Poster 1530

Engraftment of Investigational Microbiome Drug, SER-262, in Subjects Treated with Vancomycin is Associated with Reduced Rates of Recurrence after Primary *Clostridium Difficile* Infection (CDI)

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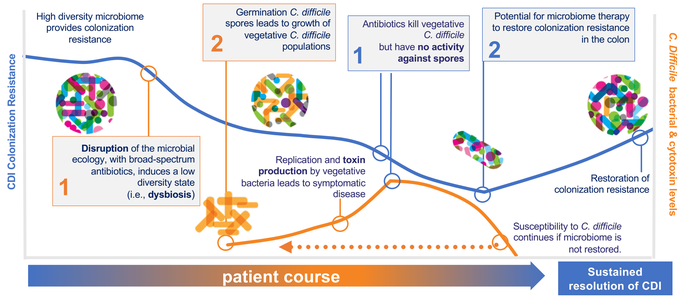
SERES THERAPEUTICS™

C. difficile infection (CDI) is a 2-hit process requiring a 2-pronged treatment approach



The leading risk factor for CDI is exposure to antibiotics, which create a low diversity state (i.e. dysbiosis), impairing colonization resistance and predisposing patients to recurrence, the majority of which occur within 1-3 weeks. Recurrence rates following vancomycin or metronidazole are high (24% and 27%, respectively) (Vardakas IJAA, 2012). Notably, metronidazole is no longer recommended due to poor primary efficacy and poor stool drug concentrations (McDonald CID, 2018).

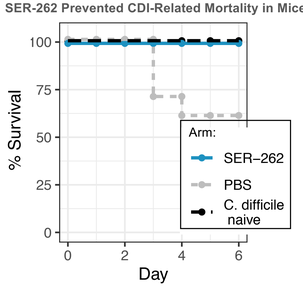
Antibiotic induced dysbiosis is characterized by a loss of Firmicutes and Bacteroidetes and an expansion of Proteobacteria. Following antibiotic treatment, rapid repair of the microbiome is key to reducing risk of recurrence.

Seres is developing investigational biotherapeutics to reduce rates of recurrent CDI

- Consortia of Firmicutes spore-forming bacteria; dosing of select Firmicutes create a scaffold for enrichment of Bacteroidetes and other Firmicutes species.
- Our lead CDI product, SER-109 is currently being evaluated in a Phase 3 study to reduce recurrence in multiply recurrent CDI (#NCT03183128). Learn more at: https://serescdiffstudy.com/

SER-262, an investigational Ecobiotic® drug developed to reduce the risk of recurrent *C. difficile* infection (rCDI)

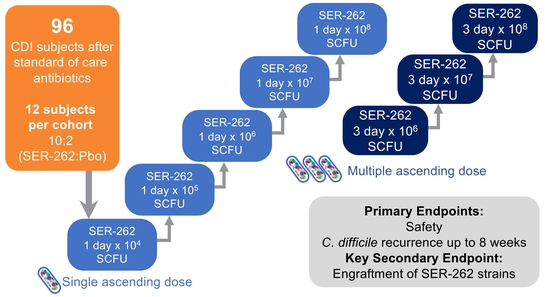
- First in-class, rationally-designed live biotherapeutic. Entered clinic in July 2016; trial complete in Aug 2018.
- Consists of 12 fermented strains of Firmicutes, dosed as spores via oral capsule.
- Defined & standardized product, manufactured using Good Manufacturing Practice (GMP).
- Defined biotherapeutic has a lower risk of transmitting pathogens compared to FMT.



Survival curve of mice in primary CDI model. Mice were dosed with SER-262 or PBS at day -1 and challenged with a pathogenic CDI strain at day 0 (10 mice per arm).

References:
Vardakas, et al. 2012. International Journal of Antimicrobial Agents
McDonald et al, 2018. Clinical Infectious Diseases.

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



Subject Inclusion:
- Subjects enrolled after clinical resolution of primary CDI following treatment with metronidazole or vancomycin (per PI discretion)

Endpoints
- **Safety & tolerability**
- **CDI recurrence**: Defined as ≥3 unformed stools/day for 2 consecutive days, a (+) CDI test (free toxin or PCR) and the decision to treat by the investigator
- **SER-262 strain engraftment**

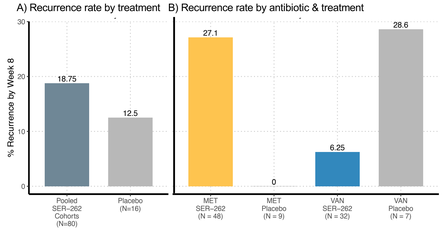
Additional Methods
- **SER-262 strain engraftment:** Evaluated using custom Nanostring probes.
- **Subject microbiome composition:** Species were identified from whole metagenomic shotgun (WMS) sequencing of stool samples, using MetaPhlAn software.
- **Statistics and Significance:** All comparisons are based on one-sided Mann-Whitney U tests. Asterisks indicate 1-sided p-value significance levels p<0.05. The number of samples varied by time-point, arm and outcome.

SER-262 had a favorable safety profile as compared to placebo.

- Across dose cohorts, patients receiving SER-262 had fewer TEAEs and GI AEs than PBO patients.

Recurrence following SER-262 varied by antibiotic used for primary CDI episode

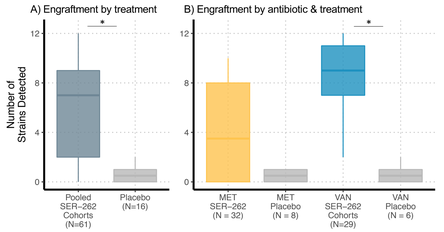
- The primary efficacy endpoint was not met (CDI recurrence in SER-262 compared to placebo).
- A significant benefit was observed between SER-262 and placebo arms in subjects who first received vancomycin.
- Recurrence rates in subjects receiving metronidazole & placebo were divergent from historical rates. Recurrence rates in subjects receiving vancomycin & placebo were similar to historical rates.



Percentage of subjects in treatment arms that experienced rCDI by week 8. A) Recurrence rates in placebo and combined SER-262 arms. B) Recurrence rates separated by the antibiotic used for primary CDI and study treatment.

Engraftment of SER-262 varied by antibiotic used for primary CDI episode

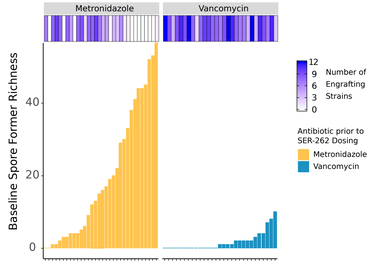
- SER-262 was observed to engraft with a maximum of 12 out of 12 strains. Detection was minimal in subjects receiving placebo.
- We did not observe a relationship between dose cohort and number of strains engrafting.
- Greater engraftment of SER-262 was observed in subjects receiving vancomycin as compared to subjects receiving metronidazole, consistent with clinical outcome.



The number of SER-262 strains detected 7 days after dosing with SER-262. A) Engraftment in placebo and combined treatment arms. B) Engraftment separated by the antibiotic used for primary CDI and study treatment. Sample numbers were restricted by FBMR agreements.

Antibiotic treatment potentiates SER-262 engraftment

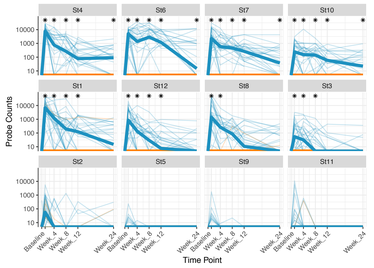
- Treatment with vancomycin results in a greater reduction in spore forming species richness and therefore may open an ecological niche for SER-262 species, permitting greater SER-262 engraftment.



The number of spore forming bacterial detected in subject fecal samples following antibiotic treatment, but prior to SER-262 dosing. Each vertical bar represents a single subject's baseline sample. The upper ribbon indicate the number of SER-262 strains detected in each subject one week after dosing.

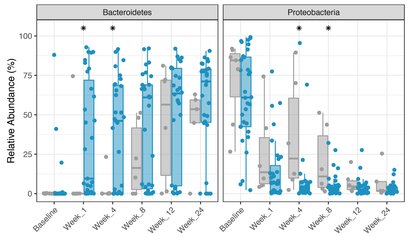
SER-262 strains detected 24 weeks following dosing in VAN subjects

- Abundance of SER-262 strains was greatest immediately following dosing. Detection up to 24 weeks after dosing suggests durable engraftment.
- Engraftment varied between subjects and between strains.



Abundance of each SER-262 strain over the duration of our study identified in vancomycin-treated subject samples. Thin lines outline the trajectory of each subject, colored by whether the subject received SER-262 or placebo. Thicker lines trace the median probe counts within each treatment group.

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 shift towards health induced by a composition of 12 species.

Fig. Relative abundances of Bacteroidetes and Proteobacteria in vancomycin-treated subject microbiomes. Each point represents an individual subject sample.

CONCLUSIONS:

- SER-262, the first fermented investigational biotherapeutic in a Phase 1b study, was safe and well-tolerated.
- Engraftment of SER-262 strains was not significantly dose responsive; however engraftment was significantly associated with reduced baseline microbial diversity resulting from prior treatment with vancomycin.
- Engraftment of SER-262 Firmicutes strains accelerated the restoration of a broader healthy gut community, potentially leading to lower rates of recurrence compared to those treated with vancomycin plus placebo. These data suggest full-spectrum microbiome therapeutics are not necessary to achieve this 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 rCDI.
- These data on a first-in-class investigational product are instrumental in the design & clinical development of other designed consortia at Seres.

Clinical Trials Registration: NCT02830542