Summary Basis for Regulatory Action

Date:	April 26, 2023
From:	Christina Houck Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA STN:	125757/0
Applicant:	Seres Therapeutics Inc.
Submission Receipt Date:	Rolling BLA Submission: May 24, 2022, and August 26, 2022
Action Due Date:	April 26, 2023
Proper Name:	Fecal Microbiota Spores, Live
Proprietary Name:	VOWST
Indication:	To prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI).

Recommended Action: The Review Committee recommends approval of this product.

Director, Product Office

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office DBPAP) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Siobhan Cowley, PhD, OVRR/DBPAP Amy Yang, PhD, OVRR/DBPAP Steven Derrick, PhD, OVRR/DBPAP Miriam Ngundi, PhD, OCBQ/DMPQ Kathleen Jones, PhD, OCBQ/DMPQ Varsha Garnepudi, MS, OCBQ/DBSQC Kouassi Ayikoe, PhD, OCBQ/DBSQC Brianna Davis, OCBQ/DBSQC
Clinical • Clinical (DVRPA) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	 Joohee Lee, MD, OVRR/DVRPA Jonathan Reich, MD, OBPV/DE Char-Dell Edwards, MS, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	 Zhong Gao, PhD, OBPV/DB Fang Chen, PhD, OBPV/DB
Labeling • Promotional (OCBQ/APLB) • PNR • Container/Carton • Suffix	 Michael Brony, PharmD, OCBQ/APLB Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA Lisa Stockbridge, OCBQ/APLB
Other Reviews not captured above categories, for example: Consults • Clinical data standardization • PLLR • CMC Regulatory Coordinators	 Brenda Baldwin, PhD, OVRR/DVRPA Cara Fiore, PhD, OVRR/DVRPA Jennifer Bridgewater, MPH, OVRR/DBPAP Sheila Dreher-Lesnick, PhD, OVRR/DBPAP
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1. Introduction

On August 26, 2022, Seres Therapeutics Inc. submitted a Biologics License Application (BLA) for licensure of VOWST, completing their rolling BLA submission. The non-proprietary name of the product is fecal microbiota spores, live-brpk and the investigational name is SER-109. The requested indication for VOWST is to prevent the recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI).

VOWST is a bacterial spore suspension in capsules for oral administration. Each capsule contains 1×10^6 to 3×10^7 spore colony-forming units (SCFU). The dosage is 4 capsules taken orally once daily for 3 consecutive days, initiated 2 to 4 days after completing antibacterial treatment for rCDI and after taking a laxative (10 ounces of magnesium citrate) on the preceding evening. VOWST is prepared from stool donations obtained from qualified healthy donors. (b) (4) stool donations from a single donor are (b) (4) to produce a batch. The Applicant treats the stool with ethanol to kill fecal

organisms that are not spores, followed by filtration (b) (4) steps to remove solids and residual ethanol. VOWST is ultimately formulated in 92% ± 4% w/w glycerol in saline. The shelf life for the final Drug Product (DP) is 36 months from the date of manufacture stored at 2° to 25°C. The date of manufacture is defined as the date of the first day of capsule filling of the formulated bulk.

The VOWST clinical program 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 [non-IND], SERES-005, SERES-013) conducted in the United States and Canada. A total of 573 participants were exposed to at least one dose of VOWST across the five prospective studies. Data from two studies, SERES-012 and SERES-013, evaluated the 3-day dosing regimen for licensure. SERES-004 and SERES-005 evaluated a 1-day dosing regimen and provided supportive safety data. SERES-001, which was the first-in-human study (non-IND) that evaluated varying doses of SER-109 for 1 to 2 days, was viewed as a background study. The majority of the minimum safety database of 300 participants for the 3-day regimen was obtained from SERES-013, an open-label extension trial associated with SERES-012.

2. Background

Clostridioides difficile (*C. difficile*) is a Gram-positive, toxin-producing, spore-forming bacterium that causes persistent diarrhea in infected individuals and can also lead to more severe outcomes such as pseudomembraneous colitis, toxic megacolon, and death. The U.S. Centers for Disease Control (CDC) has identified *C. difficile* as one of its top three public health priorities. It is the leading cause of nosocomial infection in the U.S. having recently surpassed methicillin-resistant *Staphylococcus aureus* (MRSA) and is responsible for the deaths of 14,000 Americans each year due to the consequences of severe diarrhea and colitis. Antibiotics are thought to induce susceptibility to CDI by causing dysbiosis in the colonic microbiome that creates ecological niches and liberates metabolic resources for *C. difficile*. Since *C. difficile* spores can survive indefinitely outside the body, and because health care settings are often sites of significant antibiotic use, *C. difficile* transmission rates in hospitals, long term acute care facilities and nursing homes have been on the rise.

An episode of rCDI is defined as CDI occurring within 8 weeks of a previous episode of CDI. rCDI may be due to relapse of a previous episode of CDI by the same strain or reinfection by a different strain. Risk factors for rCDI include age >65 years, antibiotic use, gastric acid suppression, infection with a 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. 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. rCDI complications include dehydration, hypotension, kidney failure, severe diarrhea and rarely, toxic megacolon, colonic rupture, septicemia, and death. A chart review of 3,958 patients with CDI found that those with rCDI (n=421) had an increased risk of death within 6 months after completion of their initial CDI treatment compared with patients who did not develop a recurrence after adjusting for baseline characteristics, comorbidities, and medications received (hazard ratio 1.33; 95% confidence interval (CI) 1.12–1.58).

Treatment options for rCDI are limited, and the standard-of-care antibacterial therapy options for rCDI (e.g., fidaxomicin and vancomycin) can be complex and prolonged. Bezlotoxumab (ZINPLAVA™), a human monoclonal antibody directed against *C. 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.

The Applicant initiated product development of VOWST under IND 16262, first submitted in 2014. Over the course of VOWST product development, the Food and Drug Administration (FDA) held several consultations with the Applicant. Table 1 provides a list of key regulatory activities associated with this BLA submission.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	June 4, 2014
2. IND submission	December 8, 2014
3. Breakthrough Therapy Designation Granted	June 11, 2015
4. Orphan Drug designation granted	August 19, 2015
5. Type B Breakthrough Therapy Initial Multidisciplinary	November 12, 2015
6. Type B Breakthrough Therapy Meeting	February 13, 2017
7. Pre-BLA meeting	November 18, 2021
8. BLA 125757/0 submission	May 24, 2022, and August 26, 2022
9. BLA filed	October 25, 2022
10. Mid-Cycle communication	Canceled upon Sponsor's request
11. Late-Cycle meeting	Canceled upon Sponsor's request
12. Action Due Date	April 26, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Composition

VOWST consists of Firmicutes bacterial spores sourced from stool collected from qualified human donors, formulated in 88% to 96% w/w glycerol in saline, and encapsulated for oral administration. VOWST is a white opaque capsule printed with "SER109". Each capsule contains 1×10^6 to 3×10^7 SCFU. It is dosed orally at 4 capsules each day (to achieve a daily dose of (b) (4) SCFU) for 3 consecutive days.

Manufacturing Overview

The source material for VOWST is donor human stool. The Applicant qualifies donors through screening via questionnaire, physical examination, and blood and stool testing for pathogens of concern. The manufacturing process is initiated at the Cambridge, MA site when stool donations from the same donor are with ethanol to a final concentration of to kill fecal organisms that are not spores. The resulting is stored and shipped at to .

At the site, the Applicant The resulting Drug Substance (DS) is stored at . The DS is formulated to the desired spore concentration in 92% ± 4% w/w glycerol in 0.9% saline, followed by capsule filling and over-encapsulation to create the (DP). The DP is then filled into 40 cc HDPE bottles, which are stored and shipped at prior to secondary packaging at (b) (4). VOWST has a 36-month shelf life when stored at 2°C to 25°C. The dating period for the final DP begins on the date of manufacture, which is defined as the date of the first day of capsule filling of the formulated bulk.

FDA identified deficiencies in the Applicant's potency assay validation studies, (b) (4) assay, and donor screening assays. These deficiencies, and all other deficiencies identified during the review process, were adequately addressed by the Applicant during the BLA review. The CMC product information and data in this BLA support manufacturing consistency and product quality.

Drug Substance

Manufacturing Process

One page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

Drug Product

Manufacturing Process

The DP manufacturing process consists of the following (b) (4) steps:

(b) (4)

(b) (4). Next, (b) (4)-checks are performed to confirm over-encapsulation of each capsule, which are then inspected for defects.

(b) (4) Primary Packing: 12 capsules are packed into each 40 cc white HDPE bottle, which are then sealed with a foil induction seal and child-resistant closure. A (b) (4)-check is performed to confirm the number of capsules per bottle, and the Applicant bulk-packages the DP bottles into transport boxes for storage and shipment to the secondary packaging facility for labeling.

Operations in the DP manufacturing area are conducted at controlled (b) (4) temperature ((b) (4)) and humidity ((b) (4)). The entire process must be completed in (b) (4) .

Process Validation

For the Applicant's DP process validation study, three PPQ lots ((b) (4)) were manufactured at commercial scale to demonstrate that the manufacturing process is repeatable and consistently produces lots that meet their pre-determined quality attributes. Process parameter results of all PPQ lots were within the operating ranges and all lots met the DP release specifications. The Applicant compared the process performance indicators and release testing data sets for three PPQ and (b) (4) clinical DP lots. Overall, the statistical analyses indicate that the processes for the Applicant's PPQ and clinical DP lots are comparable.

DP Specifications

VOWST DP release specifications (proposed and final) are included in Table 2 below:

Table 2: VOWST DP Release Specifications (Proposed and Final)

Test	Method (SOP#)	Proposed acceptance criteria	Final acceptance criteria
Identity	(b) (4)	(b) (4)	(b) (4)
Potency	Spore colony forming unit assay for viable spore content (TM-0006)	(b) (4)	(b) (4) $1 \times 10^6 – 3 \times 10^7$ SCFU/capsule
Bioburden	Microbial enumeration by (b) (4)	(b) (4)	(b) (4)
(b) (4)			

Test	Method (SOP#)	Proposed acceptance criteria	Final acceptance criteria
(b) (4)			
Appearance and physical characteristics	Visual inspection (TM-0009)	(b) (4)	White, opaque capsules consistent with size 00 standard. Possible (b) (4). Printed with "VOWST" in blue ink on capsule body.
Container Closure Integrity Testing (CCIT)	(b) (4)	(b) (4)	Acceptance criteria met
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Stability

The proposed storage for commercial DP lots is 36 months at 2-25ºC. The Applicant assessed stability data from (b) (4) Phase 3 clinical and (b) (4) PPQ DP lots. The stability samples were stored in the same containers as those used for the commercial process (induction-sealed 40 cc white wide-mouth round HDPE bottles with white 33 mm ribbed side text tops). The clinical lot stability samples were stored as (b) (4) capsules/bottle whereas the commercial DP and PPQ stability samples were stored as 12 capsules/bottle. The Applicant provided 36 months of stability results for five clinical DP lots stored at (b) (4) 2-8°C, and 25°C/ (b) (4) . The Applicant also provided 6 months of results for ongoing stability testing of (b) (4) PPQ DP lots stored at 2-8°C and 25°C/ (b) (4) for up to 36 months. Stability results for all the lots and temperature conditions met the commercial lot release acceptance criteria. Therefore, the DP appears to be sufficiently stable to support 36 months of storage at ≤ 2-25°C.

Post-licensure, the Applicant will monitor a minimum of (b) (4) batches per year for stability at 2-8°C and 25°C/ (b) (4) and monitor potency, (b) (4) , appearance (at 0, 6, 12, 24, 36, and (b) (4) months), identity, (b) (4) , and CCIT (at 0, 12, 24, 36, and (b) months). The Applicant will also perform (b) (4) bioburden testing on (b) (4) per (b) (4) stored at 2-8°C and 25°C/ (b) (4) .

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the VOWST DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to Center for Biologics Evaluation and Research (CBER) for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of VOWST are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 3: Manufacturing Facilities Table for VOWST (fecal microbiota spores, live-brpk)

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
(b) (4) *DS manufacturing; DP manufacturing; DP primary packaging and labeling*	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) VAI
Seres Therapeutics, Inc. 200 Sidney St. Cambridge, MA 02139 *DS intermediate manufacturing* *DP release testing*	3012828816	070561786	PLI	CBER/DMPQ December 2022 NAI
Seres Therapeutics, Inc. (b) (4) *DP release testing*	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) NAI
(b) (4) *DP release testing*			Waiver	ORA NAI

Acronym/Initialism key: CBER – Center for Biologics Evaluations and Research; DMPQ – Division of Manufacturing and Product Quality; ORA – Office of Regulatory Affairs; DS – drug substance; DP – drug product; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated; NAI – No Action Indicated

CBER/DMPQ conducted a PLI at (b) (4). A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER/DMPQ conducted a PLI at Seres Therapeutics, Inc., in Cambridge, MA in December 2022. A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

CBER/DMPQ conducted a PLI at Seres Therapeutics, Inc., in (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

ORA performed a surveillance inspection at (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

e. Container/Closure System

VOWST DP capsules are contained in a 40-cc opaque white high-density polyethylene (HDPE) bottle capped with a foil-lined polypropylene cap. The bottle and cap are manufactured by (b) (4) , and the foil liner is manufactured by (b) (4) Each bottle contains 12 capsules. Seres Therapeutics, Inc. conducted the container closure integrity testing at the Cambridge, MA facility, employing the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

3. Nonclinical Pharmacology/Toxicology

Nonclinical and toxicology studies are not required for this product.

4. Clinical Pharmacology

The mechanism of action of VOWST has not been established.

5. Clinical/Statistical

a. Clinical Program

The clinical development program for VOWST included five studies (SERES-001, SERES-004, SERES-005, SERES-012, and SERES-013) submitted and reviewed under BLA STN 125757 and IND 16262. The two Phase 3 studies, SERES-012 and SERES-013, were reviewed to support the safety and efficacy of VOWST. Placebo-controlled SERES-012 was the primary study evaluated to demonstrate the effectiveness of VOWST. The open-label extension study SERES-013 provided most of the subjects to fulfill the minimum safety database of 300 for the dosing regimen of VOWST being licensed. SERES-013 also provided descriptive efficacy data out to 24 weeks. All the studies of SER-109 were conducted in the United States and Canada. SERES-004, SERES-005, SERES-012, and SERES-013 were conducted under US IND. A total of 573 participants 18 years of age and older with documented CDI were

exposed to at least one dose of SER-109 across the five studies. Out of the 573 participants, 349 received the 3-day regimen of SER-109. The median age was 66 years. Most were White (92.3%), non-Hispanic or Latino (92.6%), or female (68.8%). The age strata were balanced, with 52.8% of subjects ≥65 years of age.

Table 4: Clinical Studies Evaluating the Safety and Efficacy of SER-109 for the Prevention of rCDI Infection

Study Number	Design 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	Part 1 $3.4 \times 10^7 – 2.3 \times 10^{10}$ SporQ for 2 days Part 2 $8.6 \times 10^7 – 1.9 \times 10^8$ 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	1×10^8 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	1×10^8 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 from SERES-012 (4 SER-109 recipients, 25 placebo recipients) 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

This SBRA will focus on studies SERES-012 and SERES-013, which evaluated the 3-day dosing regimen for licensure. The other studies evaluated varying doses for 1 to 2 days and were viewed as supportive or background studies and are briefly discussed.

Studies SERES-012 and SERES-013

Study SERES-012 was a Phase 3, randomized, double-blinded multi-center trial powered to evaluate the ability of VOWST versus placebo to reduce the risk of CDI recurrence (based on three-part case definition of at least two consecutive days of ≥3 unformed bowel movements, a positive toxin assay, and clinical determination of the need for antibacterial treatment) over 8 weeks after study treatment. The study enrolled 182 subjects 18 years of age or older with a confirmed diagnosis of recurrent CDI (with a total of ≥3 episodes of CDI within 12 months). The CDI episode at study entry was defined as diarrhea (≥3 unformed stools per day for at least 2 consecutive days) and a

positive *C. difficile* stool sample using a toxin assay. Subjects were required to have symptom resolution, defined as <3 unformed stools in 24 hours for 2 or more consecutive days prior to randomization, following 10 to 21 days of standard-of-care antibacterial treatment with vancomycin or fidaxomicin. Subjects were stratified by antibacterial received (vancomycin or fidaxomicin) and age (<65 years or ≥65 years) and randomized 1:1 to receive a dose of VOWST or placebo once daily for 3 consecutive days. The statistical criterion for success was an upper bound of the 95% confidence interval of the point estimate of CDI recurrence in VOWST recipients compared to placebo recipients that was < / = 0.833. When enrollment challenges precluded enrollment of the proposed 320 subjects, the Applicant revised the sample size to 182. The FDA agreed provided that the success criterion was maintained.

The primary efficacy analysis for SERES-012 was conducted in the intent-to-treat population (ITT), which included all randomized subjects. Subjects were analyzed as having received the treatment to which they were randomly assigned. Following 8 weeks of treatment, there were statistically significantly fewer VOWST recipients with CDI recurrence (11 of 89 or 12.4%) than placebo recipients (37 of 93, or 39.8%). The point estimate of the relative risk (RR) of CDI recurrence in the SER-109 to placebo in the ITT population was 0.32. The corresponding 95% CI (0.18, 0.58) met the pre-specified treatment success criterion of an upper bound < / = 0.833.

Study SERES-013 was an open-label study that enrolled subjects from SERES-012 who had a CDI recurrence within 8 weeks after treatment (Cohort 1) and *de novo* subjects with rCDI (Cohort 2). The study duration for both cohorts was approximately 27 weeks, including a 3-week screening period, a primary efficacy assessment period of 8 weeks after treatment, and a 16-week follow-up period. The primary role of SERES-013 was to ensure that the Applicant provided a minimum safety database of 300 who received the 3-day regimen of VOWST. The continued assessment of efficacy was an added advantage, but without a placebo control the success criterion used for SERES-012 was not applicable. Efficacy was evaluated descriptively as a rate of recurrence of CDI, using the same case definition of CDI recurrence as SERES-004. CDI recurrence rates were reported for both cohorts at Weeks 8, 12, and 24 after treatment.

Cohort 1 was composed of 29 subjects who experienced per-protocol rCDI within 8 weeks of completing treatment with VOWST 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]). Of the 29 subjects, 4 subjects (13.8%; 95% CI: 3.9, 31.7) had CDI recurrence up to Week 8, all of which were observed recurrences, not imputed.

Cohort 2 was composed of 234 subjects and was designed to examine safety and tolerability in adult subjects who received VOWST 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). Of the 234 subjects, 19 subjects (8.1%; 95% CI: 5.0, 12.4) had CDI recurrence up to Week 8, of which 12 (5.1%) subjects had observed recurrences and 7 (3.0%) subjects had imputed recurrences (4 early terminations; 3 with missing component). Up to Week 12, 23 subjects (9.8%; 95% CI: 6.3, 14.4) had CDI recurrence, of which 14 (6.0%) subjects had observed

recurrences and 9 (3.8%) subjects had imputed recurrences (5 early terminations; 4 with missing component).

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

Supportive Clinical Studies (SERES-004, SERES-005, SERES-001)
Study SERES-004 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study. The study enrolled 89 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 VOWST [1×10^8 spore equivalents (SporQs)] or matching placebo and stratified by age (<65 years, ≥65 years). Subjects received a single dose of VOWST 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 antibacterial treatment were eligible to enroll. The primary efficacy endpoint was recurrence of CDI by Week 8, evaluated through either a Polymerase Chain Reaction (PCR) test or a toxin test, among the Intent-to-Treat (ITT) population. The assumed CDI recurrence rate in the placebo arm was 60% and 30% in the VOWST arm. The efficacy success criterion (lower bound of the 95% CI of the RR ratio (placebo/VOWST) of 1.2) was not met.

Study SERES-005 was a Phase 2 open-label extension study and enrolled 72 adults ≥18 years of age with rCDI, with 34 subjects from SERES-004 who had a CDI recurrence within 8 weeks of treatment and 38 *de novo* subjects, who were enrolled through expanded access. The study was subsequently amended to permit enrollment of 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, were followed weekly through the 8-week efficacy period and followed up for safety through Week 24. Available safety data did not indicate any unusual or new signals. The most common treatment emergent adverse event (TEAE) by MedDRA PT was diarrhea (27.8%). This study was terminated early once it was determined, based on top-line data, that SERES-004 did not meet success criteria for efficacy.

Study SERES-001 was an open-label non-IND study that evaluated one- and two-day regimens of an earlier formulation of VOWST in two parts in a total of 30 adults aged 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. CDI recurrence was defined differently than in the 4 later studies, as >3 unformed bowel movements in a 24-hour period, and the presence of *C. difficile* in the stool could be confirmed by toxin or PCR testing. In addition, efficacy was presented in terms of the absence of CDI recurrence during the 8 weeks after treatment (i.e., clinical response). Fifteen adults in Part 1 received VOWST (mean dose of 1.7×10^9 spore equivalents (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 $1x10^8$ 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. Clinical response was observed in 26 of the 30 (86.7%) subjects. The most common TEAEs by PT 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. No deaths occurred.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for one foreign and three domestic Clinical Investigators (CI) who participated in the conduct of Protocol SERES-012. The inspections did not reveal any substantiative issues that impacted the data submitted in this original BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In accordance with §21 Code of Federal Regulations (CFR) 601.27 (d) any product for an indication for which Orphan Drug Designation (ODD) is granted is exempt from pediatric studies under the Pediatric Research Equity Act (PREA). As the initial BLA submission for SER-109 is to support an indication covered by its ODD, an agreed upon initial pediatric study plan is not required for BLA submission. Therefore, the BLA is exempt from PREA requirements.

6. Safety and Pharmacovigilance

Safety data were collected from SERES-012/SERES-013 with 349 unique subjects who received the 3-day regimen of VOWST and from 111 unique subjects who received a 1-day regimen of SER-109, in SERES-004 and SERES-005, which were considered as supportive evidence. The majority of the safety database came from the open-label extension study, SERES-013 (n=259). Safety data from SERES-012/SERES-013 and SERES-004/SERES-005, were analyzed in an integrated summary of safety (ISS).

In SERES-012, the most common adverse reactions (defined as adverse events (AE) [inclusive of solicited and unsolicited] assessed as definitely, possibly, or probably related to SER-109 by the investigator) reported by ≥ 5% VOWST 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%) VOWST recipients and 11 (12.0%) placebo recipients with most resolving within days and none being 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 out to 6 months after treatment. SAEs using diary cards were collected for 7 days after treatment.

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 VOWST recipients and 20.7% (19/92) of SERES-012 placebo recipients reported at least one SAE within 6 months post first dose of investigational product. Across SERES-004 and SERES-005, 17.1% (19/111) of VOWST 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.

With regard to AESIs, in the SERES-012/SERES-013 integrated dataset, there were 3 events of bacteremia and 4 events of sepsis (bacterial sepsis, sepsis, or urosepsis) in 7 subjects. None of these AESIs were considered related or possibly related to VOWST. In SERES-012/SERES-013, 8.0% of VOWST 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.

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). Neither of the subjects with sepsis had an organism isolated from blood cultures and were not considered related to the study drug.

The most common adverse reactions (reported in ≥5% of subjects and more frequently observed in VOWST recipients) were abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%), and diarrhea (10.0%). The safety review revealed imbalances of UTIs, and fatalities between the VOWST groups and corresponding placebo groups. The imbalance in UTIs was likely due to confounding factors (i.e., more females in the VOWST arm compared to the placebo arm and 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. Nonetheless, the pharmacovigilance plan includes UTI as an important potential risk for monitoring.

There were 11 VOWST recipients with fatal TEAEs among the 349 VOWST recipients (3.2%) in SERES-012/-013 (3.2%) and 5 VOWST recipients with fatal TEAEs in SERES-004/-005 (4.5%) compared to 0% in the corresponding placebo recipients. 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 VOWST.

A total of 16 deaths occurred, and they were all in VOWST recipients. Time to death varied widely (from Study Day 5 to Study Day 164). Most deaths (75.0%) occurred in the uncontrolled studies SERES-013 and SERES-005. Although none of the deaths were considered to be related to VOWST by study investigators and the narratives provided to the BLA describe alternative causal factors (i.e., acute events, progression of pre-existing conditions, CDI recurrence), the lack of a comparator arm and presence of confounders limit a definitive assessment of causality.

Pharmacovigilance

The Applicant submitted a pharmacovigilance plan for SERES. There are no important identified risks associated with the product and post-marketing requirements or commitments are not being sought at the time of licensure. One potential risk includes urinary tract infection (UTI), although there were confounding factors that might have contributed to the imbalance. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: AEs 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:

    - The Applicant will submit all SAEs, regardless of expectedness, and all UTIs, regardless of seriousness, as expedited (15-day) reports to FAERS.

    - In the narrative summary of periodic safety reports, the Applicant will include aggregate analysis and assessment for: SAEs, UTIs, AEs (regardless of seriousness) in individuals who receive SER-109 while pregnant or lactating, and in individuals who are <18 years of age.

- Voluntary sponsor study: The Applicant plans to conduct a General Safety Surveillance study using integrated administrative claims and electronic health records (EHR) data from large U.S. healthcare database(s). The study design will include a comparator arm (standard of care treatment for rCDI).

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy or safety-related postmarketing requirement study. There is no safety-related postmarketing commitment study for this product.

7. Labeling

The proposed proprietary name, VOWST, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on November 3, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on November 14, 2022. On January 12, 2023, the Applicant was advised that their proposed proper name suffix was found unacceptable. In an email dated February 9, 2023, the Applicant requested an FDA-generated suffix, and, on March 31, 2023, a suffix was provided for the proper name: fecal microbiota spores, live-brpk.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Package Insert (PI), package and container labeling on March 8, 2023, and found them acceptable from a promotional and comprehension perspective. Comments were provided on the package and container labels.

8. Advisory Committee Meeting

A determination was made that an Advisory Committee meeting was not required for this product since there were no major safety or effectiveness issues to be discussed.

9. Other Relevant Regulatory Issues

On October 25, 2022, FDA granted priority review designation to this BLA.

10. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Review Committee recommends approval of VOWST for the labeled indication and usage based on a review of the clinical and product-related data submitted in the original BLA.

b. Benefit/Risk Assessment

The Applicant has submitted data to support the safety and effectiveness of VOWST. The Review Committee agrees that the risk/benefit balance for VOWST is favorable and supports approval for use in adults 18 years of age and older.

c. Recommendation for Postmarketing Activities

The review committee agrees with the pharmacovigilance activities in the Applicant's proposed pharmacovigilance plan, which includes enhanced pharmacovigilance for all SAEs and all UTIs, and a voluntary postmarketing study for general safety surveillance using integrated administrative claims and EHR data from large U.S. healthcare database(s).