES-012 and SERES-013. In these two studies a comparison was made between SER-109 treated subjects and placebo treated subjects in the following categories: TEAEs, subjects with a serious TEAE, and subjects with a serious treatment emergent AESI.

The ISS reports serious non-death adverse events in 5 SER-109 treated patients in study SERES-012 and in 6 SER-109 treated patients in SERES-013. The 5 serious adverse events in SERES-012 were, two patients who developed urinary tract infections (*Klebsiella* and *E. Coli*), an abdominal abscess, a case of osteomyelitis adjudicated by reporter to be unrelated to SER-109 therapy, and a case of cellulitis in a diabetic adjudicated by reporter to be unrelated to SER-109 therapy.

The 6 serious adverse events in SER-013 were a right frontal lobe stroke, a case of *E. Coli* bacteremia and COVID19 acute infection that was eventually fatal roughly half a year after contracting these infections, esophageal abscess, an *E Coli* urinary tract infection, and a case of peritonitis.

Reviewer Comment: Patients requiring this therapy have multiple co-morbidities and the occurrence of the above serious adverse events was related to underlying conditions or alternative etiologies. None of the described events appear to be secondary to SER-109. These comparisons did not demonstrate a significant difference between the two groups.

4.5.2 Serious Adverse Events in Non-targeted Studies

The two non-targeted studies which were evaluated for differences between the SER-109 treated and placebo treated subjects were SERES-004 and SERES-005. SERES-001 was a placebo controlled study but the ISS does not compile these results in this analysis. Of the two studies only 004 was a randomized placebo controlled trial.

SERES-004 was a randomized double-blind placebo control study. Serious adverse events of special interest were compared across treatment groups. 2 AESIs were observed in the treatment group (sinusitis and cellulitis) and none were observed in the placebo group.

Results of SERES-005 were combined with SERES-004 and 8 AESIs were reported in the treated group and none in the placebo group (5 cases of GI complaints-mostly diarrhea or abdominal pain, 3 cases of UTI, and a case of DVT).

Comparison between SER-109 and placebo treated subjects was made for subjects with: at least 1 TEAE, a drug related TEAE, a serious TEAE, and treatment emergent AESIs. No significant difference was noted between the two groups.

Reviewer Comment: There is an imbalance in occurrence of urinary tract infections (UTI) after SER-109 compared to placebo. Urinary tract infection is deemed an adverse event of special interest (AESI) and will be monitored with passive and active surveillance in the post-licensure period. Overall, the evidence supports the safety of this therapy. The issue of urinary tract infections was included in an Information Request (IR) sent to the company on January 25, 2023 and their response is addressed in sections 9 and 10.

4.5.3 Subgroup Analysis in Targeted and Untargeted Studies

The data was analyzed according to the following variables: age, race, sex, number of previous episodes of CDI, and concomitant diseases including renal impairment, diabetes, cardiac disease, hepatic failure, previous use of antibiotics, and immunocompromise/immunosuppression. The only difference was the incidence of GI adverse events in patients with previous reports of CD Infections. The more episodes of CDI reported, the more GI adverse events reported. No safety signal in any other specific population was identified.

4.5.4 Pregnancies in Targeted and Untargeted Studies

There was a single pregnancy reported in SERES-013. This was an ectopic pregnancy which was reported as an SAE. The pregnancy was terminated without complications.

4.5.5 Long term follow-up (24 weeks) in Targeted and Untargeted Studies

In the targeted dose studies, follow-up was performed through 24 weeks. In this follow-up a slight increase in infections was noted in the SER-109 treated group as opposed to the placebo treated patients. In the SER-109 treated group 8/78 (10.3%) of patients

experienced an infection, most commonly cellulitis (3/8) as opposed to only one patient in the placebo group who experienced an episode of cellulitis.

In the long-term follow up of the non-targeted dose studies there were only 2 infections reported, making comparisons between SER-109 and placebo of limited use.

Reviewer Comment on all provided safety information: Occurrence of urinary tract infections are higher in the treated group than the placebo group. This AESI is addressed in sections 8-10. No additional safety signals are identified. The increased infection rate evident in the long-term follow-up (24 weeks) data is relatively small. A strategy for post-market surveillance of all infections is addressed in section 9.

5 Post-market data

SER-109 is not approved outside the U.S. and there is no foreign postmarketing experience with this product.

6 Pharmacovigilance Plan

6.1 Initial Pharmacovigilance Plan and Routine Pharmacovigilance

The applicant initially submitted a PVP on August 26, 2022. The PVP risk specification did not designate any adverse events to be of special interest (important identified risks or important potential risks) nor populations of concern (missing information). The applicant proposed routine pharmacovigilance activities for monitoring SER-109 in the post-market setting that include safety monitoring and signal detection and expedited and periodic safety reporting in accordance with 21 CFR 600.80. The applicant proposed AEs that are serious and unexpected will undergo expedited reporting to the FDA, routine literature searches of published data will be conducted, and periodic safety reports will be submitted to FDA. Signal detection will be performed on an ongoing basis and validated signals will be investigated to assess for any evidence that the event is due to a drug effect.

6.2 Information Requests sent to the Applicant for PVP modification and additional pharmacovigilance activities.

The applicant's premarket clinical safety database indicated an increase in urinary tract infections in patients treated with SER-109 compared to placebo treated patients. In the non-dose treated studies, 9 treated patients reported UTIs compared to one placebo treated patient. In the targeted dose studies, there were 21 UTIs in treated patients as opposed to one in placebo treated patients.

After analysis of the submitted data, it was determined that UTIs are potential risk that should be listed in the PVP. Though the clinical safety database indicates a numerical imbalance in UTIs after SER-109 compared to placebo, the biological plausibility for a causal association with SER-109 is unknown. Other risk factors may be contributing to

UTIs, such as prolongation in hospitalization, additional antibiotic therapies, or some other established risk factors for UTI in immunocompromised patients. Should the product be approved, we will continue to monitor the AESI for UTIs.

Further consideration should be given to whether there are missing populations which should be included in the PVP. *Clostridium difficile* infections are increasingly recognized in children in whom roughly $\frac{3}{4}$ are immunocompromised.² In addition, roughly half of premature infants whose mothers received antibiotics are colonized with *Clostridium difficile*.³

As a result of the analysis above, two IRs were sent to the applicant.

- a) The first IR was sent to the applicant on January 25, 2023. It requested urinary tract infections be included as a potential risk and a request for consideration of children, pregnant and lactating women, and immunocompromised individuals as missing populations in an updated PVP. Additionally, the FDA asked the applicant regarding plans for a voluntary postmarket study to further characterize the safety profile of SER-109 with endpoints of urinary tract infections and infections more broadly.

Applicant's Response: As per FDA recommendations, applicant responded to this IR by submitting an updated PVP which included pediatric populations and use in pregnant or lactating women as *Important Missing Information*. The Applicant refused to include immunocompromised individuals under *Important Missing Information*. As per the applicant, "For immunocompromised individuals, Seres believes this population has been characterized in the SER-109 clinical development program. A significant proportion of subjects in SERES-012 and the integrated dataset had immunocompromised status (28.9% of subjects in the SER-109 treated group of SERES-012 and 21.2% overall exposure in SERES-012/SERES-013). No increased safety risk was observed following administration of SER-109 to immunocompromised subjects."

The applicant also proposed a voluntary study and provided a synopsis.

Reviewer Comment: The applicant's response and the changes to the PVP are acceptable. The synopsis of the post-market study is reviewed below.

- b) The second IR was sent on March 22, 2023. It requested enhanced pharmacovigilance for urinary tract infections for 3 years post approval specifically: submitting all reports for UTIS as expedited regardless of serious, and providing aggregate assessments in periodic safety reports. Additionally, for the postmarket study the FDA asked the applicant to add a comparator arm.

Applicant's Response: Seres acknowledged the request to conduct this voluntary general applicant safety surveillance post-marketing study to further characterize the safety profile of SER-109 with a comparator arm (standard of care treatment for rCDI). Seres agreed to provide study updates, and assessments of any safety signal identified by this study in periodic safety reports.

6.3 Voluntary Post-market Safety Study

As part of the IRs above, the applicant was asked for a synopsis of the study design, including safety outcomes, planned sample size, and study duration. The applicant was also asked for planned enrollment numbers, endpoints, and milestone dates.

The applicant provided the details requested above in order to further characterize the safety profile of SER-109. The study title is: “*A Post-marketing Safety Surveillance Study of VOWST™ in Patients with Recurrent Clostridioides difficile Infection (rCDI)*”. The applicant responded by providing a protocol synopsis (Amendment 125757/0/37). The protocol meets the requests listed above.

- i) **Primary objective:**
 - 1. To compare the safety of VOWST vs standard of care (SOC) treatment in patients with rCDI, including the rates of urinary tract infections (UTIs) and other medically important infections.
 - 2. Secondary and exploratory objectives will be determined following feasibility assessment and will be provided in the full protocol.
- ii) **Primary endpoints:**
 - 1. To compare the incidence of UTIs, starting from the first day of treatment through 24-week post-treatment (i.e., Week 24), between VOWST and SOC arms.
 - 2. To compare the incidence of other medically important infections, starting from the first day of treatment through Week 24, between VOWST and SOC arms.
- iii) **Secondary endpoints:**

Secondary and exploratory endpoints will be determined following feasibility assessment and will be provided in the full protocol.
- iv) **Study design:**

Retrospective surveillance study using integrated healthcare databases and electronic health records. Patient with rCDI receiving SER-109 or SOC will be included.
- v) **Study anticipated size and duration:**

750 patients per arm over 3 years.
- vi) **Milestone dates:**
 - a. Final protocol submission: 9/30/2024
 - b. Study completion: 3/31/2028
 - c. Final study report submission: 8/31/2028

Reviewer Comment: The applicant's updated response is acceptable.

6.4 Final Pharmacovigilance Plan

The applicant's final pharmacovigilance plan (Version 2) with safety specification and planned actions is listed below.

Table 5. Summary of Safety Concerns and Planned Pharmacovigilance Actions*

Safety concern	Planned action(s)
Important Potential Risk: Urinary tract infection (UTI)	Post-marketing safety surveillance study Routine PV Enhanced PV for 3 years after product licensure: 1. submission of expedited 15-day reports for all post-marketing setting SAEs coding under the System Organ Classes 'Infections and Infestations' 2. Submission of all reports for UTIs regardless of seriousness as expedited 15-day reports
Important Missing Information: Use in pediatric population (individuals < 18 years of age)	Routine PV, assessment for individuals who are <18 years of age in periodic safety reports
Important Missing Information: Use in individuals who receive SER-109 while pregnant or lactating	Routine PV, assessment for individuals who are <18 years of age in periodic safety reports

* From PVP version 2 table 10 pg15

7 Labeling

There is no Postmarketing Experience section in the proposed label with this product.

8 Conclusion

OBPV has reviewed the data provided by the applicant. It is our conclusion that this applicant has provided sufficient data to demonstrate safety for a condition with limited treatment options which results in high mortality and prolonged length of hospital stay especially in immunocompromised patients.⁴

An increased incidence of UTIs in treated patients compared to placebo patients has been noted and the applicant has agreed to include this adverse event as an important potential risk in an updated PVP. To further characterize the safety (specifically UTI and infectious AEs) of SER-109 in the post-market setting, the applicant plans to conduct active surveillance with a voluntary post-marketing safety study. The information provided by the applicant was reviewed and is acceptable.

Furthermore, we requested the applicant consider the addition of children, pregnant or lactating patients, and immunocompromised patients to an updated PVP as a missing population. The applicant agreed to do include children, pregnant or lactating patients, under "Important Missing Information" but did not include immunocompromised patients (please see details in section 6).

9 DPV Recommendations

Should this submission be approved, the PVP (version 2) is acceptable. Based on review of the premarket clinical safety database and the Applicant's proposed PVP, OBPV/DPV recommends the following for post-marketing safety monitoring of SER-109:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.
- Enhanced pharmacovigilance (in addition to complying with the requirements under 21 CFR 600.80): Expanded adverse experience reporting to the FDA Adverse Event Reporting System (FAERS) for 3 years following product licensure, as follows:
 - o The Applicant will submit all serious adverse events (SAEs), regardless of expectedness, and all urinary tract infections (UTIs), regardless of seriousness, as expedited (15-day) reports to FAERS.
 - o In the narrative summary of periodic safety reports, the Applicant will include aggregate analysis and assessment for: SAEs; UTIs, AEs (regardless of seriousness) in children and in individuals who receive SER-109 while pregnant or lactating.
- Voluntary postmarketing study for general safety surveillance: The Applicant will conduct a retrospective surveillance study using integrated administrative claims and electronic health records (EHR) data from large U.S. healthcare database(s). OBPV/DPV will review study updates to be provided in periodic safety reports.

Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the applicant for the final agreed-upon language for the label.

10 References

¹Guh, AY, et. al., N Engl J Med. 2020 Apr 2;382(14):1320-1330.

²Meguro, M, et. al., Pediatr Gastroenterol Hepatol Nutr. 2022 Sep;25(5):387-395.

³Feraris, L, et. al., PLoS One. 2019 Feb 20;14(2):e0212568. doi: 10.1371/journal.pone.0212568.

⁴Mahatanan, R, et. al., Transpl Infect Dis. 2021 Feb;23(1):e13459. doi: 10.1111/tid.13459.