DDW 2021
May 21-23 | VIRTUAL™

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

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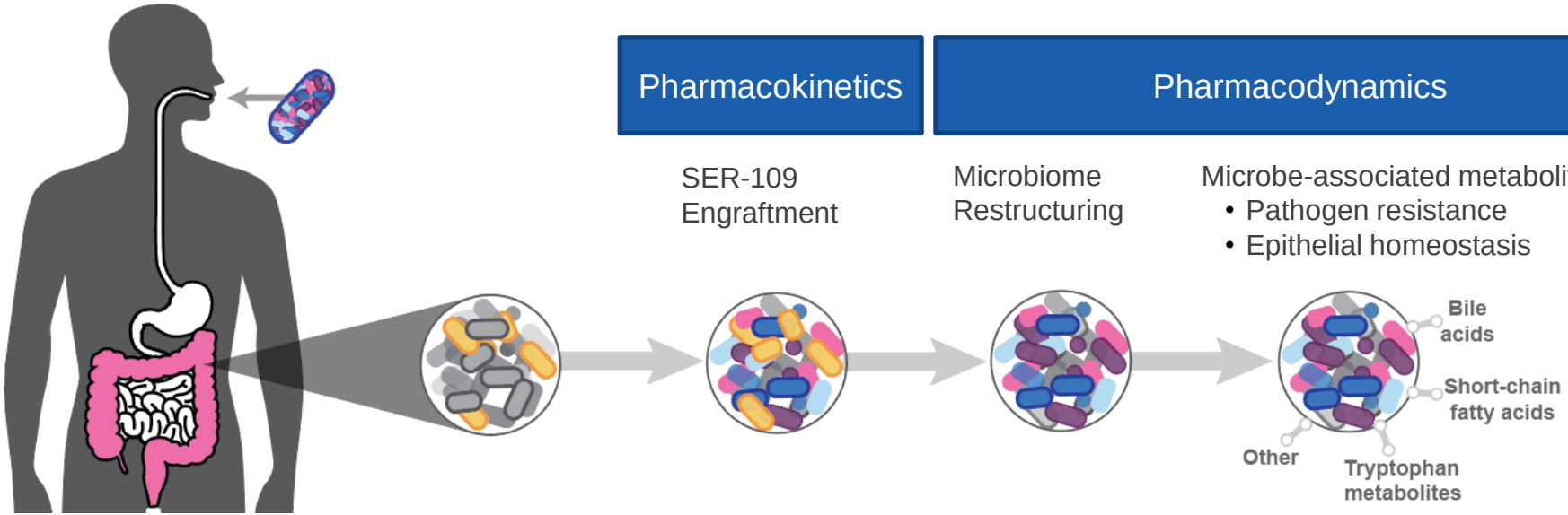
Disclosures

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



Henn et al Gastroenterology, 2021

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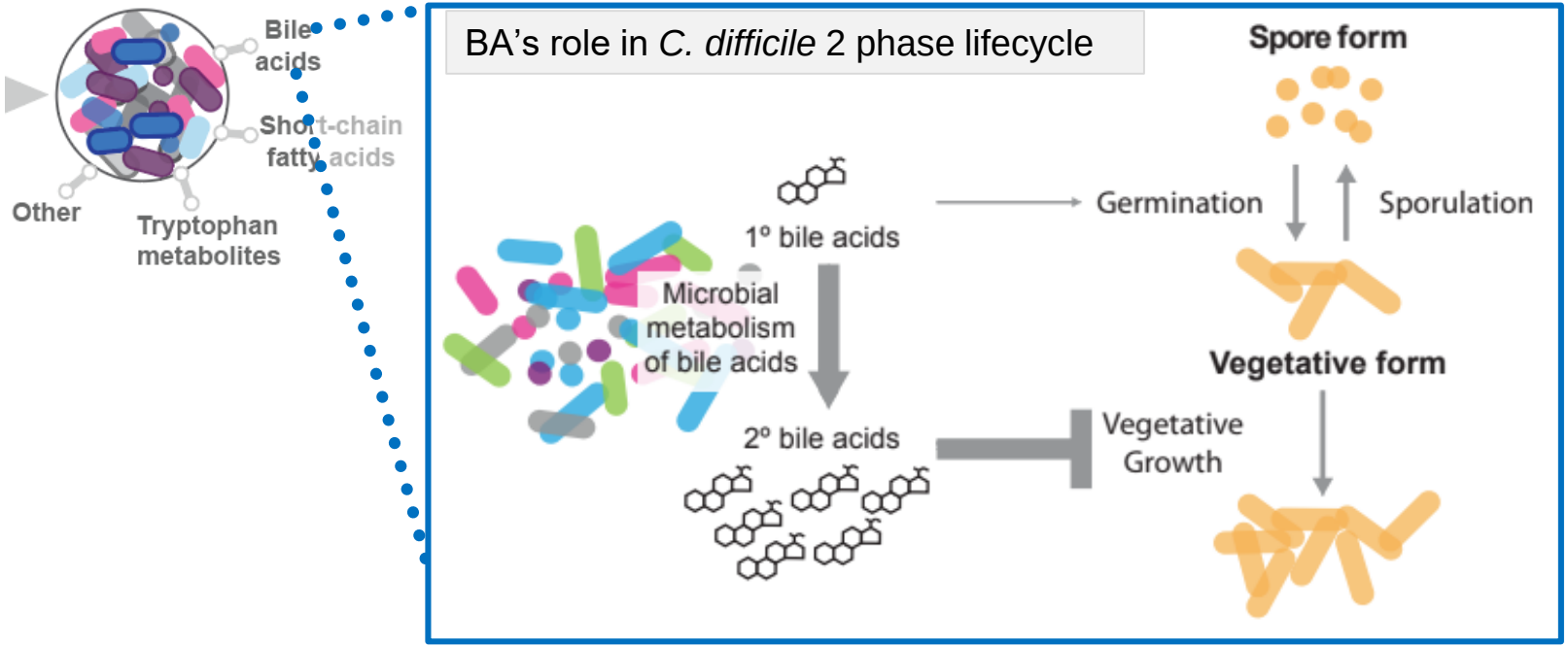
Primary & secondary bile acids are likely biomarkers

Potential MoA to reduce CDI recurrence

Key Firmicutes drive secondary BA metabolism



Vital et at. 2019. Computational and Structural Biotechnology Journal

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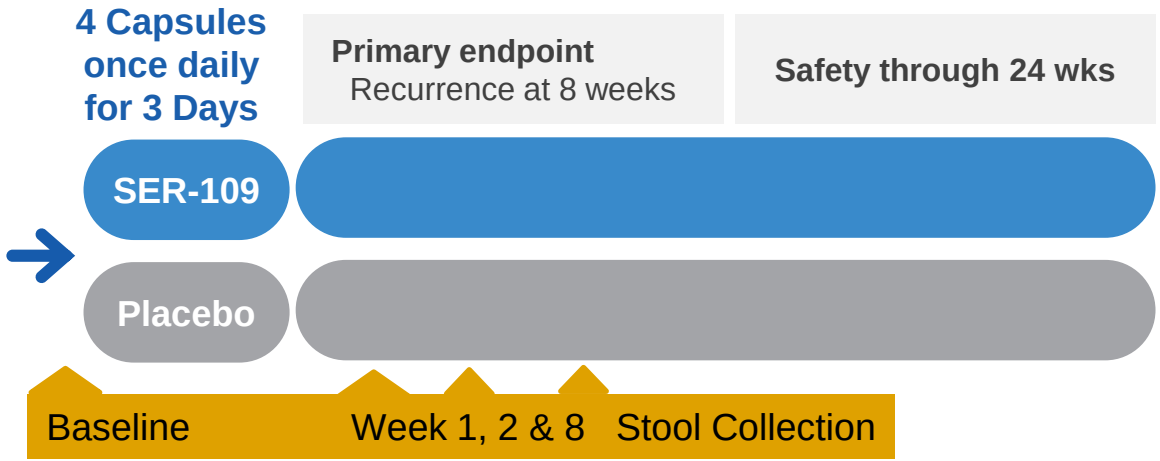
ECOSPOR-III

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



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

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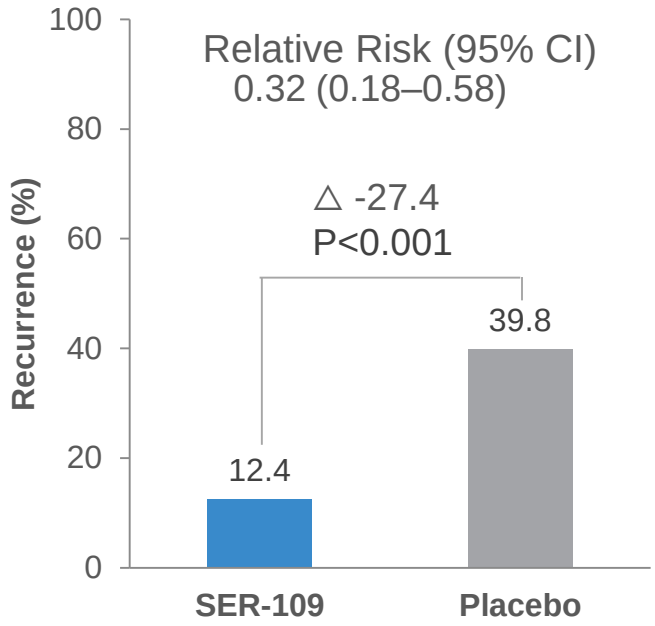
SER-109 demonstrated superiority versus placebo in the reduction of CDI recurrence rates in ITT population through Week 8

Recurrence In Overall Population

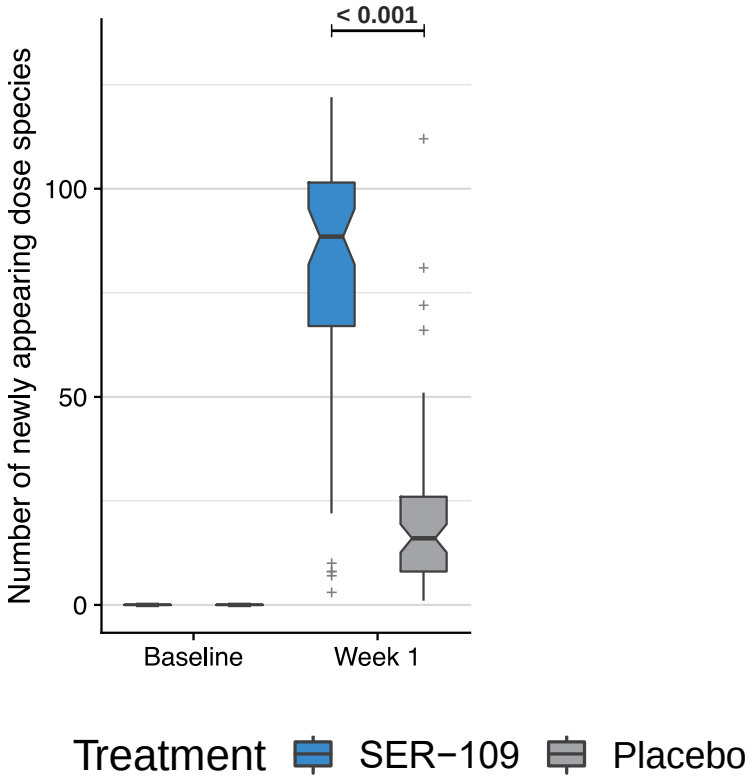


No. of Events	11	37
No. of Patients	89	93

Most recurrence events occurred rapidly

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

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)

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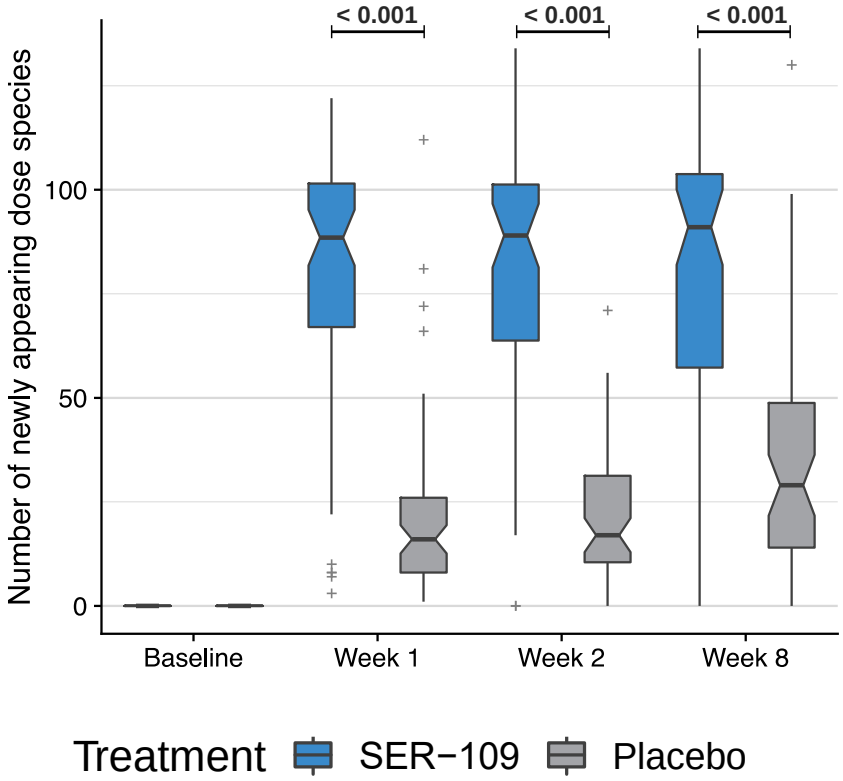
SER-109 engrafted rapidly and durably after dosing



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)

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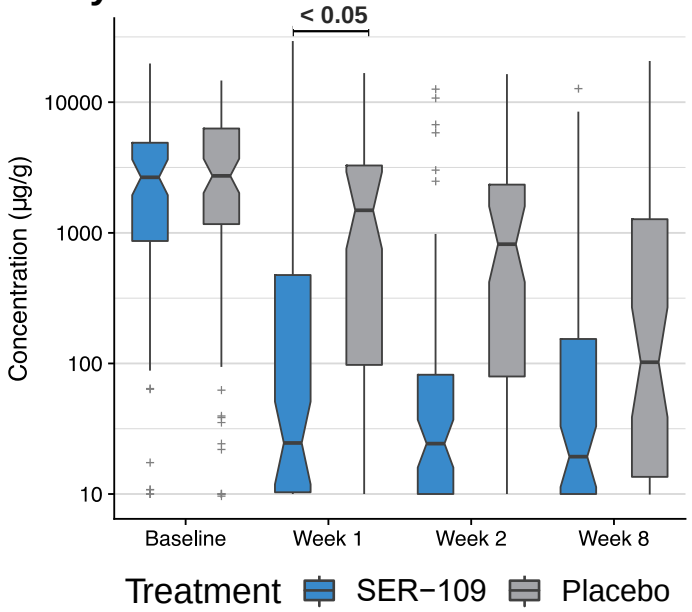
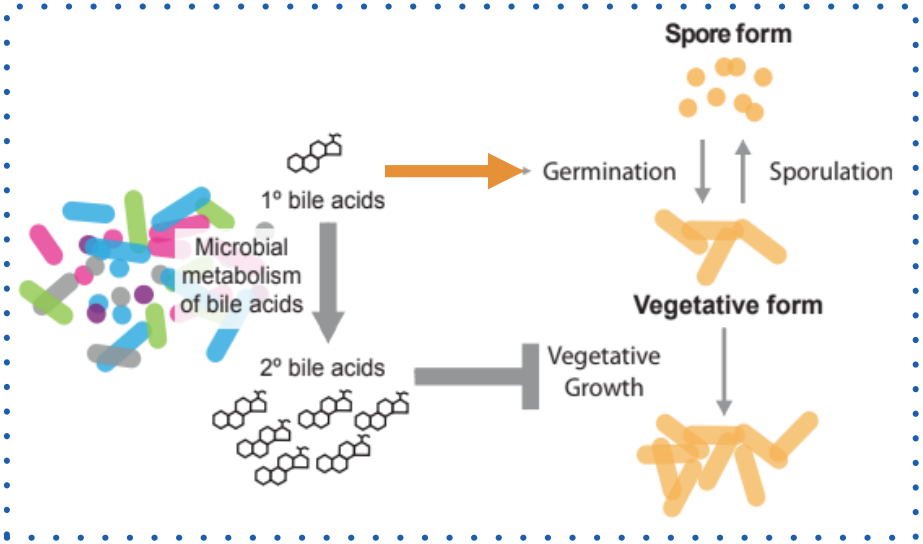
SER-109 engraftment resulted in rapid reduction in primary bile acids

Primary Bile Acids



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)

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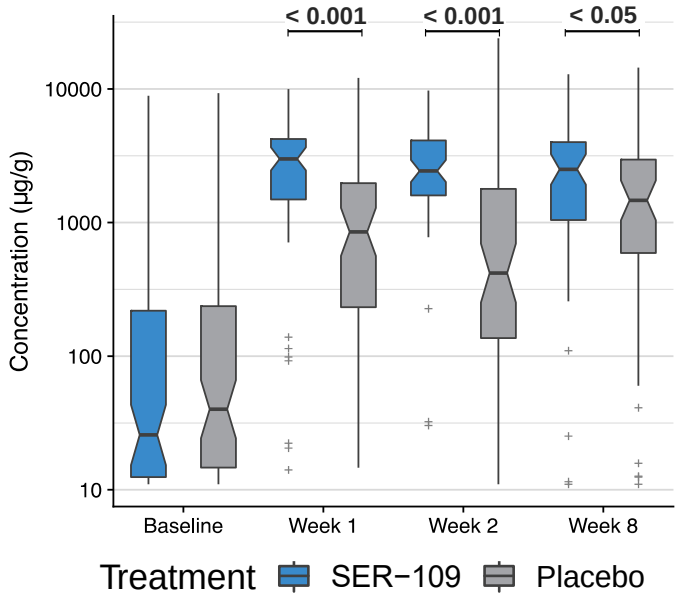
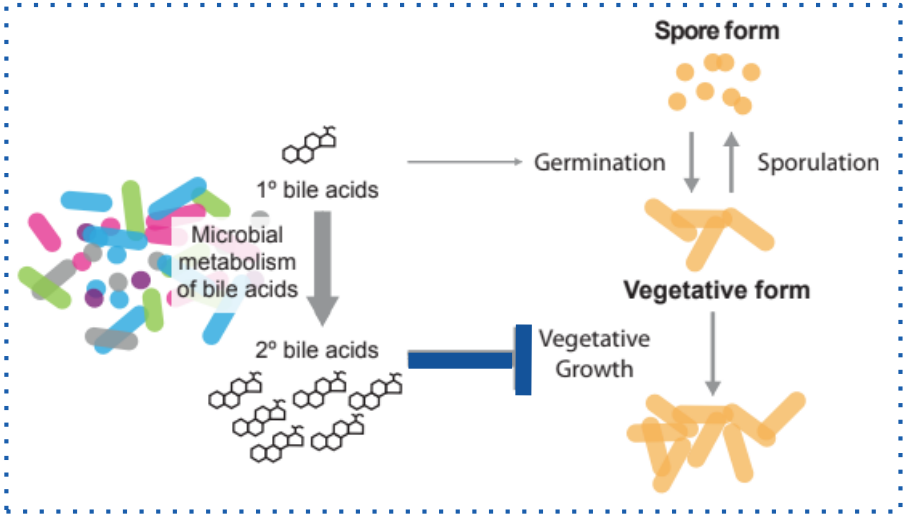
SER-109 engraftment resulted in rapid increase in secondary bile acids

Secondary Bile Acids



Secondary bile acids inhibit *C. difficile* growth



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

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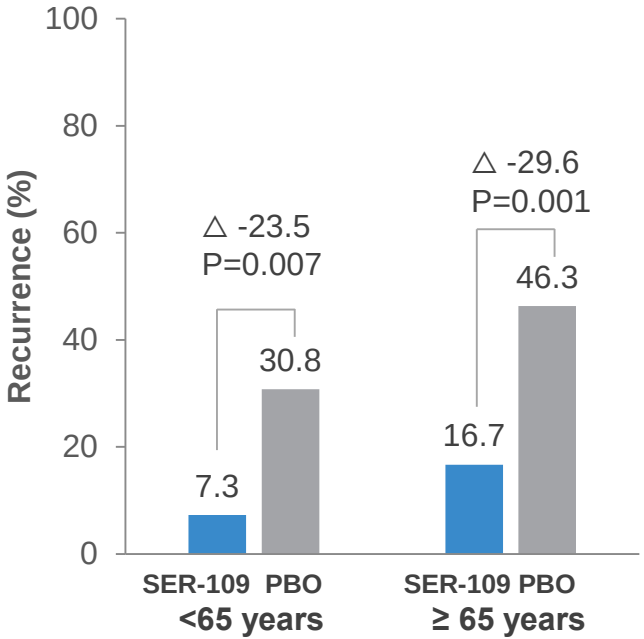
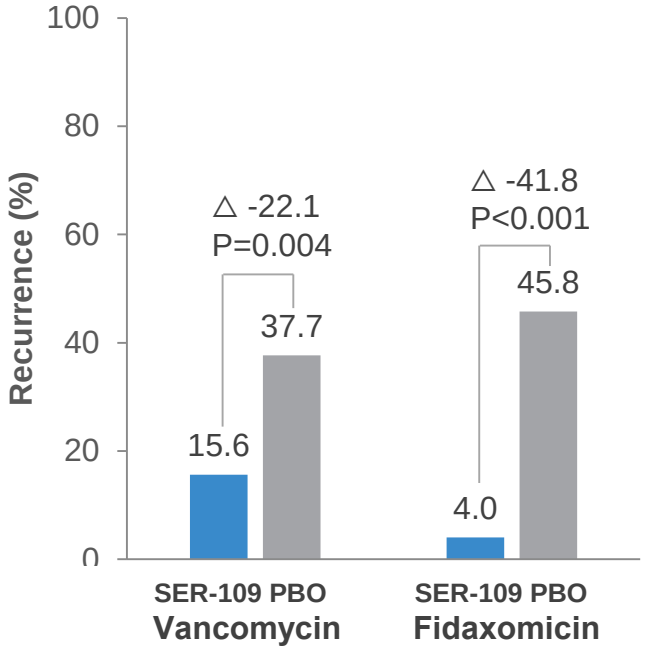
Efficacy is higher at week 8 with SER-109 vs placebo in age-stratified and antibiotic-stratified groups

Recurrence By Age



No. of Events	3	12	8	25
No. of Patients	41	39	48	54

Recurrence By Prior Antibiotic



No. of Events	10	26	1	11
No. of Patients	64	69	25	24

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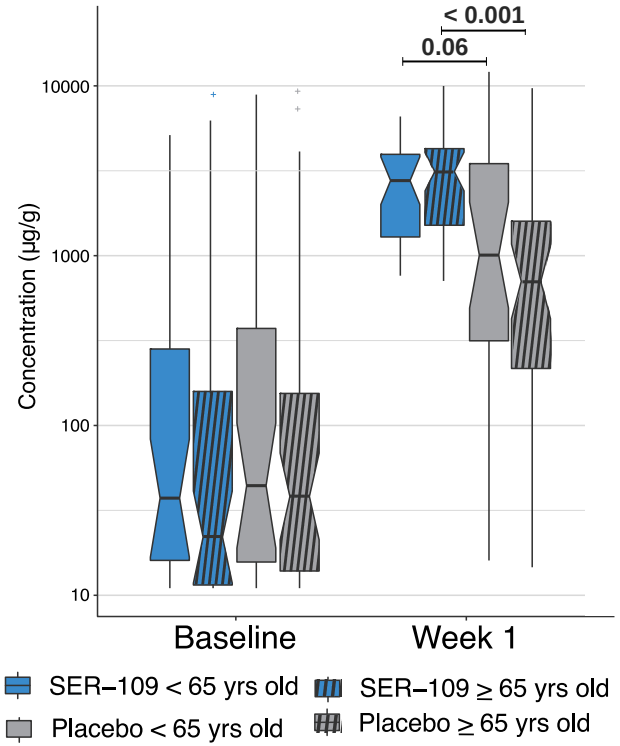
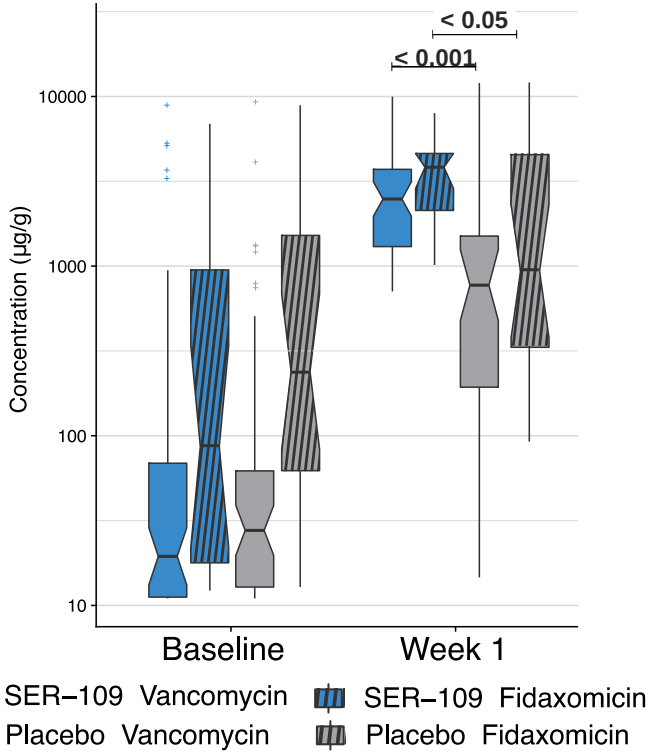
SER-109 increases secondary bile acids in both subpopulations

Age stratification



Antibiotic stratification



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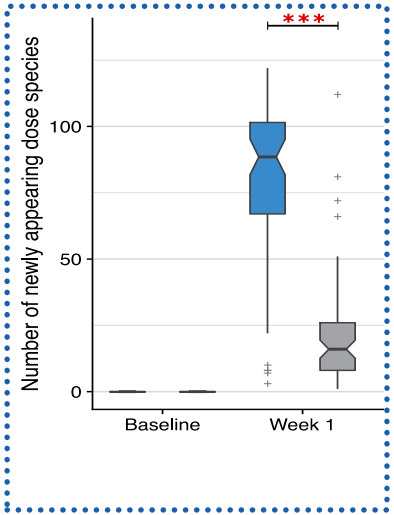
SER-109 species engraftment leads to rapid pharmacodynamic response associated with reduced CDI recurrences

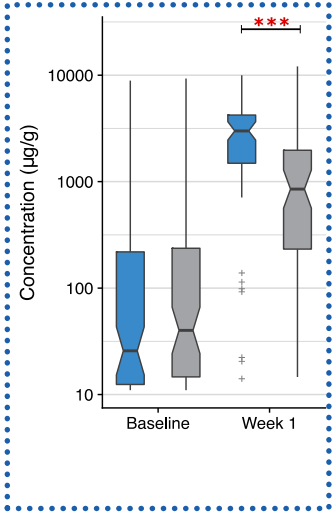
Pharmacokinetics

Engraftment



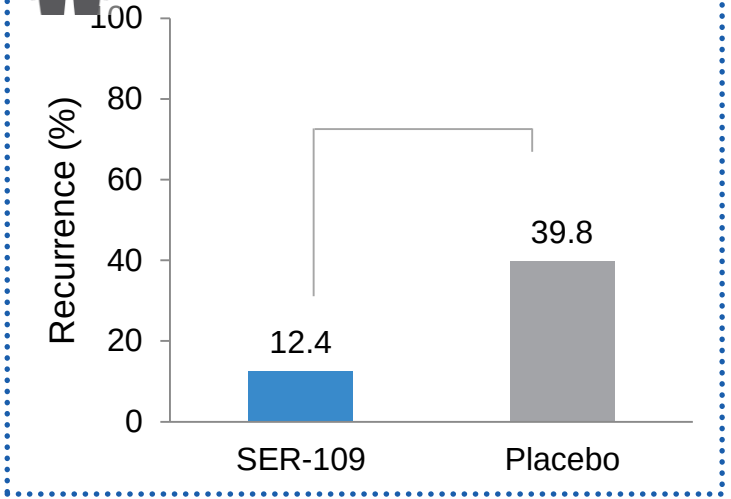
Pharmacodynamics

Microbe-associated metabolites



Clinical response

Reduction of CDI recurrence



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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

Funders: Nestlé HealthScience

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