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Poster Fr572

24-WEEK EFFICACY AND SAFETY DATA FROM ECOSPOR-III: A PHASE 3 DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF SER-109, AN INVESTIGATIONAL MICROBIOME THERAPEUTIC FOR RECURRENT *CLOSTRIDIOIDES DIFFICILE* INFECTION

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SERES THERAPEUTICS™

Background

- *Clostridioides difficile* infection (CDI) is a two-hit process characterized by disruption of the microbiome and exposure to *C. difficile* spores. The leading risk factor for CDI is exposure to broad spectrum antibiotics, which cause collateral damage to beneficial microbes that normally reside in the GI microbiome.[1]
- Antibiotics targeted against *C. difficile* are necessary but often insufficient because they lack an effect on *C. difficile* spores that germinate within a disrupted microbiome. Thus, a sustained response is not attained in a substantial proportion of patients.[2]
- FMT studies have shown that recovery of Firmicutes bacteria is associated with a sustained clinical response, but the range of efficacy is unclear due to few controlled trials and safety concerns persist about transmission of infectious agents, which have led to hospitalizations and death.[3,4,5,6]
- SER-109, a novel investigational oral microbiome therapeutic of purified bacterial spores was developed to reduce CDI recurrence. The manufacturing processes for SER-109 are designed to inactivate potential pathogens, while enriching for beneficial Firmicutes spores, which play a central role in inhibiting the cycle of *C. difficile*.
- ECOSPOR-III, a Phase 3, double-blind, randomized trial, evaluated the superiority of SER-109 compared to placebo for treatment of patients with recurrent CDI at Week 8, the primary endpoint. SER-109 was highly effective and generally well tolerated, achieving a 68% relative risk reduction in recurrence rates compared to those treated with placebo (12.4% vs 39.8%, respectively; relative risk [RR], 0.32 [95% CI, 0.18-0.58; p<0.001 for RR<1.0; p<0.001 for RR<0.833])
- Here we report the final 24-week efficacy and safety data for ECOSPOR-III.

Methods

- Adults ≥18 years with rCDI (≥3 episodes in 12 months) were screened at 56 sites in the US and Canada.
- CDI was defined as ≥3 unformed stools/day for ≥48 hours with a positive *C. difficile* toxin assay.
- After completion of 10-21 days of vancomycin or fidaxomicin, adults with symptom resolution were randomized 1:1 to SER-109 (4 capsules daily x 3 days) or matching placebo and stratified by age (≥ or <65 years) and antibiotic received.
- Primary efficacy endpoint was CDI recurrence rate at Week 8 (recurrent toxin positive diarrhea requiring treatment); secondary efficacy endpoint included CDI recurrence at 24 weeks. Safety was evaluated up to 24 weeks after dosing.

ECOSPOR-III

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

281 adults with history of ≥2 CDI recurrences screened at 56 sites

→ 182 toxin+ subjects with symptom resolution on antibiotics for 10 to 21 days randomized after administration of 10 oz magnesium citrate to minimize residual antibiotic

→ 4 Capsules of SER-109 or Placebo Daily for 3 Days
- SER-109
- Placebo

Primary endpoint: Recurrence at 8 weeks
Safety through 24 weeks

Adult Study Participants ≥18 Years
- 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

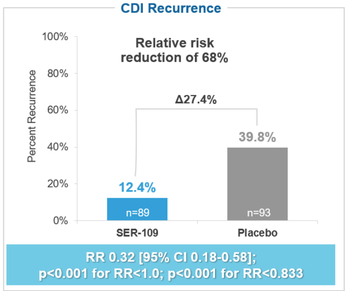
ClinicalTrials.gov Identifier: NCT03183128

Baseline Demographics (ITT Population)

Characteristic	SER-109 (N = 89)	Placebo (N = 93)
Age (yrs), mean (SD)	65.6 (16.5)	65.5 (16.7)
< 65 years, n (%)	41 (46.1)	38 (40.9)
≥ 65 years, n (%)	48 (53.9)	55 (59.1)
Sex, n (%)		
Female*	60 (67.4)	49 (52.7)
Prior antibiotic, n (%)		
Vancomycin	64 (71.9)	69 (74.2)
# prior CDI episodes, n (%)		
2	49 (55.1)	61 (65.6)
≥3	39 (43.8)	32 (34.4)
Missing	1 (1.1)	0 (0.0)
N = Population size; n = Number of Subjects.		

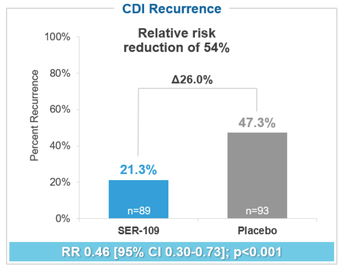
*More females were in the SER-109 than the placebo arm (p=0.0427)

SER-109 was Superior to Placebo in Reducing CDI Recurrence at Week 8



- A qualifying episode at study entry was defined as: a) ≥3 unformed bowel movements over 2 consecutive days b) a positive *C. difficile* toxin test and c) symptomatic resolution on 10-21 days of standard-of-care antibiotics
- SER-109 met the primary endpoint of superiority compared to placebo
- By the alternative metric of sustained clinical response, 87.6% of the SER-109 recipients achieved this benchmark compared to 60.2% on placebo

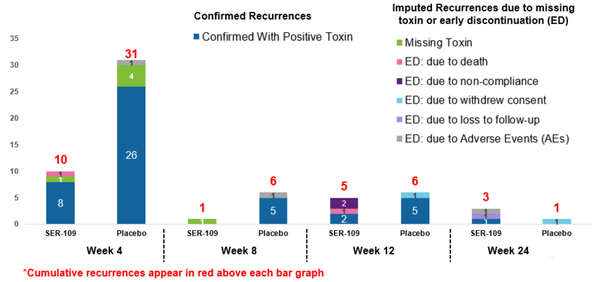
SER-109 Maintained Durable Efficacy at Week 24



The absolute risk reduction in CDI recurrence at Week 24 was similar to that observed at Week 8 (26% vs. 27.4%, respectively)

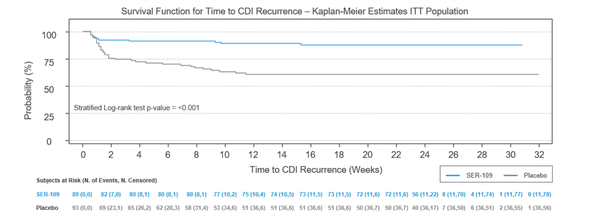
- At Week 24, recurrences occurred as follows
  - **SER-109:** 19 recurrences
    - 11 confirmed with toxin+ stool samples
    - 8 imputed as recurrences
  - **Placebo:** 44 recurrences
    - 36 confirmed with toxin+ stool samples
    - 8 imputed as recurrences

Timing of Confirmed and Imputed Recurrences Through Week 24



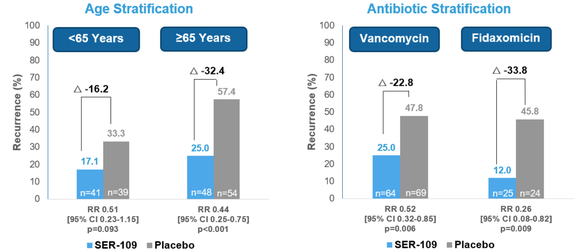
*Cumulative recurrences appear in red above each bar graph

The Natural History of Recurrent CDI Is Characterized by Rapid Recurrence: In ECOSPOR III, SER-109 Reduces Risk of Recurrence Compared with Placebo



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

At Week 24, SER-109 Demonstrated Significantly Higher Efficacy Over Placebo in Patients Aged ≥65 and Both Antibiotic Stratified Groups



Safety

Summary of Subjects with Treatment Emergent Adverse Events (TEAEs) up to Week 24

	SER-109 (N=90) n (%)	Placebo (N=92) n (%)
Any TEAE	84 (93.3)	84 (91.3)
Treatment Related/Possibly Related TEAEs	46 (51.1)	48 (52.2)
Most Frequently Reported Treatment Related/Possibly Related TEAEs		
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 TEAEs	15 (16.7)	19 (20.7)
Serious TEAEs Leading to Study Withdrawal	1 (1.1)	1 (1.1)
TEAEs leading to Death*	3 (3.3)	0

*3 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.

Treatment Emergent Adverse Events by Preferred Term Occurring in ≥5% Subjects Through Week 24

	SER-109 (N=90) n (%)	Placebo (N=92) n (%)
Flatulence	63 (70.0)	70 (76.1)
Fatigue	53 (58.9)	58 (63.0)
Abdominal distension	49 (54.4)	49 (53.3)
Abdominal pain	46 (51.1)	56 (60.9)
Constipation	28 (31.1)	22 (23.9)
Decreased appetite	26 (28.9)	34 (37.0)
Diarrhea	22 (24.4)	20 (21.7)
Chills	21 (23.3)	22 (23.9)
Nausea	16 (17.8)	30 (32.6)
Urinary tract infection	8 (8.9)	1 (1.1)
Vomiting	3 (3.3)	10 (10.9)
Clostridioides difficile colitis	1 (1.1)	8 (8.7)

Conclusions

- In ECOSPOR III, SER-109, an oral investigational live microbiome therapeutic, significantly reduced recurrence compared to placebo over 24 weeks after dosing with an observed safety profile comparable to placebo.
- By enriching for Firmicute spores, SER-109 met the primary endpoint of reducing CDI while mitigating risk of transmitting infectious agents.
- SER-109 may represent a potential paradigm shift in the clinical management of patients with recurrent CDI.
- An open-label study for patients with ≥1 episode of CDI is currently enrolling (ClinicalTrials.gov Identifier: NCT03183141).

References

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