Administration of SER-109, an Investigational Microbiome Therapeutic to Prevent Recurrent *Clostridioides difficile* Infection (CDI)

ICD-10 Coordination and Maintenance Committee Meeting
March 7-8, 2023

Background on SER-109

- **Description**: SER-109 is a novel investigational microbiome therapeutic administered to reduce recurrent *C. diff* infection (CDI). SER-109 is a consortium of purified Firmicutes bacteria spores—a dominant component of the healthy microbiome—from donor samples.

- **Approval status**: On October 26, 2022, the FDA accepted the BLA for SER-109 and provided a PDUFA action date of April 26, 2023. In 2015, the FDA granted SER-109 Orphan Drug Designation and Breakthrough Designation for the treatment of CDI.

- **Naming convention**: Subject to FDA approval, the trade name for the product SER-109 will be finalized.

- **New Technology Add-on Payment (NTAP) application pending**: A New Technology Add-on Payment (NTAP) application for SER-109 was submitted and presented at the Town Hall for the FY 2024 consideration.

- **Mechanism of action**: SER-109 does not have the same or similar mechanism of action as any currently approved treatment for CDI. SER-109 prevents recurrent CDI by repairing the microbiome by replenishing Firmicutes bacteria.

SER-109 indications, usage, and documentation

- **Indications and usage**: SER-109 is part of a two-pronged approach for treatment of recurrent CDI—first antibiotics to kill toxin-producing bacteria, followed by SER-109, which repairs the microbiome and thereby inhibits *C. diff* spore germination and bacterial replication.

- **Dosing and route of administration**: SER-109 is administered orally to patients with recurrent CDI who first completed a course of prescribed antibiotics. The proposed dose is 4 capsules taken once daily on an empty stomach before the first meal of the day for 3 consecutive days. Each capsule contains a minimum of 1x10^6 spore colony-forming units.
  - One day before the first dose, administer 10 oz of magnesium-citrate, or based on medical judgment, 250 mL polyethylene glycol electrolyte solution to reduce residual antibiotics in the gastrointestinal tract.
  - The recommended dosage and administration are subject to final FDA approval.

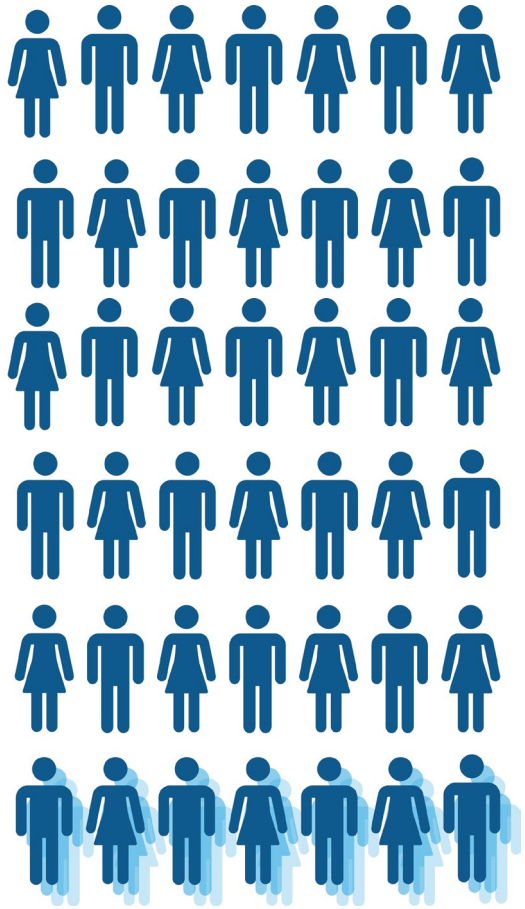
- **Medical record documentation**: Documentation would be found in the progress notes and medication administration record (MAR). While some patients with recurrent CDI may be hospitalized and receive SER-109 in the inpatient setting, for the majority of cases, SER-109 is a pharmacy-dispensed product in the outpatient setting.

- **Administration**: 525 individuals have had SER-109 exposures as of November 17, 2022

- **Adverse events (AEs)**: AEs remained consistent across clinical trials for SER-109, even when dosage amount increased from Phase II to Phase III. AEs were primarily gastrointestinal and mild to moderate in nature.

Recurrent *C. difficile* infection (CDI) is a significant unmet medical need

- **Infectious disease caused by toxin-producing bacteria, resulting in diarrhea, abdominal pain, fever, and nausea**
- **Leading cause of hospital-acquired infection in the U.S.**
  - **~453K** cases of primary CDI within the U.S. each year
  - Nearly **170K** episodes rCDI per year (100K episodes of first recurrence; ~70K episodes of 2+ recurrences)
  - Estimated **~$5.4B** in CDI healthcare burden each year
  - Each CDI patient results in **~$34,000** in direct healthcare expenses per year; substantial additional indirect costs



Nearly

170,000

rCDI episodes per year

OVER

20,000

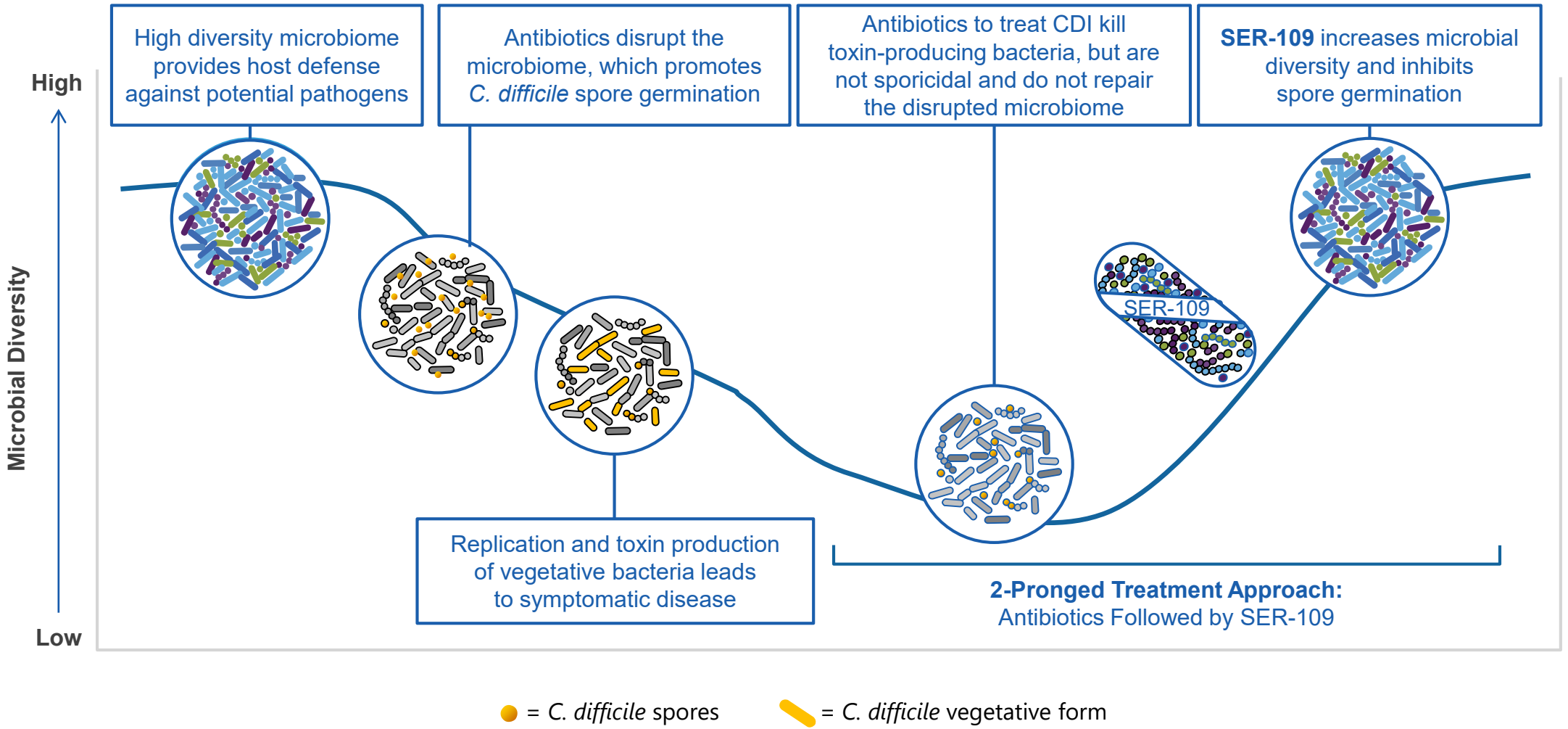
CDI deaths per year

~25% patients facing recurrence

Abbreviation: rCDI: recurrent CDI.

Sources: Desai et al., Epidemiological and economic burden of *Clostridium difficile* in the United States: estimates from a modeling approach, BMC Infectious Diseases (2016) 16:303; Guh AY et al. NEJM 2020

C. difficile infection (CDI) is a two-hit disease process requiring a two-pronged treatment approach



Adapted from: Khanna S, et al. Antibiotics 2022,11,1234.
https://doi.org/10.3390/antibiotics11091234

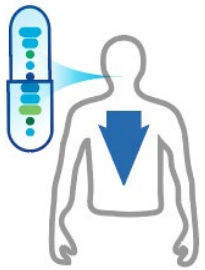
SER-109 is an investigational, spore-based microbiome therapeutic designed to break the cycle of recurrence

Scientific Rationale
SER-109 restores microbe-associated functions that prevent recurrent CDI

Granted Breakthrough Therapy and Orphan Drug Status by FDA

Firmicutes Spores Have Key Role in Preventing *C. diff* Spore Germination and Growth
Resistant to gastric acid, allowing formulation into oral capsules

SER-109



Oral formulation of Firmicutes bacteria spores

Safety Profile
Clinical trials consistently observed SER-109 to be well tolerated

Oral Dosing
4 capsules for 3 days

Mitigation of Risk in Manufacturing
Processes designed to inactivate vegetative bacteria, parasites, fungi, and viruses, thereby mitigating risk to patients beyond donor screening alone

Abbreviations: GI: Gastrointestinal.

Sources: **1.** McGovern BH, et al. Clin Infect Dis. 2021;72(12):2132-2140; **2**. McGovern BH, et al. *Clin Infect Dis* 2020;ciaa387; **3.** McChalicher Open Forum Infect Dis 2022

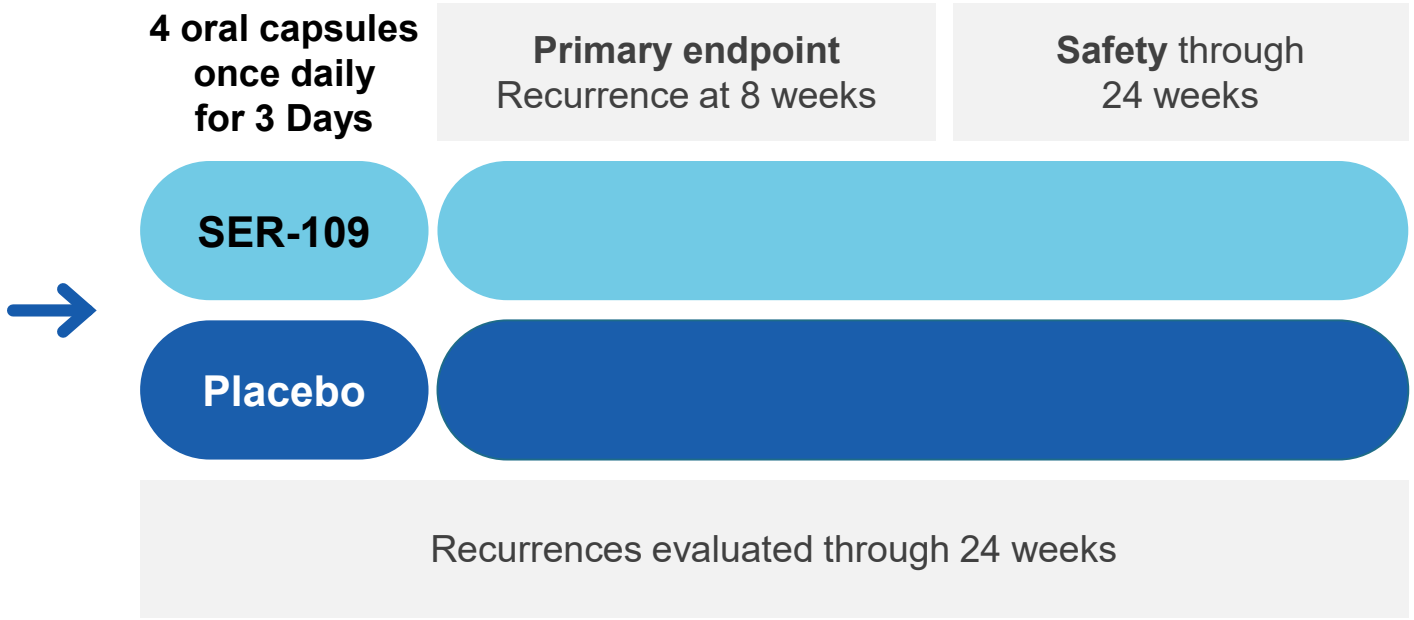
ECOSPOR III

Ph3 Double-blind, Placebo-controlled trial of SER-109 for recurrent CDI

281 adult subjects with ≥ 3 CDI episodes within 12mo* screened

182 toxin+ adult subjects with symptom resolution on antibiotics for 10–21 days enrolled

10 oz magnesium citrate administered prior to randomization to minimize residual antibiotic

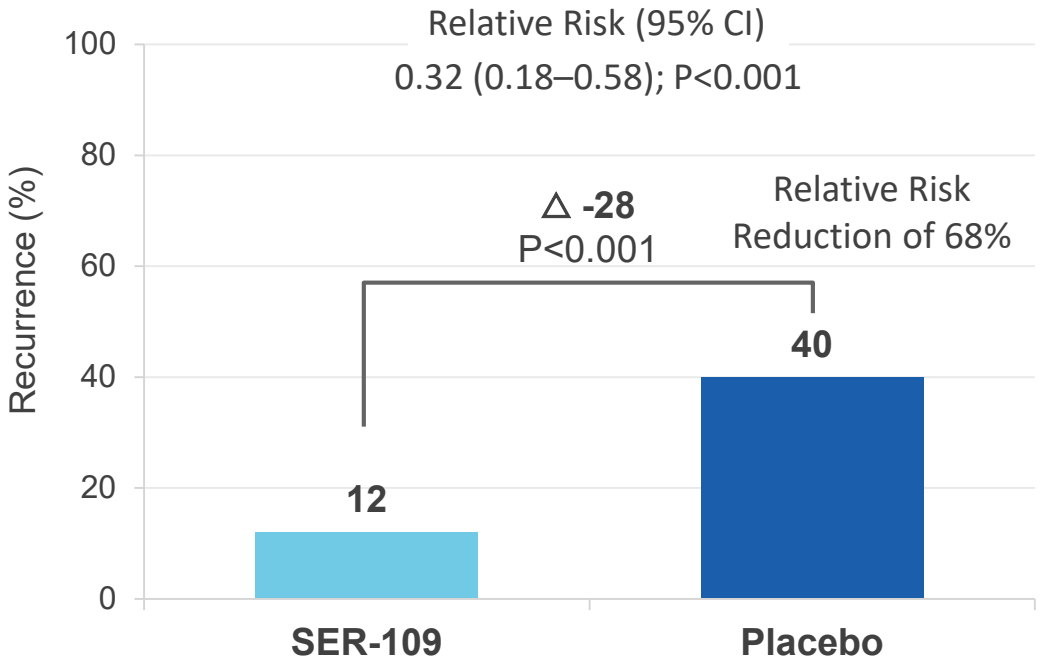


- Subjects were stratified by age and antibiotic received
- Toxin testing required at study entry and at suspected recurrence to ensure enrollment of patients with active disease and accurate assessment of endpoint
- All subjects had acute infection
- No chronic suppressive antibiotics allowed
- Subjects who recurred on study were eligible for screening for an open-label extension
- $3x10^7$ Spore Colony Forming Units (SCFU) dose per day

*Inclusive of current episode
Abbreviations: rCDI: recurrent *Clostridioides difficile* infection.
Source: Feuerstadt P, et al. N Engl J Med 2022;386:220-9

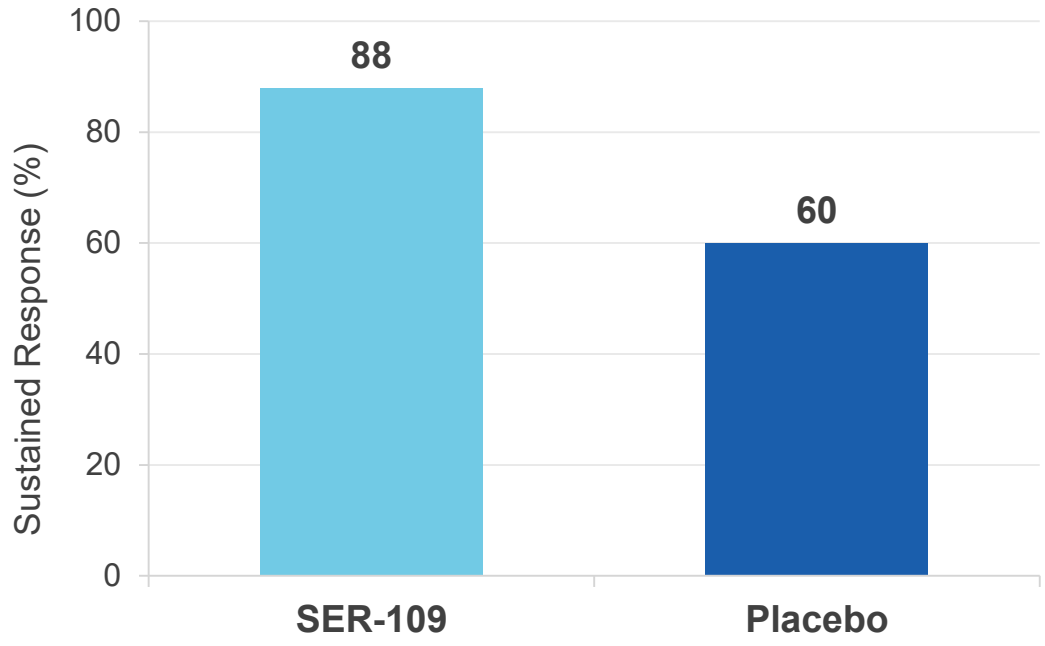
ECOSPOR III: SER-109 superior to placebo in reducing risk of rCDI at 8 weeks meeting the primary efficacy endpoint

Recurrence In ITT Population



	SER-109	Placebo
No. of Events	11	37
No. of Patients	89	93

Sustained Clinical Response*

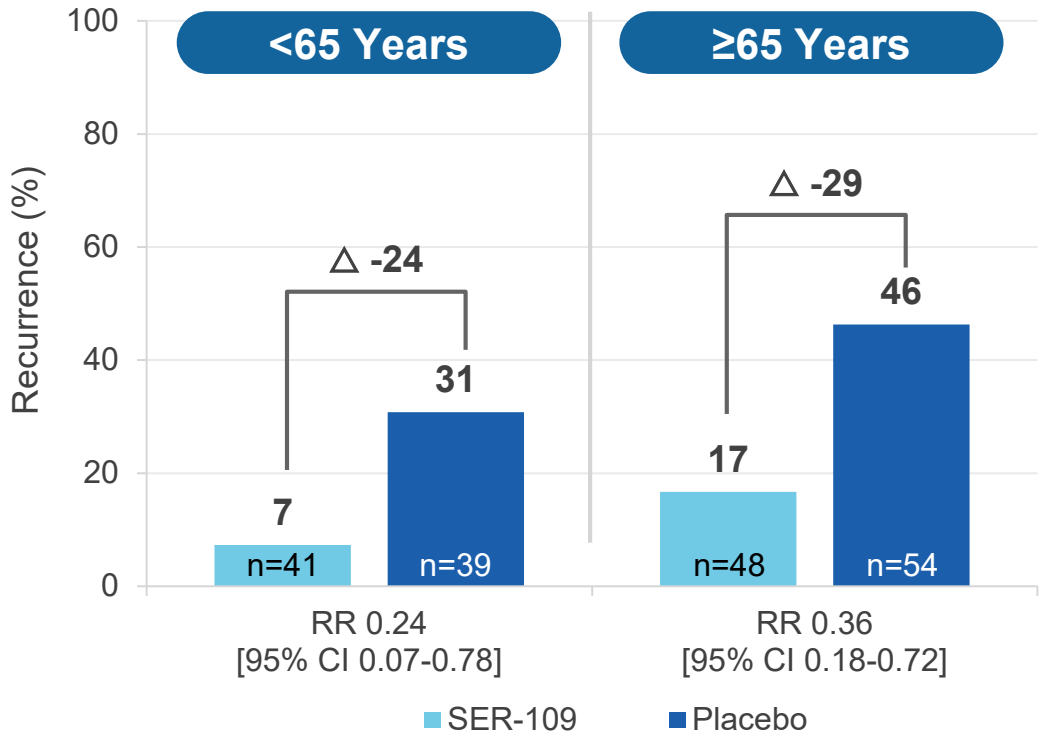


	SER-109	Placebo
No. of Events	78	56
No. of Patients	89	93

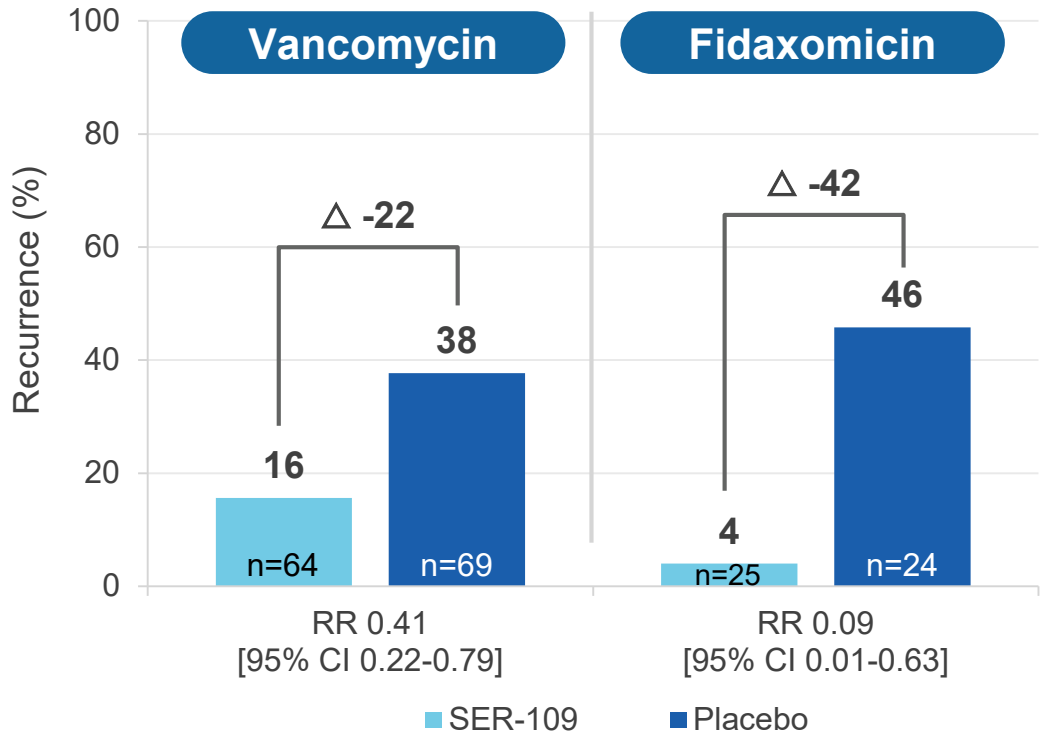
*Sustained Clinical Response = Absence of recurrence treated with antibiotics through 8 weeks
Abbreviations: CI: confidence interval; ITT: intent to treat.
Source: Feuerstadt P, et al. N Engl J Med 2022;386:220-9

Recurrence was lower at week 8 with SER-109 vs Placebo in both age-stratified groups and when stratified by antibiotic

Recurrence According to Age



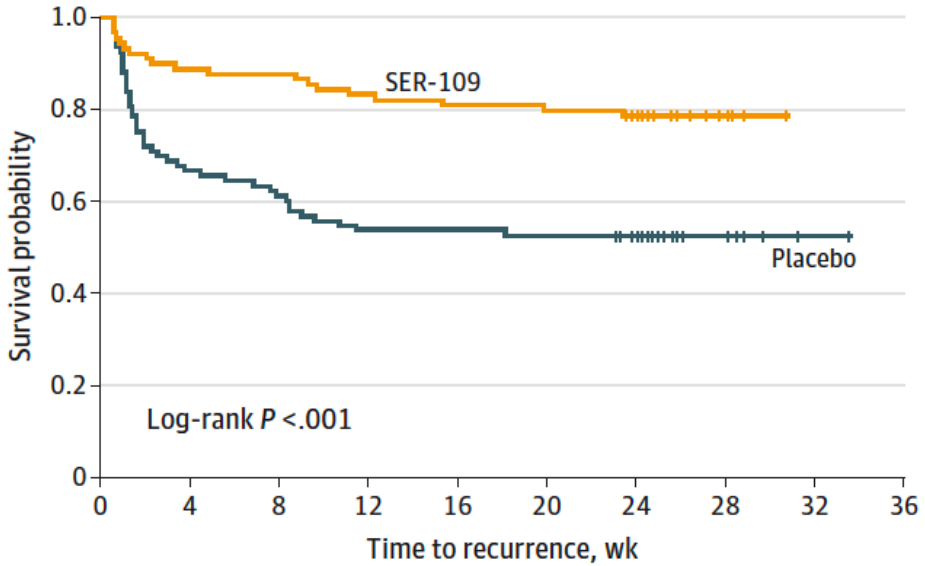
Recurrence According to Previous Antibiotic



Abbreviations: CI: confidence interval; RR: relative risk.
Source: Feuerstadt P, et al. N Engl J Med 2022;386:220-9

Time to recurrence of CDI is rapid

Survival Function for Time to CDI Recurrence: Kaplan-Meier Estimates ITT Population



No. of patients at risk

Placebo	93	62	57	50	50	49	42	6	1
SER-109	89	79	78	74	72	71	62	4	0

Majority of recurrences (65%) occurred by week 4

Data highlight importance of early microbiome repair in reducing risk of rCDI

Durability of response to SER-109 maintained through 24 weeks

In ECOSPOR III, an early reduction of recurrence is observed with SER-109 compared with placebo that is maintained over time

Abbreviations: ITT: intent to treat; wk: week.
Source: Cohen SH, et al. JAMA. 2022; doi: 10.1001/jama.2022.16476

SER-109 is shown to be well-tolerated

Summary of Subjects with Adverse Events (AEs) up to Week 24

	SER-109 (N=90) n (%)	Placebo (N=92) n (%)
Any Adverse Event (AE)	84 (93.3)	84 (91.3)
Treatment Related / Possibly Related AEs	46 (51.1)	48 (52.2)
Most Frequently Reported Treatment Related / Possibly Related AEs		
Flatulence	39 (43.3)	41 (44.6)
Abdominal Distention	28 (31.1)	27 (29.3)
Abdominal Pain	25 (27.8)	33 (35.9)
Fatigue	20 (22.2)	21 (22.8)
Constipation	15 (16.7)	10 (10.9)
Serious AEs	15 (16.7)	19 (20.7)
Serious AEs Leading to Study Withdrawal	1 (1.1)	1 (1.1)
AEs leading to Death*	3 (3.3)	0

*Three deaths occurred on the SER-109 arm, all reported as unrelated by the blinded investigator; the causes for deaths were 1) worsening of pre-existing glioblastoma; 2) subdural hematoma after a fall in a subject on anticoagulation; and 3) pre-existing atrial fibrillation with rapid ventricular response and sepsis in a subject on hemodialysis. In Subject 3, a cardiac echo was performed with ejection fraction of 15-20% and a brain natriuretic peptide was 34,999 pg/mL. Antibiotics were discontinued and blood cultures remained without growth at five days.

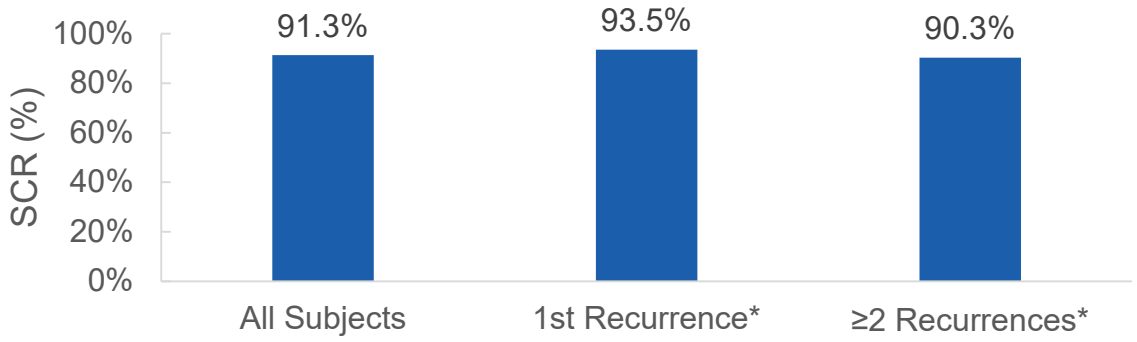
Source: Korman L, et al. DDW Annual Meeting 2021. Poster Fr572.

ECOSPOR IV reaffirms and extends safety and efficacy findings of ECOSPOR III[1]

Open-label study providing 24-week data for an additional 263 patients administered SER-109 at commercial dose to fulfill FDA request for the SER-109 safety database

• Age ≥65 years 52% • Female 68% • 1st recurrence* 29% • PCR test 26%

Sustained Clinical Response (SCR) at week 8



	All Subjects	1st Recurrence*	≥2 Recurrences*
No. of Events	240	72	168
No. of Patients	263	77	186

Sustained clinical response at 24 weeks: 227/263 (86.3%)[2]

Most frequently reported TEAEs by preferred term in ≥5% through week 8

TEAE	N=263 N (%)
Diarrhea	59 (22)
Flatulence	20 (8)
Nausea	20 (8)
Abdominal pain	18 (7)
Fatigue	12 (5)
Urinary tract infection	12 (5)
Abdominal distention	11 (4)

8 deaths reported through 24 weeks; none were deemed related or possibly related to study drug by investigators

*Not including qualifying episode.
Abbreviations: FDA: Food and Drug Administration; PCR: polymerase chain reaction; TEAE: Treatment-emergent adverse event.
Sources: **1.** Khanna S, et al. ACG Annual Meeting 2022. Oral abstract 63; **2.** Data on file.

