Key Findings from SER-109 Phase 2 Study Analyses

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Leading the Microbiome Revolution

January 31, 2017

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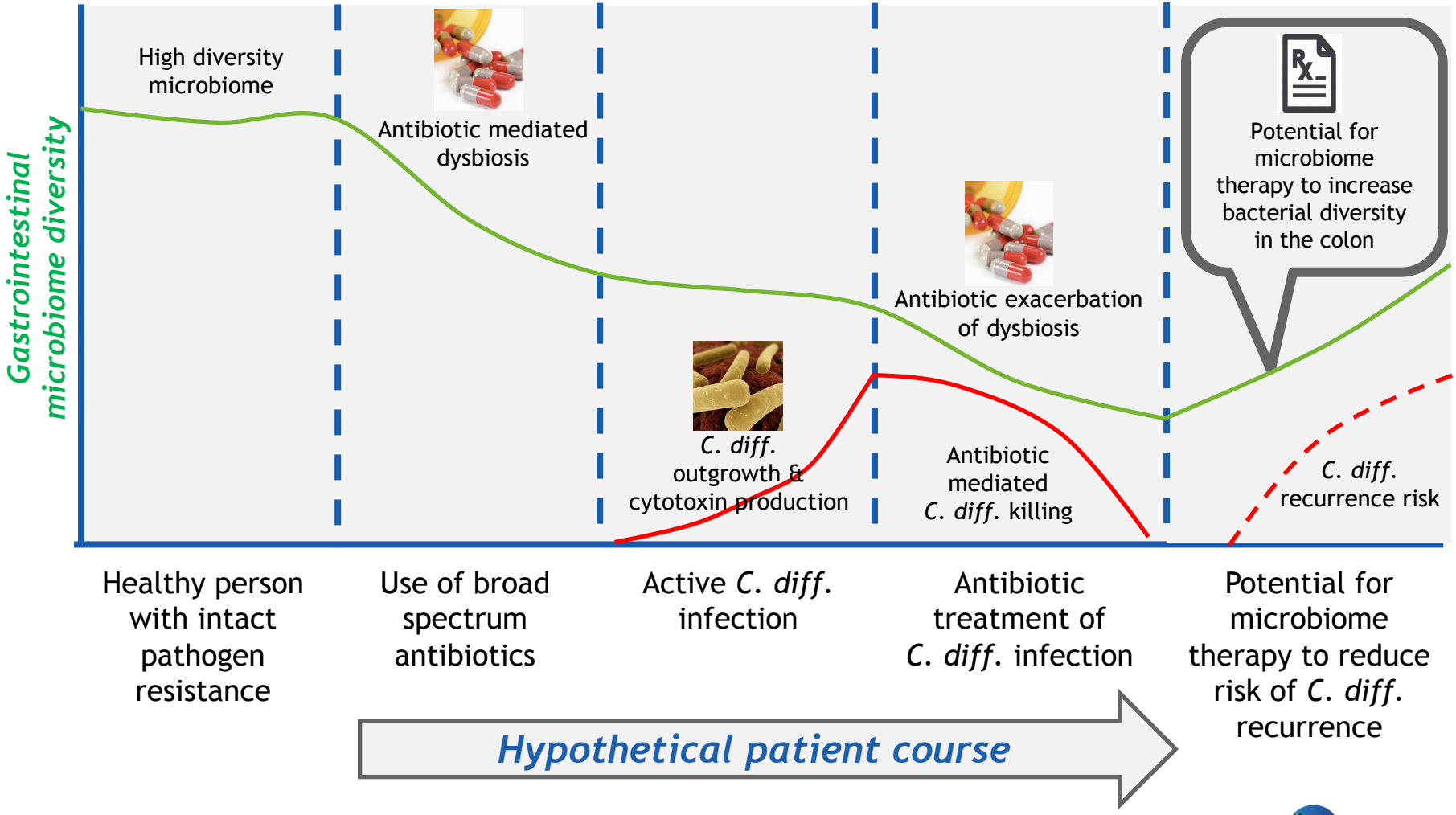
Microbiome dysbiosis and potential for therapeutic intervention



SER-109 overview

- Lead product candidate, completed Phase 2 study in patients with recurrent *C. difficile* infection
- Oral, biologically sourced, spore based therapeutic candidate
- Intended to catalyze an increase in the diversity of commensal microbes to repair a dysbiotic, disease state microbiome
- Therapeutic objective: Reestablish colonization resistance, and reduce the risk of further recurrences of *C. difficile* infection

SER-109 capsules

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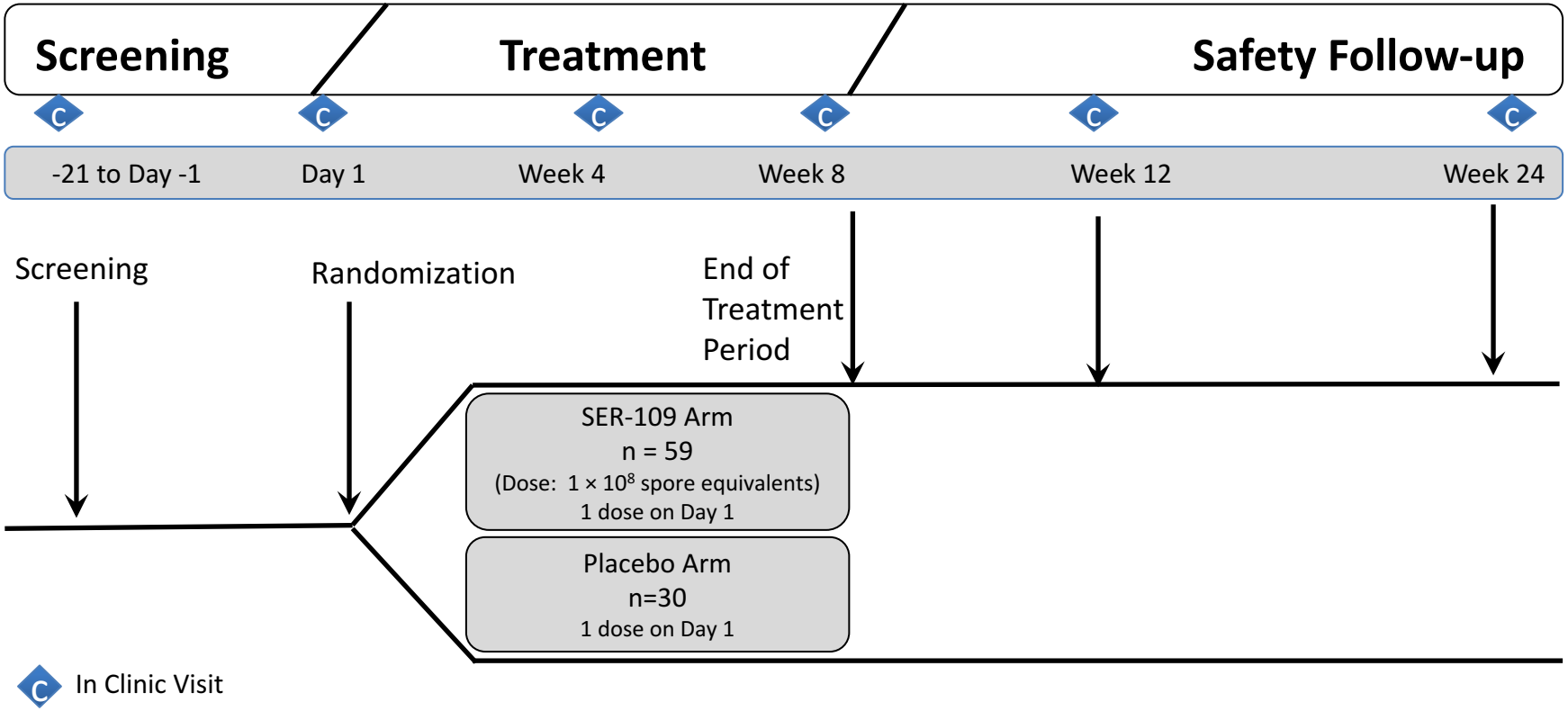
SER-109 Phase 2 ECOSPOR study overview



SER-109 Phase 1b and Phase 2 (8-week) study results

	Phase 1b Open Label, Single-Arm (n=30; 4 sites)	Phase 2 – Interim results Randomized, Placebo-Controlled (n=89; randomized 2:1; 28 sites)
Primary Endpoint	CDI recurrence up to 8 weeks defined by: >3 unformed stools over 1 day	CDI recurrence up to 8 weeks defined by: ≥3 unformed stools/day for ≥2 days
Efficacy	• 13% recurrence per protocol • 3 of 4 patients with recurrent transient diarrhea, did not require antibiotic treatment and tested negative for C. difficile at 8 weeks	• SER-109: 44% (26 of 59) recurrence • Placebo: 53% (16 of 30) recurrence • Relative risk recurrence between arms not significant • ≥65 and <65 years of age had differential results
Safety	• Most AEs were mild to moderate and transient • Most frequent AEs were gastrointestinal symptoms similar in nature to that seen in FMT trials or following CDI	• SER-109 is well-tolerated with an acceptable safety profile, it was associated with a small increase in gastrointestinal adverse effects, particularly diarrhea, compared to placebo (25% vs 14%)

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Comparison of SER-109 Phase 1b and Phase 2 studies

	Parameter	Phase 1b	Phase 2
Study Design	Overview	Open label; investigator sponsored; 4 sites; n=30	Placebo controlled randomized 2:1 SER-109:placebo; 28 sites enrolled subjects, n=89
	Endpoint	• CDI recurrence at up to 8 weeks defined by: • ≥ 3 unformed stools over 1 day • Positive *C. difficile* stool test (PCR or ELISA toxin assay)	• CDI recurrence at up to 8 weeks defined by: • > 3 unformed stools/day over 2 or more days • Positive *C. difficile* stool test (PCR or ELISA toxin assay) • Assessment by investigator that antibiotic is required
	Stratification	No prespecified stratification	<65 years old and ≥65 years old
	Antibiotics use prior to randomization	CDI antibiotic type selected by investigator; any duration	10 to 21 days, limited to vancomycin or fidaxomicin
	Inclusion criteria: Prior CDI recurrences	• ≥ 3 CDI episodes within 12 months, inclusive of current episode	• ≥ 3 CDI episodes within 9 months, inclusive of current episode
	Timing of SER-109 / PBO relative to antibiotic use	2 day post stopping antibiotics	2-4 days post stopping antibiotics
	Dose	Variable, from 3 X 10^7 to 2 X 10^9 spore equivalents Cohort 1 (n=15): 30 capsules over 2 days; Cohort 2 (n=15): 1-7 caps over 1 day	1 X 10^8 spore equivalents 4 capsules over 1 day
Study Demographics	Median prior recurrences	3 (2 to 6 range)	3 (2 to 7 range)
	Average age	61.9	64.5
	% Female	67%	67%
Drug Product	Manufacturing process	• Drug lots based on material from 7 donors	• Drug lots based on material from 3 new donors • Additional purification steps added to increase spore purity
	Formulation	• 1 to 30 capsules depending on spore concentration, desired dose	• 4 capsules, modified to facilitate automated fill

Note: Selected parameters

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SER-109 Phase 2 24-week study results

- Phase 2 efficacy results
  - 5 additional patients recurred after the 8 week primary endpoint in the SER-109 arm but 3/5 (60%) were patients who terminated the trial early (i.e., lost to follow-up - imputed recurrences)
  - 1 additional patient recurred in the placebo arm; this patient also terminated the trial early and was lost to follow-up
- Phase 2 safety results
  - SER-109 was generally well tolerated
  - The most common SER-109 treatment arm adverse events included diarrhea and abdominal pain
  - SER-109 may result in mild GI symptoms, as noted with fecal microbiota transplantation
  - Severe adverse event rate (15.0% for SER-109, 10.3% for placebo)
    - No SAEs were classified as drug related

Note: In study recurrences were diagnosed based on various *C. difficile* testing methodologies (i.e., PCR, GDH, cytotoxin)

SER-109 Phase 2 open label extension study results

- Open label extension (OLE) study (SERES-005) design:
  - Phase 2 subjects who experienced a *C. difficile* recurrence in the first 8 weeks following drug administration had the option to enroll in the 24-week OLE study to assess safety and efficacy
  - Same SER-109 regimen as Phase 2 study (i.e., SER-109 treatment following antibiotic course to treat acute *C. difficile* recurrence)
  - 34 subjects entered the OLE study (21 from SER-109 arm; 13 from placebo arm)
- Study results:
  - SER-109 was found to be generally well tolerated. The most common AEs observed were diarrhea and abdominal pain
  - Recurrences in the OLE study: 11/34 overall (68% non-recurrence)

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SER-109 Analyses & Findings

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Organization of SER-109 study analyses

Analysis component	Key issues addressed
Clinical	• Detailed analyses of clinical data • Investigation of *C. difficile* diagnostics
Pharmacodynamics / microbiome analyses	• Investigation of drug activity
Chemistry, Manufacturing and Controls (CMC)	• Drug product distribution and handling • Phase 1b to Phase 2 manufacturing and formulation changes, and potential impact on drug activity

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Comparison of common *C. difficile* diagnostic tests

Test	Basis of test	Comments
PCR	• Detects genes encoding cytotoxins • Most sensitive test • Does not distinguish *C. difficile* carriage from active infection	• Most common test in U.S. • Used for 80.9% of entry tests and 74% of exit tests in Phase 2 study
EIA GDH	• Enzyme immunoassay for GDH, an essential *C. difficile* protein • Does not distinguish *C. difficile* carriage from active infection	• Only used in conjunction with EIA cytotoxin test • Increases specificity of cytotoxin test
EIA Cytotoxin	• Enzyme immunoassay for cytotoxin • Detects both cytotoxins A and B • Less sensitive than PCR	• Cytotoxin protein is the signature of an active infection

Misdiagnosis of *C. difficile* carriage as infection could impact both: 1) inclusion of the proper patient population, and 2) accurate measurement of the study endpoint

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Analysis of *C. difficile* diagnostic test: Qualifying episode

- PCR was the most common method used to qualify patients for enrollment into Phase 2 study: 72 of 89 (80.9%) subjects were diagnosed by PCR
  - Qualifying Phase 2 stool samples were not available for re-testing by Cytotoxin EIA
- Available stool samples that qualified subjects for the open label extension study were re-tested to examine the hypothesis that PCR diagnostics may have enabled inclusion of non-eligible subjects:
  - Of the 34 subjects entering the open label extension study, 31 were re-tested
  - 15/31 (44%) tested positive by cytotoxin either on study or at retest (16/31 subjects who tested positive by PCR did not test positive by cytotoxin)

- Applying this information to the Phase 2 study, some subjects may have entered the study without recurrent *C. difficile* infection
- Inclusion of misdiagnosed patients may have reduced Phase 2 study power, and complicated the interpretation of study results

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Analysis of *C. difficile* diagnostic test: Phase 2 recurrence endpoint results

- 32 of 42 (76%) of Phase 2 stool samples associated with a presumed recurrence were available to be analyzed by re-testing for cytotoxin by an independent laboratory

	Testing laboratory results				
	Placebo		SER-109		RR (95% CI)
Source of Recurrence C. *difficile* Test Results	n	Number with Recurrence (%)	n	Number with Recurrence (%)	
On Study (all test methods)	30	16 (53.3%)	59	26 (44.1%)	1.22 (0.79, 1.88)
Re-Test Results: Recurrence results based only on positive cytotoxin test, either on study or at re-test (i.e., high confidence recurrences)	21	7 (33.3%)	44	11 (25.0%)	1.46 (0.71, 3.03)

Note: Dataset demonstrates the Phase 2 endpoint *C. diff.* diagnostic results, and includes a portion of the dataset described on slide 13

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

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SER-109 Microbiome Response & CMC Analyses

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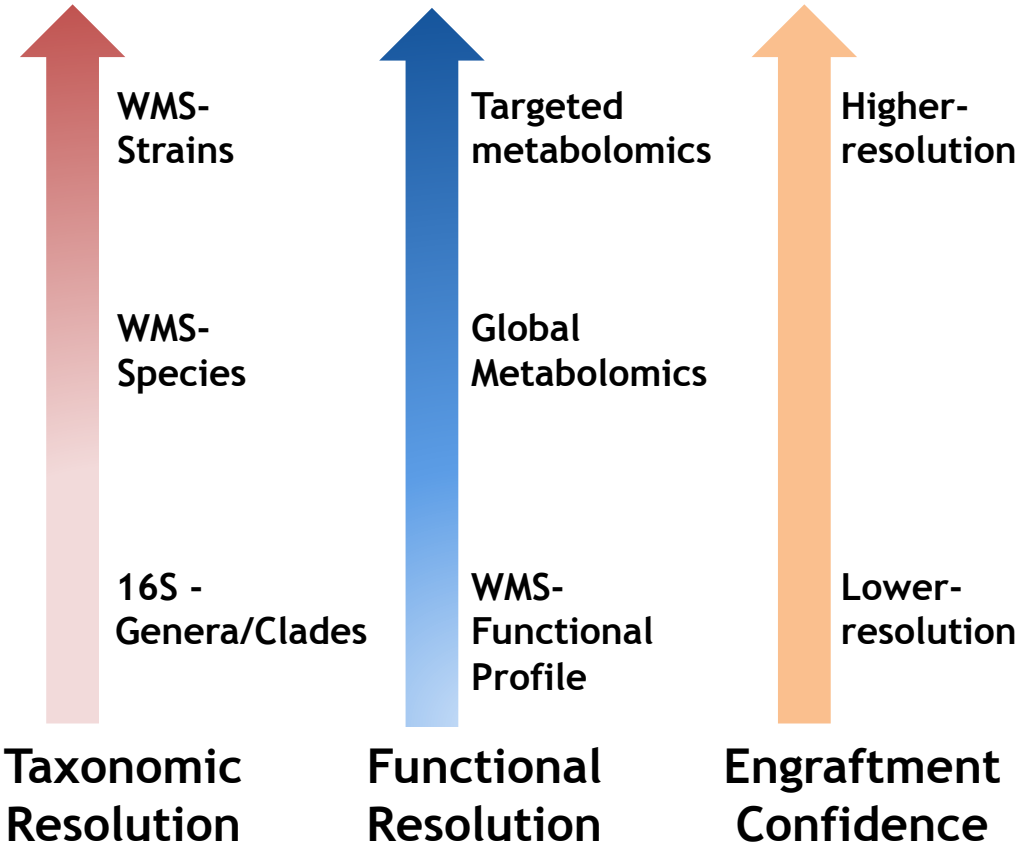
Seres microbiome platforms

- Microbiome dynamics interrogated using genomic, metabolomic, and microbiology platforms
- Genomic tools leverage 16S ribosomal gene sequencing, and Whole Metagenomic Sequencing (WMS) data types
- Metabolomic tools leverage broad global profiling and targeted functional data for specific metabolic pathways
- As part of the Phase 2 analyses, tools & algorithms to assess microbiome pharmacokinetics & pharmacodynamics at high-resolution have been refined:
  - Developed novel computational approaches to detect & model engraftment of specific species & strains using WMS data
  - Broadened functional profiling capabilities to model microbiome dynamics; developed novel algorithms for high-resolution, integrated analysis of WMS and metabolomic data sets



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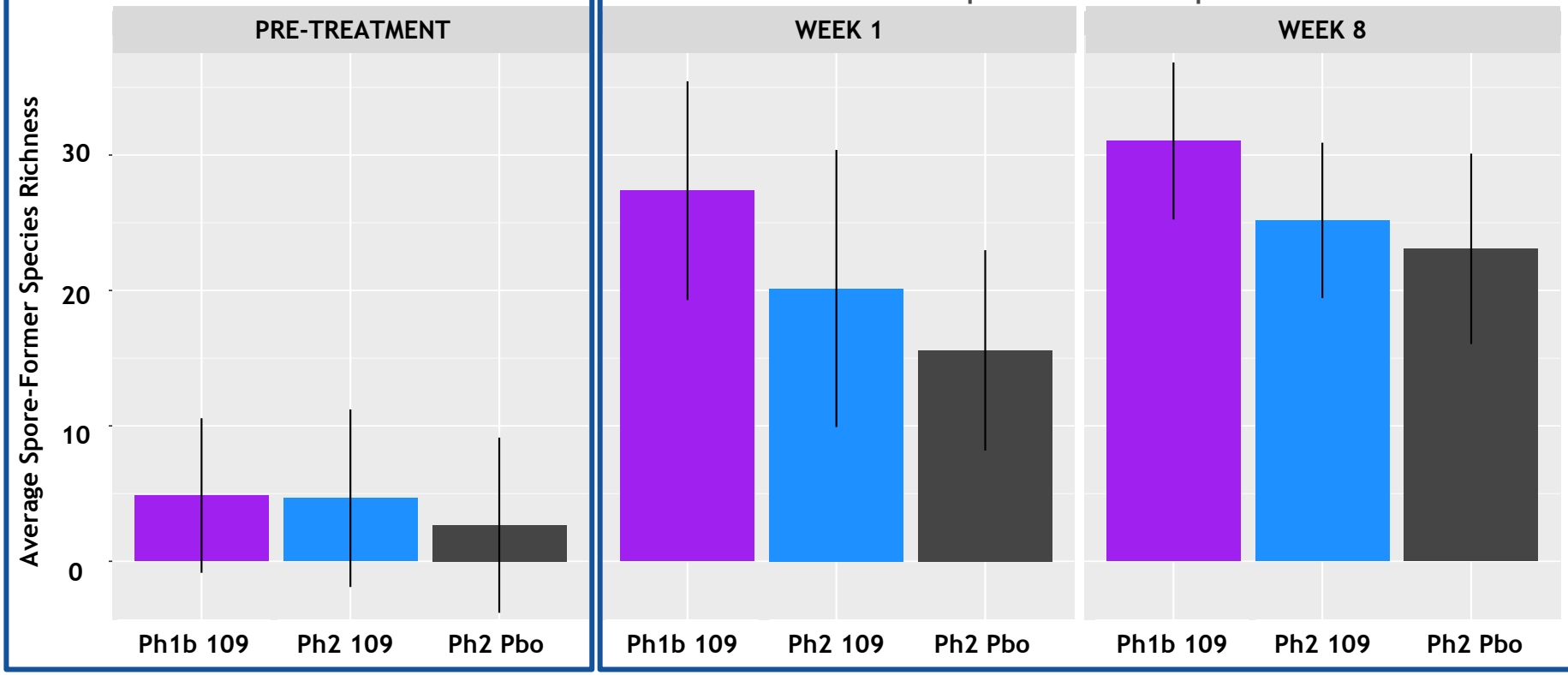
SER-109 treatment demonstrates increased microbiome diversity

Comparable dysbiosis in commensal spore-former bacterial diversity in Ph1b & Ph2 subjects prior to treatment

Dysbiotic microbiome is on average 5 fold lower diversity than Human Microbiome Project healthy controls

Demonstrated in Ph2 an increase in diversity of commensal spore-former bacteria with significantly greater response in SER-109 vs Pbo at Week 1

Ph2 increase in commensal spore-former bacteria is significantly less robust at Weeks 1 & 8, and achieved maximum change more slowly as compared to Ph1b response



Note: Data reported as mean ± standard deviation

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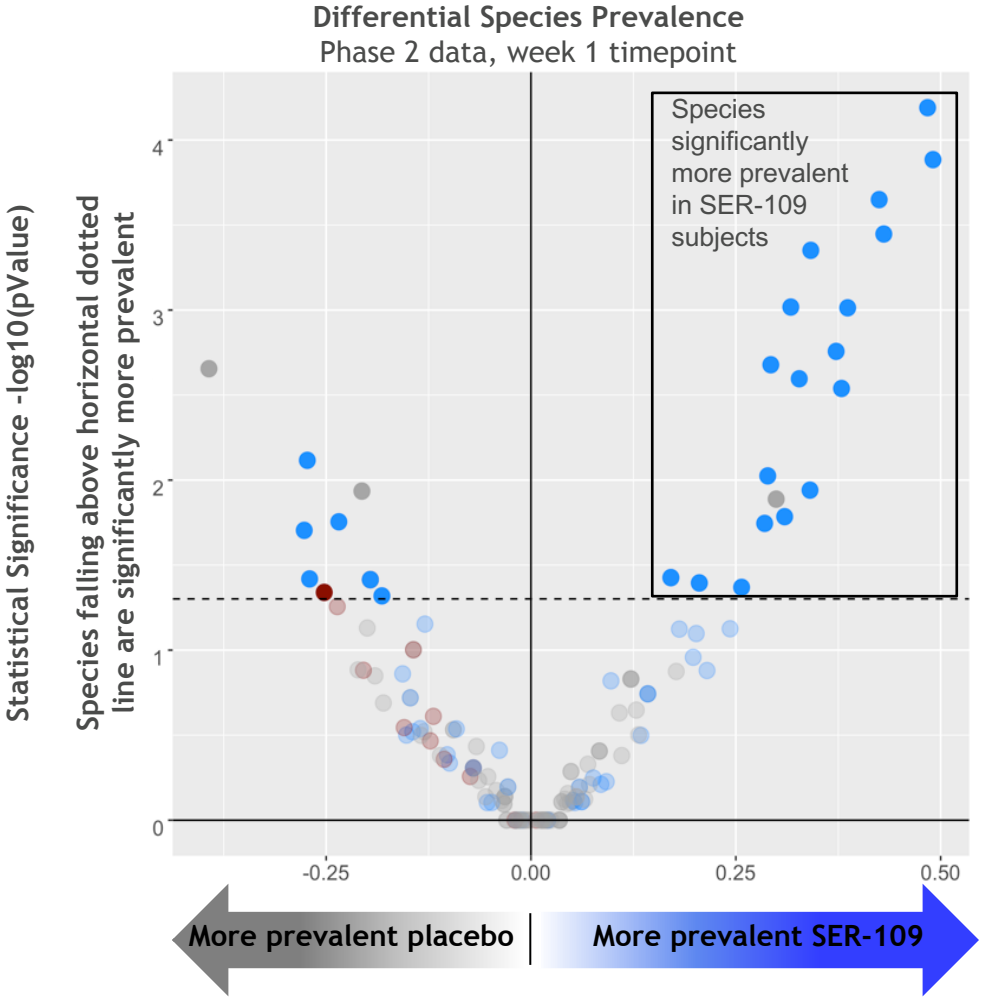
Increased prevalence of SER-109 associated bacterial species observed in Phase 2 patients treated with SER-109



Differential prevalence plot; non-transparent, colored points represent species that are significantly more prevalent in SER-109 or Placebo. Spore-former species (blue), opportunistic pathogens (maroon), other (grey)

- 20 spore-forming species were significantly more prevalent in subjects treated with SER-109 as compared to placebo
  (Note: some points are overlapping and appear as a single point in plot)
- 6 spore-forming species were significantly more prevalent in placebo treated subjects
- Opportunistic pathogens were more prevalent in placebo treated subjects
  (Note: none were more prevalent in SER-109 subjects)

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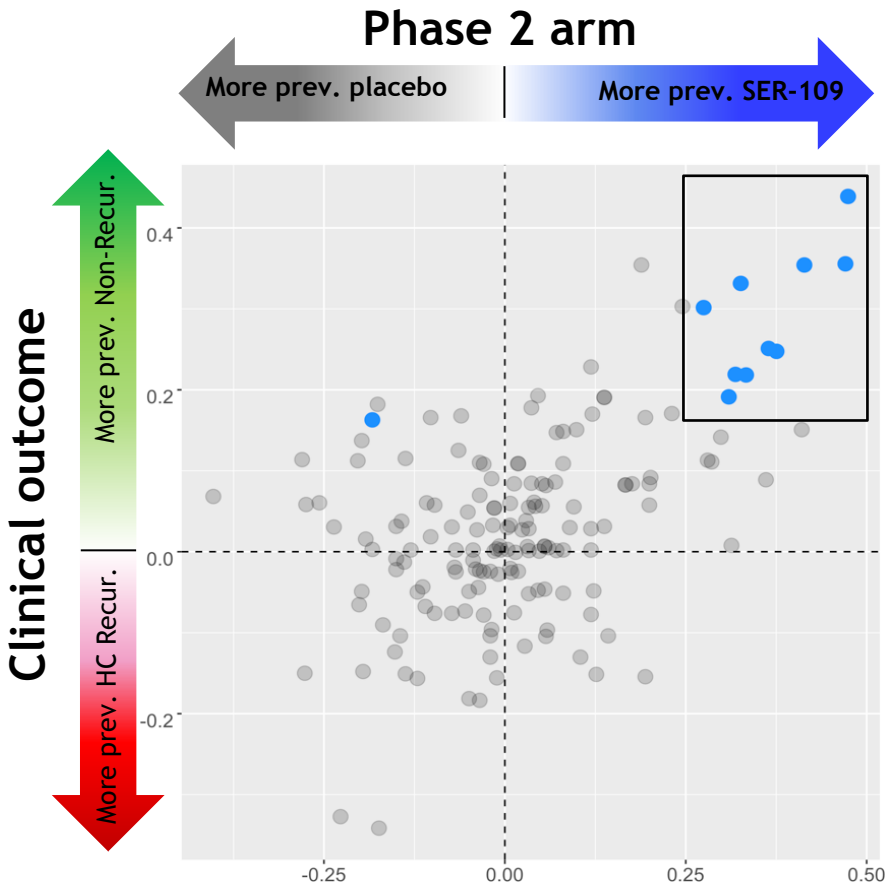
Microbiome signatures specific to SER-109 treatment may lead to positive clinical outcome



Differential prevalence plot; 1-week data; colored points represent species that are significantly more prevalent in arm:outcome category

HC-R indicates high confidence recurrences, defined as recurrences associated with a positive *C. diff.* cytotoxin diagnostic test

- Commensal spore-former species richness is significantly less in cytotoxin-positive recurrent subjects versus non-recurrent subjects (not shown)
- High-resolution genomic analyses have identified bacterial species that are significantly more prevalent in SER-109 treated subjects who did not recur (black box)
- Metabolomic functional analysis (not shown) provided supporting evidence of microbiome driven changes in metabolic activity that may increase pathogen resistance

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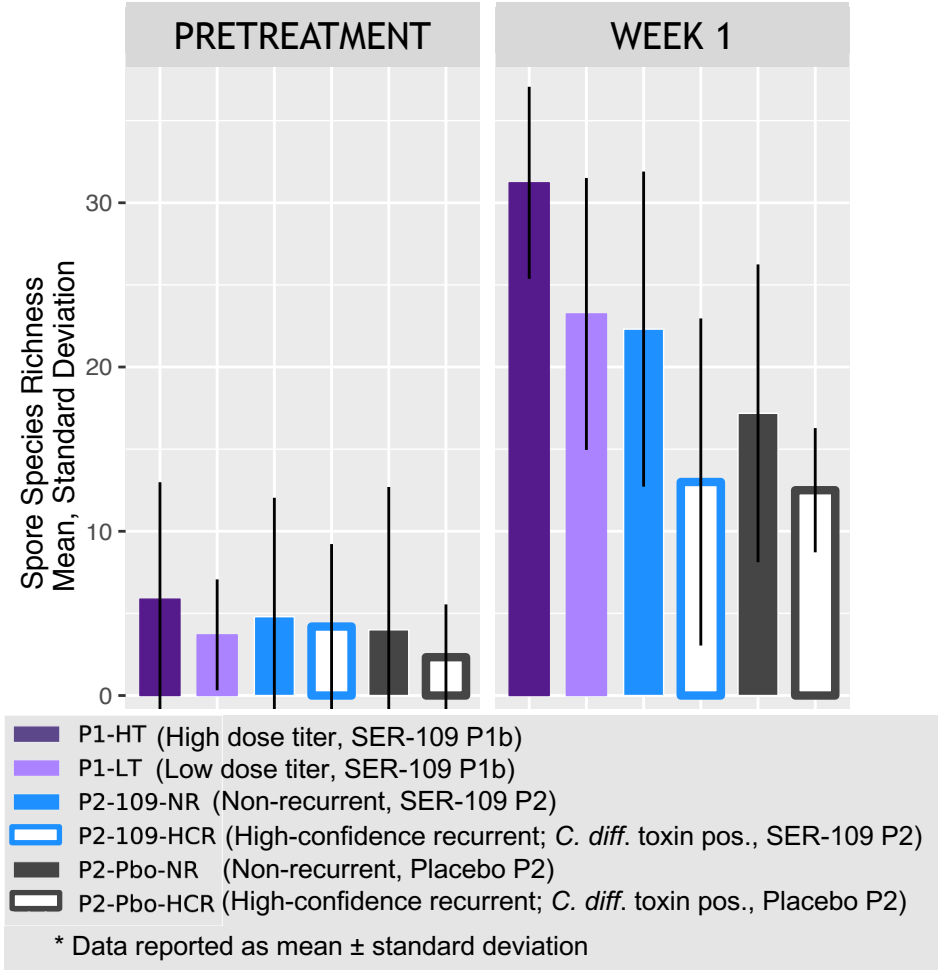
Dose impacts Phase 1b vs. Phase 2 microbiome dynamics



- Phase 1b subjects who received a higher dose (dark purple) achieved a significantly greater increase in diversity of commensal spore-former bacteria by 1wk post-treatment as compared to all other groups
- Phase 1b (light purple) and Phase 2 (blue) subjects treated with a comparable dose had similar increase in spore-former richness
- Above differences were maintained at 8 weeks post-treatment (not shown)
- Placebo treated subjects (grey) had weaker response than SER-109 treated subjects (blue)
- Both SER-109 and placebo treated cytotoxin-positive recurrent subjects (outlined bars) had reduced diversity of spore-forming species

Analyses suggest that suboptimal dosing in some patients may have contributed to the previously reported SER-109 Phase 2 study outcome

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SER-109 Phase 2 CMC Analyses

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CMC: Detailed analyses did not reveal any detectable causative issues

- Several steps in the manufacturing and formulation SER-109 process were different between the Phase 1b and the Phase 2 studies
  - Changes in manufacturing to increase the purity of the SER-109 spores
  - Changes in formulation (capsule design) to enable higher throughput manufacturing
- Detailed analyses have not revealed any statistically significant differences between the Phase 1b and Phase 2 materials including:
  - Spore viability and dose, as measured by culture assays and mouse *C. difficile* preclinical challenge model
  - Spore diversity, as measured by genomic assay
  - Excipient profile

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Next Steps for SER-109 development

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Strong rationale for further SER-109 clinical development

- Phase 2 analysis data suggest parameters for future clinical development of SER-109
  - **Diagnosis -** Utilization of *C. difficile* cytotoxin assay for both patient study inclusion and assessment of recurrence endpoint
  - **Dose** - Increased SER-109 dosage seeking to favor a rapid increase in microbiome diversity following antibiotic treatment
    - Favorable safety profile observed to date supports increasing dose
- High unmet medical need remains for an effective, safe, oral therapy for recurrent *C. difficile* infection
- FDA discussions regarding a new clinical study of SER-109 are in progress

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