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An analysis of results from the first placebo-controlled trial of single-dose SER-109, an investigational oral microbiome therapeutic to reduce the recurrence of Clostridium difficile infection (CDI)

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Background: CDI treatment is characterized by a response to antibiotic therapy, but recurrence is frequent due to antibiotic-induced disruption of the microbiome. Designed to facilitate microbiome restoration, SER-109, an investigational, first-in-class microbiome therapeutic, is an ecology of bacterial spores purified from stool from healthy screened donors. In an open-label Phase 1b trial, 26 of 30 subjects with multiply-recurrent CDI (mrCDI) did not experience an additional episode up to 8-weeks following SER-109 dosing.

Material/methods: SERES-004 a randomized, double-blind, Phase 2 study evaluated the superiority of SER-109 versus Placebo to prevent recurrent CDI up to 8-weeks after treatment. Subjects with a history of mrCDI, defined as ≥3 episodes, were enrolled. Diagnosis of CDI used a *C. difficile* test (enzyme immunoassay (EIA) for GDH followed by either toxin gene (tg) PCR or toxin EIA; or tgPCR-only). Subjects with resolution of symptoms after standard-of-care CDI antibiotics were randomized 2:1 to receive SER-109:Placebo and stratified by age (<65 or ≥65 years). The primary endpoint was CDI recurrence in the 8-weeks following treatment.

Results: 89 subjects were enrolled. CDI diagnosis at entry and recurrence was by EIA-toxin in 19% and 26% and tgPCR in 81% and 74%, respectively. The primary endpoint did not show a statistically significant difference between SER-109 and Placebo arms, (44.1% vs 53.3% recurrence, respectively). SER-109 was generally safe and well-tolerated. The most commonly reported AEs for SER-109 and Placebo were: diarrhea (25% vs 14%); abdominal pain (22% vs 14%); flatulence (12% vs 3%); and nausea (10% vs 10%). A re-analysis of CDI recurrence rates (primary endpoint) was conducted based upon the subset of subjects who were considered "high-confidence recurrent subjects (HCR)". HCR subjects had the primary endpoint diagnosed by toxin EIA, not tgPCR. There was significantly greater richness of commensal spore-former species in subjects treated with SER-109 compared to placebo at week 1 (Mann-Whitney p=0.008), consistent with drug engraftment. Further, we identified 10 spore-former species, blue dots, that were significantly more prevalent in SER-109 subjects that did not recur compared to HCR subjects (Figure 1, Fisher's Exact p<0.05). A retrospective analysis of Phase 1b stool samples using high-resolution metagenomic sequencing showed greater microbiome changes associated with higher doses (dose-range 700-fold), as compared to Phase 2.

Conclusions: The study results and post-hoc analysis suggest that SER-109 in the Phase 2 trial was biologically active but a dose increase may be necessary. Furthermore, direct toxin testing (not tg-PCR) may be required to improve diagnostic accuracy, in concordance with the 2016 ESCMID CDI guidelines. SER-109's safety profile supports further clinical development to prevent recurrent CDI, a high unmet medical need.

Figure 1. Prevalence of spore-forming species in SER-109 vs Placebo arms classified as non-recurrent or HCR subjects at 1 week post-treatment.