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Characterization of Ribotypes Among Study Participants in a Phase 3 Trial of Investigational Microbiome Therapeutic SER-109 to Reduce Recurrent Clostridioides difficile Infection (rCDI)

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BACKGROUND

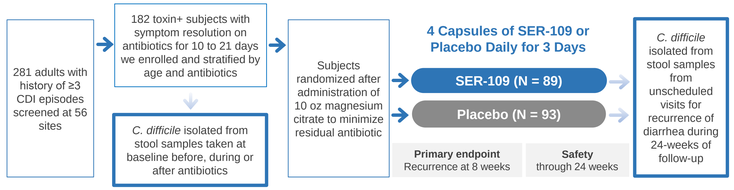
- *Clostridioides difficile* infection (CDI) is a two-hit process characterized by disruption of the microbiome and exposure to *C. difficile* spores. The leading risk factor for CDI is exposure to broad spectrum antibiotics, which cause collateral damage to beneficial microbes that normally reside in 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]
- Previously, we reported that SER-109, an investigational microbiome therapeutic comprised of purified Firmicutes bacterial spores, was superior to placebo in reducing recurrence of CDI up to 8 weeks (12.4% vs 39.8%, respectively; RR, 0.32 [95% CI, 0.18-0.58; P<0.001for RR<1.0; P<0.001 for RR<0.833]) in a Phase 3 study. [3]
- Typing of *C. difficile* strains from infections can provide insight into CDI disease and epidemiology, but strain typing data are usually not available to assess whether recurrence is due to relapse (infection by the same strain) or reinfection (infection by a new strain). Relapse is thought to be the primary driver of early recurrence, although reinfection is also observed.[4]
- Here we sought to evaluate the distribution of *C. difficile* ribotypes and whether CDI recurrence was related to relapse or reinfection in a trial of subjects with multiply rCDI.

STUDY DESIGN

ECOSPOR III

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

Figure 1. Study design



METHODS

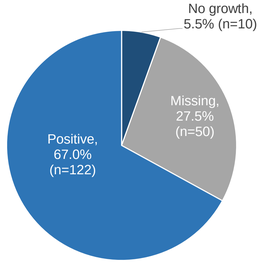
- Selective media were used to isolate *C. difficile* from baseline stool samples and from stool samples from unscheduled visits for recurrence of diarrhea during 24-weeks of follow-up. The subject's baseline sample was taken prior to randomization and without regard to whether the subject had started or completed the SOC antibiotic treatment.
- *C. difficile* was isolated from ethanol treated stool using *C. difficile* selective agar (Cycloserine-cefoxitin-fructose agar with and without horse blood) and enrichment culture (Cycloserine Cefoxitin Mannitol Broth with Taurocholic Acid Lysozyme and Cysteine). One *C. difficile* isolate was saved per stool sample.
- *C. difficile* strains were typed by PCR ribotyping as previously described by Stubbs, et al. as modified by Svenungsson, et al.[5,6] (Performed by R. Goering, PhD, Creighton University)
- In a post-hoc analysis, we evaluated the distribution and prevalence of ribotypes in study subjects and determined whether the ribotype at recurrence was indicative of relapse (identical ribotype) or reinfection (different ribotype) up to 24 weeks.

RESULTS

Baseline Ribotype Prevalence (ITT Population)

- 122 subjects (67.0%) yielded positive cultures at baseline enabling ribotyping of isolates, while 10 (5.5%) yielded no growth, and 50 (27.5%) subjects did not contribute a sample for processing (Fig 2).
- 33 different ribotypes were identified at baseline (Table 1).
- 020/014 was the most common ribotype identified in 18.9% of subjects at baseline (Table 1).
- 'Hypervirulent' ribotypes 027 and 078 (078/126) were identified in 15.6% of subjects at baseline (Table 1).

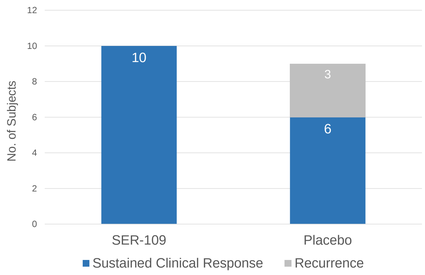
Figure 2. Baseline stool culture results (N=182 subjects)



Clinical Response in 'Hypervirulent' Ribotypes

- Of the 122 subjects with a ribotype isolated at baseline, a total of 19 patients had a 'hypervirulent' strain (027 or 078/126). None of the SER-109 treated patients recurred (Fig 3).

Figure 3. Clinical response in subjects with 'hypervirulent' ribotypes



Recurrence = defined as recurrent C. *difficile* toxin positive diarrhea requiring treatment; Sustained clinical response = subjects who did not meet criteria for recurrent CDI

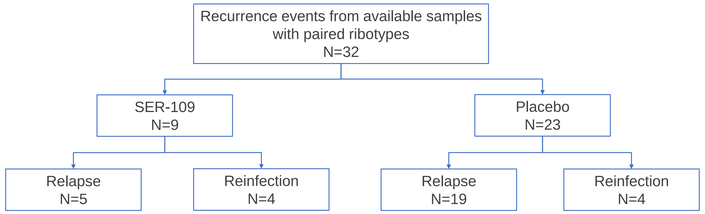
Table 1. Different ribotypes identified at baseline from positive samples (n=33)

Category	SER-109 (N=62) n(%)	Placebo* (N=60) n(%)	Total (N=122) n(%)
014/020	10 (16.1)	13 (21.7)	23 (18.9)
027	8 (12.9)	5 (8.3)	13 (10.7)
056	6 (9.7)	6 (10.0)	12 (9.8)
002	5 (8.1)	5 (8.3)	10 (8.2)
106	5 (8.1)	4 (6.7)	9 (7.4)
078 or 078/126	2 (3.2)	4 (6.7)	6 (4.9)
072	4 (6.5)	1 (1.7)	5 (4.1)
012	2 (3.2)	2 (3.3)	4 (3.3)
057	2 (3.2)	2 (3.3)	4 (3.3)
013	1 (1.6)	2 (3.3)	3 (2.5)
054	2 (3.2)	1 (1.7)	3 (2.5)
015	1 (1.6)	2 (3.3)	3 (2.5)
007	0	2 (3.3)	2 (1.6)
018	2 (3.2)	0	2 (1.6)
019	0	2 (3.3)	2 (1.6)
053	2 (3.2)	0	2 (1.6)
081	1 (1.6)	1 (1.7)	2 (1.6)
131	1 (1.6)	1 (1.7)	2 (1.6)
005	1 (1.6)	0	1 (0.8)
010	0	1 (1.7)	1 (0.8)
011	0	1 (1.7)	1 (0.8)
029	0	1 (1.7)	1 (0.8)
036	1 (1.6)	0	1 (0.8)
075	0	1 (1.7)	1 (0.8)
087	1 (1.6)	0	1 (0.8)
095	1 (1.6)	0	1 (0.8)
103	0	1 (1.7)	1 (0.8)
111	1 (1.6)	0	1 (0.8)
207	1 (1.6)	0	1 (0.8)
248	0	1 (1.7)	1 (0.8)
339	1 (1.6)	0	1 (0.8)
003	0	1 (1.7)	1 (0.8)
UNK	1 (1.6)	1 (1.7)	2 (1.6)

*1 subject had 2 ribotyped isolates (014/020 and 002), each from a different stool sample

Incidence of Relapse vs Reinfection for Recurrence Events with Paired Ribotypes

Figure 4. Recurrence type by treatment arm



- There were 47 recurrences observed in total in ECOSPOR III (11 in SER-109 treatment arm and 36 in placebo). Of those, paired ribotypes (isolated from baseline and recurrence stool samples) were available for comparison for a total of 32 recurrence events, including 9 in SER-109 subjects and 23 in placebo subjects (Fig 4).
- Relapses were more common in the study accounting for 75.0% (24/32) of recurrences.
- Relapse events were lower in the SER-109 arm than placebo (5 vs. 19), while reinfection events were comparable but low (4 vs. 4).

CONCLUSIONS

- In ECOSPOR III, SER-109, an oral investigational live microbiome therapeutic, significantly reduced CDI recurrence compared to placebo at 8 weeks after dosing with an observed safety profile comparable to placebo.
- Multiple ribotypes were isolated which is consistent with typically observed epidemiological studies.
- Low rates of recurrence with SER-109 observed in ECOSPOR III limit the ability to assess the impact of relapse versus reinfection; however, numerically, SER-109 demonstrated reduced rates of recurrence compared with placebo across ribotypes and protected against the dominant mode of recurrence (relapse) in patients with a history of multiply recurrent CDI.
- SER-109 represents 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).

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