SERES-004: First placebo-controlled trial of an investigational oral microbiome drug (SER-109) to reduce recurrence of *Clostridium difficile* infection

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Transparency Declaration

• I am an employee and stockholder of Seres Therapeutics
*Clostridium difficile* infection (CDI) is a 2-hit process requiring a 2-pronged treatment approach.

**Hypothetical patient course**

1. **Healthy person with intact colonization resistance**
2. **Antibiotics create ecologic holes in microbiome leading to dysbiosis**
3. **Exposure to *C. difficile* in a vulnerable patient leads to active infection**
4. **Antibiotics kill the vegetative forms**
5. **Risk of CDI recurrence rises with persistent dysbiosis**
   - *C. difficile* increases & cytotoxin production drives disease symptoms
   - Antibiotic exacerbation of dysbiosis
   - Disease recurs due to germination of dormant spores

Gastrointestinal microbiome diversity
**Clostridium difficile** infection (CDI) is a 2-hit process requiring a 2-pronged treatment approach

- **Healthy person with intact colonization resistance**
- **Antibiotics create ecologic holes in microbiome leading to dysbiosis**
- **Exposure to **Clostridium difficile** in a vulnerable patient leads to active infection**
- **Antibiotic mediated killing of vegetative forms only**
- **Restoration of colonization resistance**

**Hypothetical patient course**

- **Potential for microbiome therapy to increase bacterial diversity in the colon**
- **Sustained resolution of CDI**
SERES-001: Phase 1b Study of SER-109 to Prevent RCDI

30 patients with recurrent CDI responsive to antibiotics

Cohort 1
Dose = $10^7$ to $10^{10}$ spores over 2 days

Cohort 2
Dose = $1.1 \times 10^8$ spores on 1 day

Achieved Primary Endpoint (N=13)

Cohort 1 (n=2) Cohort 2 (n=2)

Achieved Primary Endpoint (N=13)

Primary endpoint achieved in 26 of 30 patients (86.7%)
Led to use of $1 \times 10^8$ spores in Phase 2 trial

Khanna, S J Infect Dis 2016
SERES-004
ECOSPOR: A Randomized Double-Blind, Placebo-Controlled, Parallel-Group Study of SER-109 to Prevent Recurrent Clostridium difficile Infection (CDI)
Study Design and Inclusion Criteria

Study subjects:

• 89 adults enrolled in 37 US sites were randomized 2:1 to active drug: placebo (both as 4 capsules)

Study population:

• ≥ 3 episodes of CDI within prior 9 months, inclusive of qualifying episode

Qualifying episode:

• ≥ 3 unformed stools per day for 2 consecutive days
• Positive *C. difficile* stool test (no specific diagnostic test required)
• Clinical response to CDI SOC antibiotics: <3 unformed stools in 24 hours for 2 or more consecutive days prior to randomization
Schematic of Study Design

Screening                         Treatment                                             Safety Follow-up

-21 to Day -1  Day 1  Week 4  Week 8  Week 12  Week 24

Screening

Randomization

End of Efficacy Period

SER-109 Arm
n = 58
(Dose: $1 \times 10^8$ spore equivalents)
1 dose on Day 1

Placebo Arm
n=29
1 dose on Day 1

In Clinic Visit
Schematic of Study Design

**Primary Efficacy Endpoint:**
Relative risk of CDI recurrence in PBO vs SER-109 arms

**Primary Safety Objective:**
To evaluate safety and tolerability

**SER-109 Arm**
- n = 58
- (Dose: $1 \times 10^8$ spore equivalents)
- 1 dose on Day 1

**Placebo Arm**
- n = 29
- 1 dose on Day 1

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**Screening**
- -21 to Day -1
- In Clinic Visit

**Randomization**
- Day 1

**Treatment**
- Week 1
- Week 4
- Week 8

**Safety Follow-up**
- Week 12
- Week 24
Primary Efficacy Endpoint Criteria for recurrent CDI:

- ≥ 3 unformed stools per day for 2 consecutive days
- Positive *C. difficile* stool test which included any of the following:
  - Enzyme immunoassay (EIA) Glutamate dehydrogenase (GDH) antigen followed by PCR or
  - EIA GDH followed by EIA toxin
  - OR a single test of
    - PCR alone
- Investigator assessment that the subject required treatment
## Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Statistic</th>
<th>SER-109 (N=59)</th>
<th>Placebo (N=30)</th>
<th>Overall (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>n</td>
<td>59</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>63.7</td>
<td>66.1</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40 (67.8)</td>
<td>20 (66.7)</td>
<td>60 (67.4)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (32.2)</td>
<td>10 (33.3)</td>
<td>29 (32.6)</td>
</tr>
<tr>
<td><strong>Number of Prior CDI Episodes</strong></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28 (47.5)</td>
<td>20 (66.7)</td>
<td>48 (53.9)</td>
</tr>
<tr>
<td>4</td>
<td>21 (35.6)</td>
<td>5 (16.7)</td>
<td>26 (29.2)</td>
</tr>
<tr>
<td>≥5</td>
<td>10 (16.9)</td>
<td>5 (16.7)</td>
<td>15 (16.9)</td>
</tr>
</tbody>
</table>
Safety Results

- SER-109 was generally well tolerated
- The most commonly reported adverse events in the SER-109 and placebo arms were gastrointestinal (GI) (55% vs 45%, respectively)
- Vast majority were mild or moderate in intensity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Arms</th>
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<tbody>
<tr>
<td></td>
<td>SER-109 N = 60</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

- Serious adverse event (SAE) rate (15.0% for SER-109, 10.3% for placebo)
  - No SAEs were classified as drug related
Primary Efficacy Endpoint:
CDI Recurrence Rates and Relative Risks in ITT Population

Prompted Root Cause Analysis Investigation:

- *C. difficile* diagnostics for subject entry and at recurrence
- Dose and dosing regimen
- Microbiome analysis of engraftment
- Phase 1b to Phase 2 manufacturing and formulation changes, and potential impact on drug activity (no findings)
Diagnostics
Hypothesis:

- Diagnostic tests in the Phase 2 study did not accurately identify:
  - Study subjects with true RCDI at study entry AND
  - True recurrence of disease after SER-109 or PBO dosing for the primary endpoint

Background Data Supporting the need for CDI Toxin Diagnostic Assays

- PCR leads to overdiagnosis [Polage JAMA Int Med 2016]
- PCR cannot differentiate carriage from disease [Smits Nat Rev 2016]

PCR was used for diagnosis of qualifying episode in 81% subjects and for recurrence during the study in 74%

- Samples were not available for re-testing for presence of free toxin for qualifying episode
Diagnostics at Time of Recurrence: Retesting for Cytotoxin by Independent Laboratory

• Samples available from recurrence time point were re-tested by an independent laboratory

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SER-109</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>Number with Recurrence (%)</td>
<td>Number with Recurrence (%)</td>
</tr>
<tr>
<td>On Study (all test methods)</td>
<td>30</td>
<td>16 (53.3%)</td>
<td>59</td>
</tr>
<tr>
<td>Positive cytotoxin testing either on-study or at re-test*</td>
<td>21</td>
<td>7 (33.3%)</td>
<td>44</td>
</tr>
</tbody>
</table>

Use of PCR to measure *C. difficile* recurrences may have overestimated study recurrences in both treatment arms as it does not identify clinical disease, and further complicated interpretation of Phase 2 study results

*Limitations of this analysis include sample handling/storage issues
Dose
Increased prevalence of engrafted SER-109 strains is correlated with non-recurrence

- Placebo vs SER-109 treated subjects differed in the prevalence of SER-109 strains at 1 week post-treatment
- There were 11 species that were significantly more prevalent (Fisher’s exact p<0.05) in subjects that received SER-109 and did not recur (blue points)
Dose Level may impact the magnitude of engraftment of SER-109 in subjects

- Diversity of commensal spore-forming species at 1 week post-treatment is associated with dose
- Higher dose, >1.5 x 10^8 SporQs can result in more SER-109 species engrafting (Phase 1b trial)
- Phase 2 subjects that did not recur had similar diversity as low dose Phase 1b subjects
- Subjects that recurred and/or received Placebo had the lowest diversity

Phase 1: high dose, low dose
Phase 2: SER-109-NR, SER-109HCR
Phase 2: Pbo-NR, Pbo-HCR
Summary

Subject selection for study entry
• Use of PCR for study entry may have led to inclusion of subjects who were colonized with *C. difficile* but had alternative causes for diarrhea

Diagnosis of recurrence
• Use of PCR at time of recurrent diarrhea may have led to over-diagnosis of recurrence

*Conclusion:* Toxin testing may be required to improve diagnostic accuracy, in concordance with the recent 2016 ESCMID CDI guidelines

Dosing Regimen and Efficacy
• Increased prevalence of engrafted SER-109 strains is correlated with non-recurrence
• Engraftment of SER-109 was more robust among the subjects who received higher doses in the Phase 1b study

*Conclusion:* SER-109 is biologically active but a dose increase may be necessary

Safety
• SER-109 was well tolerated and no SAEs were deemed drug-related
• Most common adverse events in the both arms were GI
Credits

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We would like to thank all the Investigators in the SERES-004 trial and importantly the patients who participated.

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