RAPID CONVERSION OF PRIMARY TO SECONDARY BILE ACIDS IN SUBJECTS WITH RECURRENT Clostridiodides difficile INFECTION (CDI) FOLLOWING SER-109, AN INVESTIGATIONAL MICROBIOME THERAPEUTIC

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Disclosures

Employee and share-holder of Seres Therapeutics
Pharmacology of SER-109

- **Pharmacokinetics**: SER-109 spores germinate into metabolically-active bacteria that colonize the GI tract, a process called *engraftment*.

- **Pharmacodynamics**: Engraftment induces broad compositional and functional changes associated with a clinical response.


- SER-109 Engraftment
- Microbiome Restructuring
- Microbe-associated metabolites:
  - Pathogen resistance
  - Epithelial homeostasis

**Microbe-associated metabolites**:
- Bile acids
- Short-chain fatty acids
- Tryptophan metabolites

*Henn et al Gastroenterology, 2021*
Primary & secondary bile acids are likely biomarkers

Potential MoA to reduce CDI recurrence

Key Firmicutes drive secondary BA metabolism

BA’s role in *C. difficile* 2 phase lifecycle

Vital et al. 2019. Computational and Structural Biotechnology Journal
ECOSPOR-III
Ph3 Double-blind, placebo-controlled trial of SER-109 for multiply recurrent CDI

182 toxin+ adult subjects symptom resolution on antibiotics for 10 – 21 days
Subjects stratified by age and antibiotic received

4 Capsules once daily for 3 Days

Primary endpoint
Recurrence at 8 weeks
Safety through 24 wks

SER-109
Placebo

Baseline Week 1, 2 & 8 Stool Collection

Endpoints

Primary: Superiority of SER-109 compared to placebo for reduction of recurrence of CDI
Exploratory: Compositional and functional changes in the microbiome in SER-109 vs Placebo participants
SER-109 demonstrated superiority versus placebo in the reduction of CDI recurrence rates in ITT population through Week 8

Most recurrence events occurred rapidly

- Of 48 total recurrences in the overall population that occurred by week 8, 36 (75%) occurred within two weeks.

Recurrence In Overall Population

Relative Risk (95% CI)
0.32 (0.18–0.58)

△ -27.4
P<0.001

<table>
<thead>
<tr>
<th></th>
<th>SER-109</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>No. of Events</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>89</td>
<td>93</td>
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</tbody>
</table>
SER-109 engrafted rapidly and durably after dosing

Peak engraftment achieved rapidly;
SER-109 subjects had significantly greater engraftment vs placebo at week 1 (p<0.001)

- Significance differences were maintained in subpopulation analyses (i.e. vancomycin vs fidaxomicin and under vs over 65 years old)
SER-109 engrafted rapidly and durably after dosing

Peak engraftment achieved rapidly; durable through 8 weeks

- SER-109 subjects had significantly greater engraftment at all post-dosing timepoints (p<0.001)
- Significance differences were maintained in subpopulation analyses (i.e. vancomycin vs fidaxomicin and under vs over 65 years old)

Treatment

- SER-109
- Placebo
SER-109 engraftment resulted in rapid reduction in primary bile acids

Primary Bile Acids

- SER-109 subjects had a significantly greater decrease in primary BAs from baseline at week 1 (p=0.038)

Primary bile acids are a *C. difficile* germinate

- SER-109 subjects had a significantly greater decrease in primary BAs from baseline at week 1 (p=0.038)
SER-109 engraftment resulted in rapid **increase** in secondary bile acids.

**Secondary Bile Acids**

- Treatment comparison:
  - SER-109 vs. Placebo
  - **SER-109 subjects had a significantly greater increase in secondary BAs from baseline.**
  - **SER-109 subjects had less variability in bile acid response than placebo.**

**Secondary bile acids inhibit *C. difficile growth***

- Box plots showing concentration (μg/g) over time (Baseline, Week 1, Week 2, Week 8):
  - Baseline: SER-109 > Placebo
  - Week 1: SER-109 > Placebo
  - Week 2: SER-109 > Placebo
  - Week 8: SER-109 > Placebo
  - Significant differences:
    - Baseline vs. Week 1: < 0.001
    - Week 1 vs. Week 2: < 0.001
    - Week 2 vs. Week 8: < 0.05

**Germination** → **Sporulation** → **Vegetative form**
Efficacy is higher at week 8 with SER-109 vs placebo in age-stratified and antibiotic-stratified groups

Recurrence By Age

-65 years

SER-109 PBO

Recurrence (%)

7.3 30.8

△ -23.5

P=0.007

SER-109 PBO

≥ 65 years

16.7 46.3

△ -29.6

P=0.001

Recurrence By Prior Antibiotic

- Vancomycin

SER-109 PBO

Recurrence (%)

15.6 37.7

△ -22.1

P=0.004

- Fidaxomicin

SER-109 PBO

Recurrence (%)

4.0 45.8

△ -41.8

P<0.001

No. of Events

3 12

8 25

10 26

1 11

No. of Patients

41 39

48 54

64 69

25 24
SER-109 increases secondary bile acids in both subpopulations

**Age stratification**

![Box plots showing concentration of bile acids in baseline and week 1 for different age groups.](image)

- **Baseline**:
  - SER-109 < 65 yrs old
  - SER-109 ≥ 65 yrs old
  - Placebo < 65 yrs old
  - Placebo ≥ 65 yrs old
- **Week 1**:
  - SER-109 < 65 yrs old
  - SER-109 ≥ 65 yrs old
  - Placebo < 65 yrs old
  - Placebo ≥ 65 yrs old

**Antibiotic stratification**

![Box plots showing concentration of bile acids in baseline and week 1 for different antibiotic groups.](image)

- **Baseline**:
  - SER-109 Vancomycin
  - Placebo Vancomycin
- **Week 1**:
  - SER-109 Fidaxomicin
  - Placebo Fidaxomicin

Statistical significance:
- Antibiotic stratification: $< 0.01$
- Age stratification: $< 0.001$, $< 0.05$
SER-109 species engraftment leads to rapid pharmacodynamic response associated with reduced CDI recurrences

**Pharmacokinetics**

**Pharmacodynamics**

**Clinical response**

**Engraftment**

**Microbe-associated metabolites**

- Reduction of CDI recurrence
  - SER-109: 12.4%
  - Placebo: 39.8%

**Graphs:**
- Box plots showing number of newly appearing dose species and concentration over baseline and week 1.
- Bar chart comparing recurrence rates between SER-109 and placebo.
Thank You

We are indebted to the patients and investigators of ECOSPOR-III for their participation in the trial. Without them none of this would be possible.

Seres R&D, Manufacturing, Quality, Clinical & Regulatory Teams

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