Phase 1b single & multi-ascending dose study: Evaluation of SER-262 activity over five orders of magnitude

Subject Inclusion: Subjects entered after clinical resolution of primary CDI following treatment with metronidazole or vancomycin (per protocol).
Endpoints:
- Safety & tolerability
- CDI recurrence: Defined as ≥3 unformed stools/day for ≥2 consecutive days, with (+) C. difficile toxin assay performed at least 1 week following end of treatment
- Ser-262 strain engraftment

Additional Methods:
- Subject microbiome composition: Species were identified via whole metagenomic shotgun sequencing of stool samples, using in-house pipelines.
- Statistics and Significance: All comparisons were made using Wilcoxon (U) tests. Asterisks indicate 1-tailed p-value significance levels p<0.05. The number of samples varied by time-point, arm, and outcome.

Antibiotic treatment potentiates SER-262 engraftment

- Treatment with vancomycin results in a greater reduction in spore forming species richness and therefore may open an ecological niche for SER-262 species, permitting greater SER-262 engraftment.
- Engraftment varied between subjects and between strains.

SER-262 strains detected 24 weeks following dosing in VAN subjects

- Absence of SER-262 strains was greatest immediately following dosing. Detection up to 24 weeks after dosing suggests durable engraftment.

Engraftment with SER-262 drives rapid large-scale changes in the microbiome

- Rapid recovery in abundance of non-dosed commensal bacteria (e.g. Bacteroidetes) suggests SER-262, a defined composition of 12 species, serves as a scaffold that enables community-scale changes in the microbiome.
- Decline in Proteobacteria further supports the notion that this microbiome cluster functions as an essential core-gut community.

CONCLUSIONS:
- SER-262, the first bemiriparational antibioplastic in a Phase 1b study, was safe and well-tolerated.
- Engagement of SER-262 strains was not associated with disease reoccurrence, however engraftment was significantly associated with reduced baseline microbial diversity resulting from prior treatment with vancomycin.
- Engagement of SER-262 Firmicutes strains enhanced the resistance of a broad human gut community, potentially leading to lesser rates of recurrence compared to those treated with vancomycin plus placebo. These data suggest full-spectrum microbiome therapeutics are not necessary to achieve the effect.
- Treatment of CDI with vancomycin, followed by restoration of the gut microbiome with SER-262, is a promising 2-pronged therapeutic approach to reduce CDI.
- These data on a first-in-class investigational product are instrumental in the design & clinical development of other designed consortia at Seres.