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Poster 58 E

ECOSPOR-III: A PHASE 3 DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF SER-109 AN INVESTIGATIONAL MICROBIOME THERAPEUTIC FOR TREATMENT OF RECURRENT CLOSTRIDIOIDES DIFFICILE INFECTION (rCDI)

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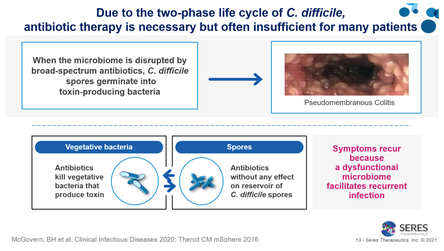
SERES THERAPEUTICS™

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]
- ECOSPOR-III, a Phase 3 double-blind placebo-controlled trial, evaluated SER-109, an oral investigational microbiome therapeutic composed of live purified Firmicutes spores for treatment of patients with recurrent CDI.
- Here we report the 8-week and 12-week efficacy and safety data for ECOSPOR-III.

METHODS

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

References:
1. McGovern BH, Ford CB, Henn MR, et al. SER-109, an Investigational Microbiome Drug to Reduce Recurrence after Clostridioides difficile infection: Lessons Learned from a Phase 2 Trial. Clin Infect Dis 2020.
2. Theriot CM, Bowman AA, Young VB. Antibiotic-Induced Alterations of the Gut Microbiota Alter Secondary Bile Acid Production and Allow for Clostridium difficile Spore Germination and Outgrowth in the Large Intestine. mSphere 2016;1.
3. Jiang ZD, Jenq RR, Ajami NJ, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: A randomized clinical trial. PLoS One 2018;13:e0205064.
4. Tariq R, Pardi DS, Bartlett MG, Khanna S. Low Cure Rates in Controlled Trials of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2019;68:1351-8.
5. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med 2019;381:2043-50.
6. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely

RESULTS

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

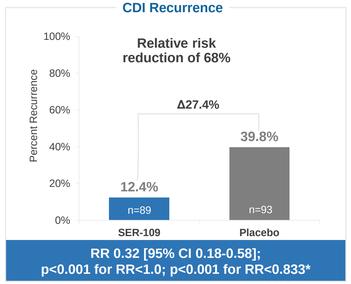
Baseline Demographics (ITT Population)

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)

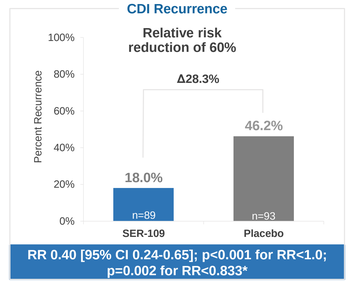
SER-109 was Superior to Placebo in Reducing CDI Recurrence at Week 8



- 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

*null hypothesis was tested sequentially at the 1-sided 0.025 α-level; if the relative risk (RR) ≥1.0 was significant then RR ≥ 0.833 was tested

SER-109 Maintained Durable Efficacy at Week 12



- The absolute risk reduction in CDI recurrence at Week 12 was similar to that observed at Week 8 (28.3% vs. 27.4%, respectively)
- Additionally, SER-109 led to lower CDI recurrence rates at Week 12 when analyzed by age strata (<65 years, P=0.049; ≥65 years, P<0.001, respectively) or antibiotic (vancomycin, P=0.003; fidaxomicin, P=0.003, respectively)

*null hypothesis was tested sequentially at the 1-sided 0.025 α-level; if the relative risk (RR) ≥1.0 was significant then RR ≥ 0.833 was tested

Safety

Summary of Subjects with Treatment Emergent Adverse Events up to Week 8

	SER-109 (N=90) n (%)	Placebo (N=92) n (%)
Any AE	84 (93.3)	84 (91.3)
Study drug related or possibly related AEs	46 (51.1)	48 (52.2)
Most frequently reported treatment related/possible related TEAEs		
Flatulence	63 (70.0)	70 (76.1)
Fatigue	53 (58.9)	58 (63.0)
Abdominal Distention	49 (54.4)	49 (53.3)
Abdominal Pain	46 (51.1)	56 (60.9)
Constipation	28 (31.1)	22 (23.9)
Serious TEAEs	7 (7.8)	15 (16.3)
Serious AEs leading to study withdrawal	0	1
TEAEs leading to death*	2	0

*3 deaths occurred on the SER-109 arm, all reported as unrelated by the blinded investigator; one patient died within the 8-week period after dosing. 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.

CONCLUSIONS

- In ECOSPOR III, SER-109, an oral investigational live microbiome therapeutic, significantly reduced recurrence compared to placebo at 8 and 12 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).