TITLE: Clinical Evaluation of SER---109, a Rationally Designed, Oral Microbiome---Based Therapeutic for the Treatment of Recurrent *Clostridium difficile*

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BODY:

BACKGROUND: Fecal microbiota transplant (FMT) is highly efficacious for the treatment of recurrent *C. difficile* infection (CDI), but it has multiple liabilities, including invasive delivery, the cost and complexity of donor management, variability of the FMT preparation, and the potential to transmit pathogens. There is a critical need to identify an efficacious, orally delivered community of microbes to replace FMT and maximize utility for patients and clinicians. Seres Health, Inc. has designed SER---109, an oral Ecobiotic® ecology of commensal spores, that effectively treated *C. difficile* in mouse and hamster models.

AIMS: The aim of this Phase I/II clinical study was to characterize the safety and efficacy profile of SER---109 for the treatment of recurrent CDI. A secondary aim was to characterize the dose---response to SER---109.

STUDY DESIGN: This study was a single---arm, open---label evaluation of SER---109 in patients with recurrent CDI. The primary efficacy endpoint was the absence of recurrent CDI over the 8---week period. CDI was defined as > 3 watery bowel movements in a 24 hour period accompanied by a positive *C. difficile* test. At Week 8, patients were evaluated for symptoms of CDI and for safety, and had a *C. difficile* test performed to assess carriage. Safety was assessed by phone contact on Day 4 and Weeks 1, 2, and 4 and a physical exam on Week 24. Fecal samples were collected on Day 4 and Weeks 1, 2, 4, 8 and 24 for genomic and microbiological analysis. Inclusion criteria were: age 18---90 yrs; ≥ 3 laboratory---confirmed *C. difficile* episodes over the previous 12 months; able to take oral dosage form; life expectancy > 3 months; able to give informed consent. Exclusion criteria were: immunosuppression (acute leukemia or any allogeneic BMT; autologous BMT within 6 months; cytotoxic chemotherapy within 2 months; ANC < 1000/uL); history of IBD, IBS---D or total colectomy; liver cirrhosis; pregnancy or nursing; anticipated need for antibiotics within 6 weeks; prior FMT; admission or anticipated admission to ICU. Patients were required to be adequately controlled with antibiotics for CDI prior to receiving SER---109. On Day ---1, antibiotics were stopped and patients underwent a bowel preparation to minimize antibiotic in the GI tract and fasted overnight. SER---109 was administered on Days 0 and 1.

RESULTS: Fifteen patients were enrolled. Median age was 70 years (mean 64; range 22 --- 88); 10/15 (67%) were female. The median number of prior CDI episodes was 3 (mean 3.8; range 3 --- 8). 13/15 patients (87%) reached the endpoint and were CDI free during the 8---week post---treatment period. Two patients reported transient, self---limited diarrhea within 9 days of treatment with a positive PCR test for *C. difficile*. Neither patient required therapy for CDI in the judgment of the treating investigator, and both reached the 8---week time point with no additional diarrhea and a negative 8---week test for *C. difficile*. Therefore, the overall clinical cure rate was 15/15 (100%). There were no drug--- related SAEs. AEs included transient, self---limiting diarrhea and mild abdominal discomfort. This safety profile is consistent with that reported following cessation of antibiotic treatment or FMT for recurrent CDI. SER---109 was efficacious over a 700---fold dose range, $3x10^7$ to $2x10^{10}$ spores. At the low end, this is at least 10,000---fold below the bacterial dose in a conventional FMT. SER---109 rapidly reconstituted the diversity of the gut microbiome. Engraftment of spores from SER---109 was documented by 16S genomic analysis. In addition, augmentation of the microbiome ecology was also observed, defined as the expansion by 1---log or more of species not in SER---109 and undetectable (or at very low levels) in the patient prior to treatment. Augmented populations notably included non--- spore forming Bacteroides, which were below the limit of detection in in 11 patients prior to SER---109 treatment, and increased as much as 10^6---fold post---treatment as measured by microbiological analysis.

CONCLUSION: SER---109, a rationally designed, first---in---field oral Ecobiotic microbial therapeutic, was remarkably efficacious with a 100% cure rate for the treatment of recurrent CDI and an excellent safety profile. The spore ecology worked at low dose and rapidly repaired the dysbiosis caused by chronic antibiotic treatment for *C. difficile* by inducing the formation of a diverse, healthy microbiome through engraftment of spore forming species and augmentation of non---spore formers.