IDWeek 2021
Poster #639

TIME TO RECURRENCE OF *CLOSTRIDIOIDES DIFFICILE* INFECTION (rCDI) IS RAPID FOLLOWING COMPLETION OF STANDARD OF CARE ANTIBIOTICS: RESULTS FROM ECOSPOR-III, A PHASE 3 DOUBLE-BLIND, PLACEBO-CONTROLLED RANDOMIZED TRIAL OF SER-109, AN INVESTIGATIONAL MICROBIOME THERAPEUTIC

T. Louie[1], M. Sims[2], R. Nathan[3], S. O'Marro[4], P. Kumar[5], E. Wang[6], R. Stevens[6], K. Brady[6], B. McGovern[6] and L. von Moltke[6]

[1]University of Calgary, Canada, [2]Beaumont Health, Michigan, [3]Mountain View Hospital, Nevada, [4]Springfield Clinic, Illinois, [5]Georgetown University Hospital, Washington DC, [6]Seres Therapeutics, Massachusetts

SERES THERAPEUTICS™

aimmune™ THERAPEUTICS
A Nestlé Health Science Company

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 tract.[1]
- Although *C. difficile* targeted antibiotics rapidly kill vegetative toxin-producing bacteria, they do not eradicate the metabolically-inactive *C. difficile* spores that germinate in a disrupted microbiome. Thus, a sustained response is not attained in a substantial proportion of patients who continue to experience recurrent CDI.[2]
- SER-109, a novel investigational oral microbiome therapeutic of purified bacterial spores was developed to reduce CDI recurrence.
- In ECOSPOR-III, a Phase 3, double-blind, randomized trial, SER-109 was superior to placebo in reducing CDI recurrence at Week 8, the primary endpoint.[3] SER-109 achieved 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]). The observed safety profile of SER -109 was comparable to placebo.[4]
- The natural history of CDI recurrence after antibiotics may be helpful to understand the window of opportunity for microbiome repair.
- Here we describe results for the secondary endpoint, time to recurrence, in this well-characterized study population.

ECOSPOR-III
Ph3 Double-blind, Placebo-Controlled Trial of SER-109 for Multiply Recurrent CDI

281 adult subjects ≥18 years 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 stratified by age and antibiotic received

4 Capsules once daily for 3 Days

	Primary endpoint	Safety
SER-109	Recurrence at 8 weeks	through 24 weeks
Placebo		

Recurrences evaluated 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

Methods

- 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.
- Efficacy analyses were performed on the intent-to-treat (ITT) population which included all randomized patients analyzed according to intended assignment, rather than drug received. Safety was assessed in the as-treated population.
- For the primary endpoint, subjects who were lost-to-follow-up, terminated from the study prematurely, or died without a CDI recurrence before 8 weeks after treatment were designated in the protocol as having recurrence for the primary analysis.
- Confirmed recurrence was defined as ≥ 3 unformed stools/day for ≥ 48 hours, ± *C. difficile* stool toxin test,* and an investigator decision to treat.
- Time to CDI recurrence was analyzed using observed data and Kaplan-Meier methods. Data were not imputed for subjects lost to follow-up or discontinued from study in order to have a better estimate of the natural history of disease.
- Subjects who did not have a CDI recurrence were censored on the date of study completion, study discontinuation or death.

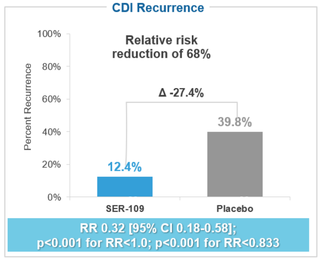
* Six subjects did not have *C. difficile* stool toxin test but had ≥3 unformed stools/day for ≥48 hours coupled with antibiotic treatment for recurrent CDI.

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.		

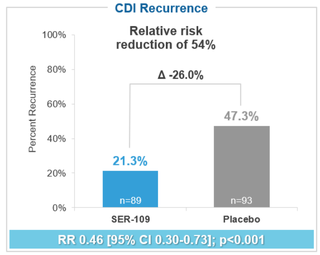
* Demographic characteristics and CDI risk factors were balanced by treatment arm although more females were in the SER-109 arm

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
- Number Needed to Treat for SER-109 = 3.6

SER-109 Maintained Durable Efficacy at Week 24

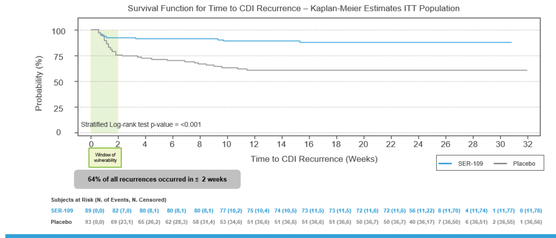


The absolute risk reduction in CDI recurrence at Week 24 was similar to that observed at Week 8 (26% vs. 27.4%, respectively)

- At Week 24, recurrences occurred as follows
  - **SER-109:** 19 recurrences
    - 11 confirmed (9 toxin+ stool sample)
    - 8* imputed as recurrences
  - **Placebo:** 44 recurrences
    - 36 confirmed (31 toxin+ stool samples
    - 8* imputed as recurrences

* Lost-to-follow-up, terminated from the study prematurely, or died without a CDI recurrence were designated in the protocol as having recurrence for the primary analysis.

The Natural History of Recurrent CDI Is Characterized by Rapid Recurrence



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

ECOSPOR III – Recurrence events over 30 days and 24 weeks

Table: Number of Recurrence Events Observed in Subjects with rCDI Through 30 days

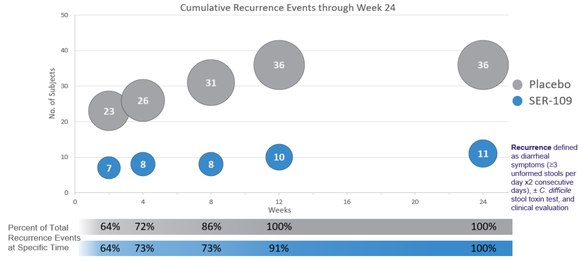
Day	5	10	15	20	25	30
SER 109 N = 8	4	3	0	0	1	0
Placebo N = 26	5	13	5	1	1	1
Total N = 34	9	16	5	1	2	1

Table: Specific Time of Recurrence Events Observed in 47 Subjects with rCDI Through 24 weeks

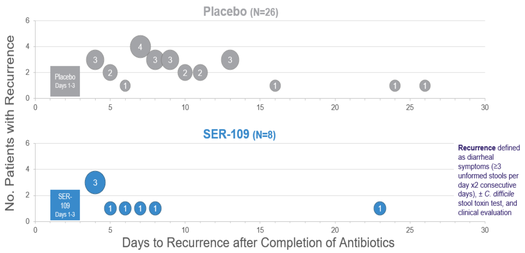
Week	1	2	4	8	12	24	Cumulative Total
SER 109 N = 89	6	1	1	0	2	1	11 (12.7%) *
Placebo N = 93	10	13	3	5	5	0	36 (38.4%)
Combined N = 182	16	14	4	5	7	1	47

N represents total number of subjects in randomized arms
* P < 0.001 compared to Placebo

CDI recurrence is rapid following antibiotic discontinuation although events were observed beyond 8 weeks



CDI recurrence is rapid after antibiotic discontinuation with most events occurring within 1 to 2 weeks



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 eiection fraction of 15-20% and a brain natriuretic peptide was 34.999 pg/mL. Antibiotics were

Conclusions

- In ECOSPOR III, SER-109, an oral investigational live microbiome therapeutic, significantly reduced recurrence compared to placebo at 8 weeks, meeting the primary endpoint, and maintained durability over 24 weeks after dosing, with an observed safety profile comparable to placebo.
- Two-thirds of all recurrences occurred within 14 days of antibiotic completion highlighting the potential need for rapid repair of the disrupted microbiome.
- However, the significant number of late recurrences in the placebo arm also highlights that rCDI trials with shorter periods of follow-up after treatment completion may underestimate recurrences.
- This two-pronged approach, of antibiotics followed by SER-109, may represent a new paradigm in the 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

1. McGovern BH, Ford CB, Henn MR, Pardi DS, Khanna S, Hohmann EL, et al. SER-109, an Investigational Microbiome drug to Reduce recurrence AFTER *Clostridioides difficile* infection: Lessons learned from a Phase 2 trial. Clinical Infectious Diseases. 2020;72(12):2132–40.
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(1).
3. Berenson C, Korman L, Kraft CS, Sims M, Lashner B, Wang EE, Brady K, Ford CB, O'Brien EJ, Lombardo MJ. 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. Presented at Society of Hospital Medicine; May 3-7, 2021. Plenary session.
4. Korman L, Lashner B, Kraft C, Sims M, Wang EE, Brady K, Ford CB, Lombardo MJ, Litcofsky KD, Mahoney JC, McChalicher CW. Fri572. 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 treatment of recurrent *Clostridioides difficile* infection. Gastroenterology. 2021 May 1;160(6):S-368.

Acknowledgement

We would like to acknowledge the contribution of Seun Makinde, MD of Seres Therapeutics Medical Affairs for preparation and review of this scientific poster.

The authors are grateful to the patients and investigators who participated in the ECOSPOR III trial.