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Leading the Microbiome Revolution

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**

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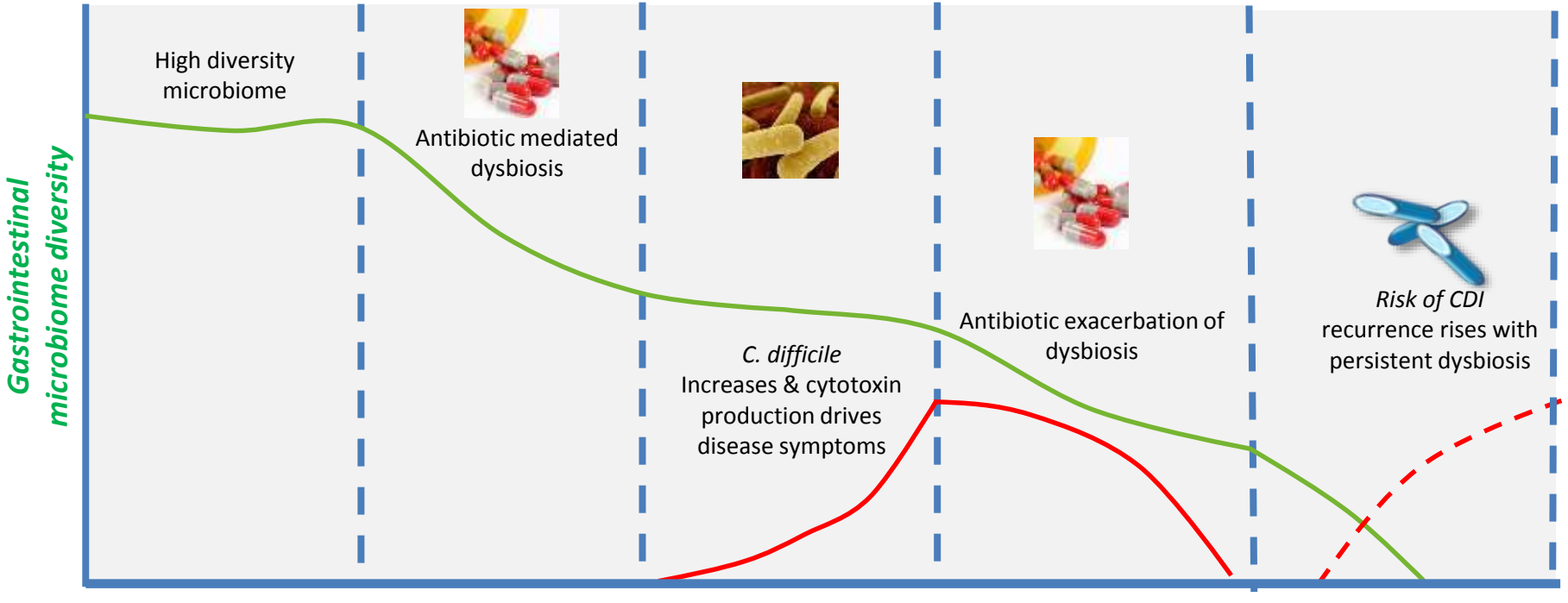
Clostridium difficile infection (CDI) is a 2-hit process requiring a 2-pronged treatment approach



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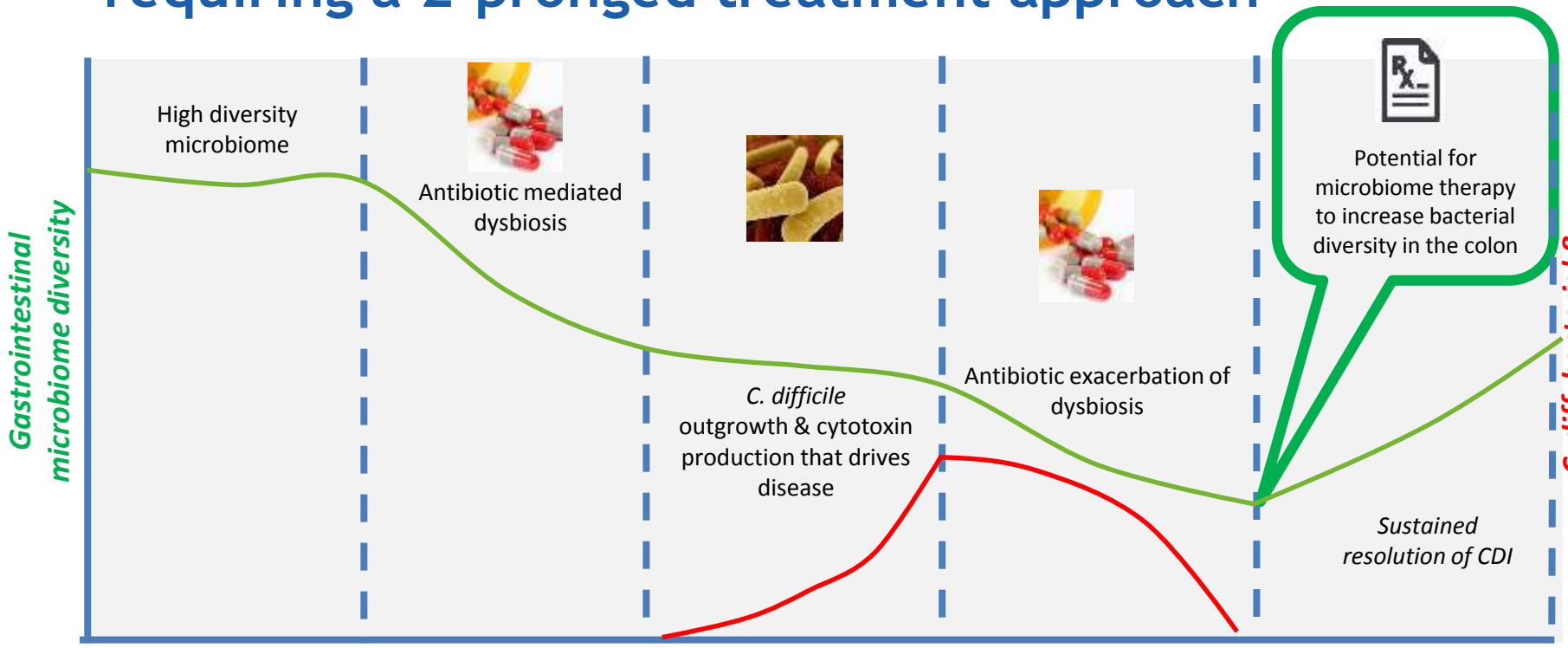

Healthy person with intact colonization resistance

Antibiotics create ecologic holes in microbiome leading to dysbiosis

Exposure *to C. difficile* in a vulnerable patient leads to active infection

Antibiotic mediated killing of vegetative forms only

Restoration of colonization resistance

Hypothetical patient course

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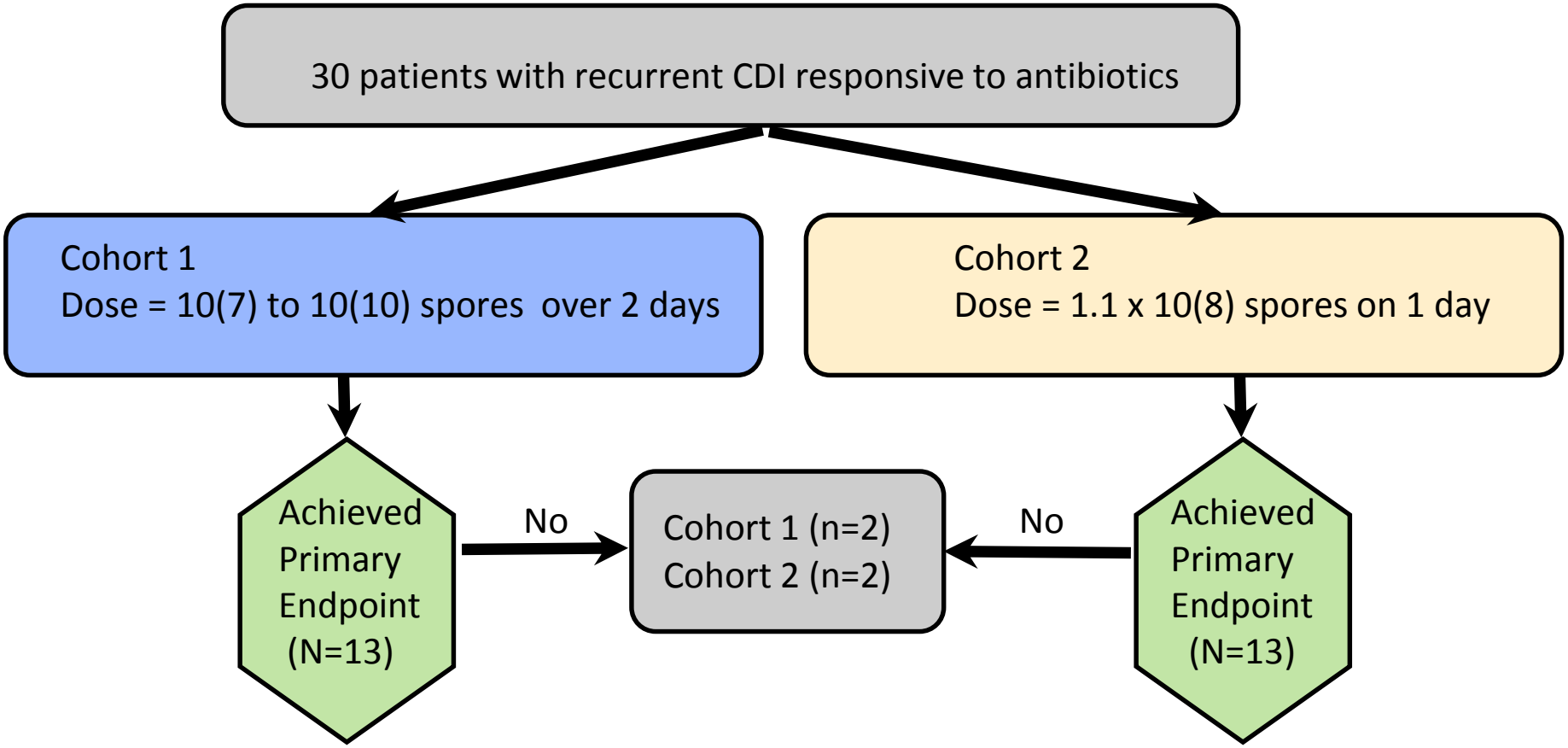
SERES-001: Phase 1b Study of SER-109 to Prevent RCDI



Primary endpoint achieved in 26 of 30 patients (86.7%)
Led to use of 1x10(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

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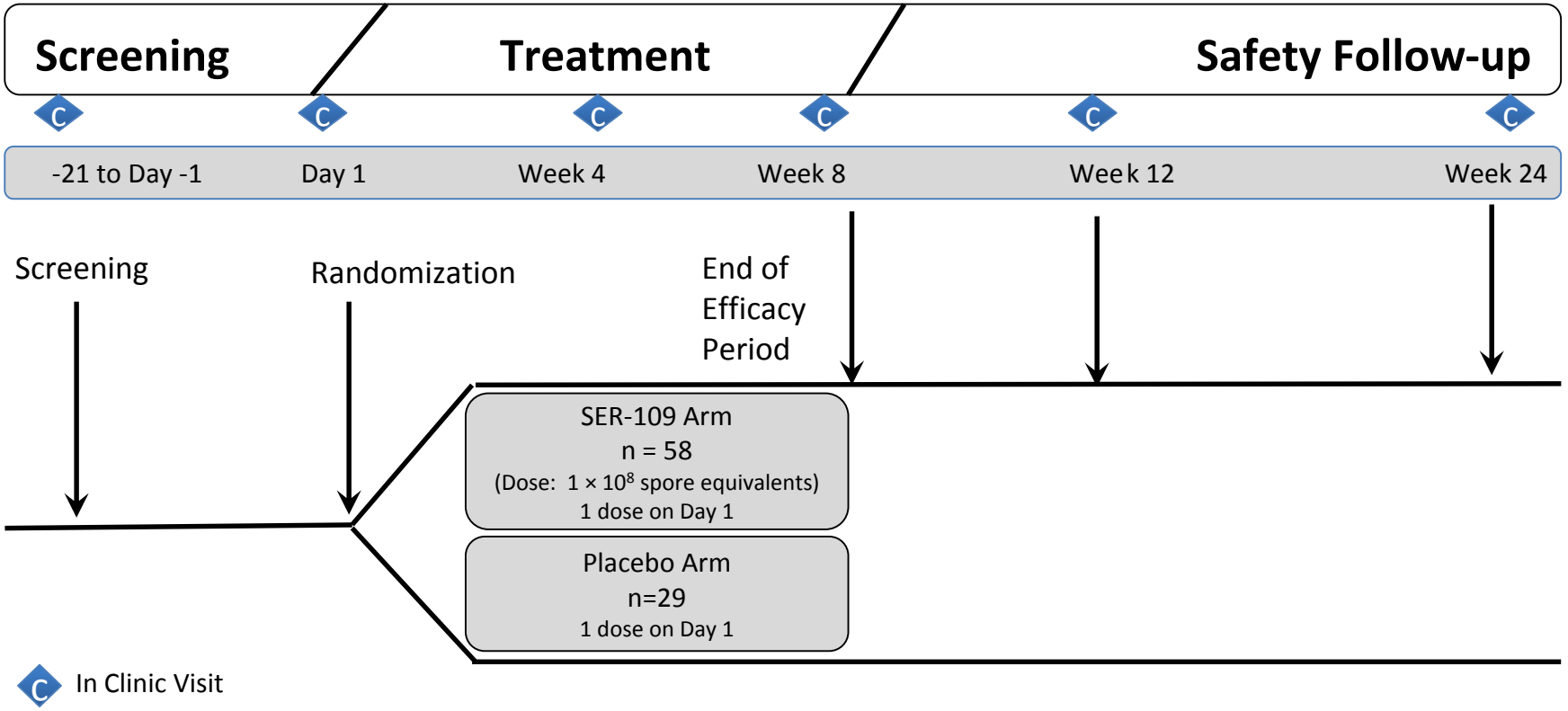
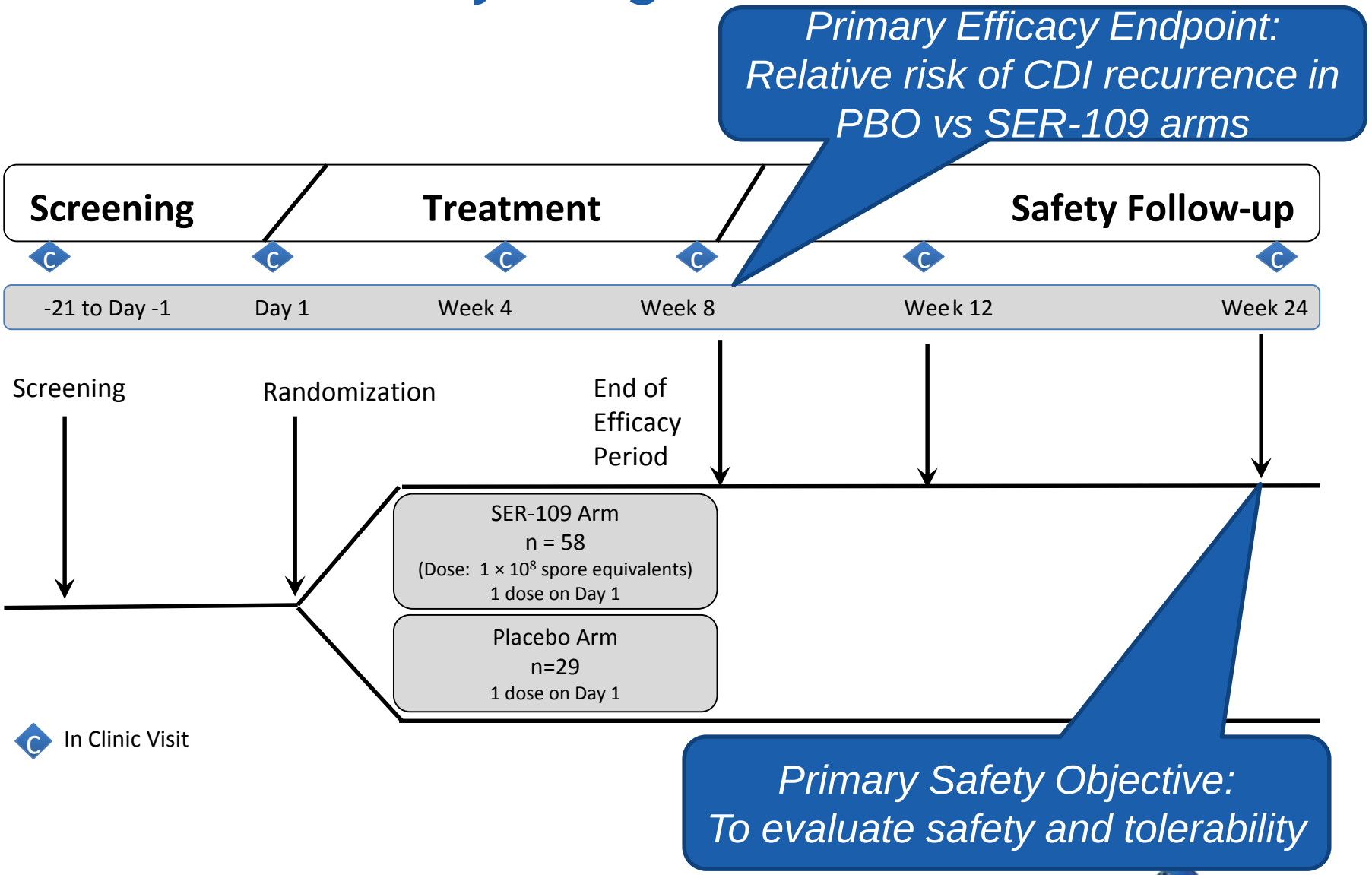
Schematic of Study Design



Schematic of Study Design



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

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Demographic and Baseline Characteristics

	Statistic	SER-109 (N=59)	Placebo (N=30)	Overall (N=89)
Age (years)	n	59	30	89
	Mean	63.7	66.1	64.5
Sex	n (%)			
Female		40 (67.8)	20 (66.7)	60 (67.4)
Male		19 (32.2)	10 (33.3)	29 (32.6)
Number of Prior CDI Episodes	n (%)			
3		28 (47.5)	20 (66.7)	48 (53.9)
4		21 (35.6)	5 (16.7)	26 (29.2)
≥5		10 (16.9)	5 (16.7)	15 (16.9)

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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

Adverse Event	Treatment Arms	
	SER-109 N = 60 N (%)	Placebo N = 29 N (%)
Diarrhea	15 (25)	4 (14)
Abdominal pain	13 (22)	4 (14)
Flatulence	7 (12)	1 (3)
Nausea	6 (10)	3 (10)
Constipation	3 (5)	1 (3)

- Serious adverse event (SAE) rate (15.0% for SER-109, 10.3% for placebo)
  - No SAEs were classified as drug related

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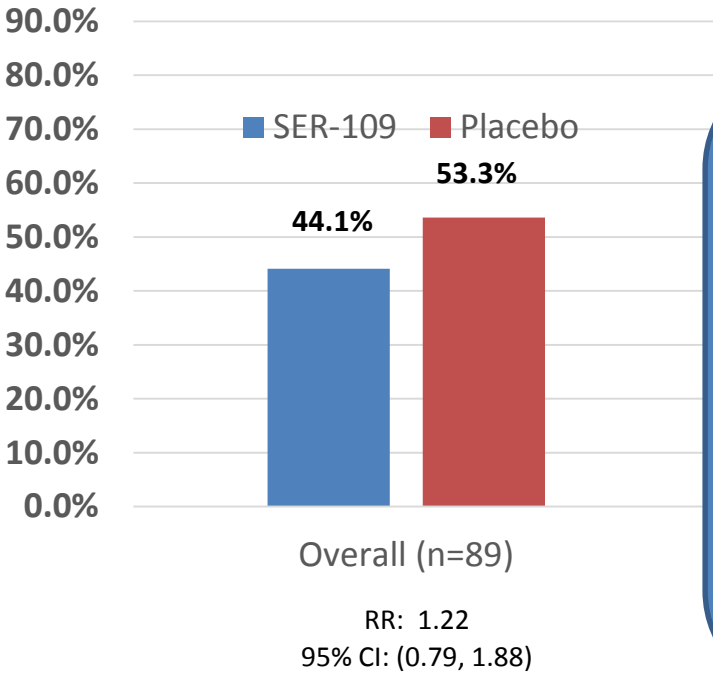
Primary Efficacy Endpoint:
CDI Recurrence Rates and Relative Risks in ITT Population



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)

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Diagnostics

CDI Diagnostics in SERES-004

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

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Diagnostics at Time of Recurrence: Retesting for Cytotoxin by Independent Laboratory

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

	Testing laboratory results				
	Placebo		SER-109		RR (95% CI)
Diagnostic Test	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)
Positive cytotoxin testing either on-study or at re-test*	21	7 (33.3%)	44	11 (25.0%)	1.46 (0.71, 3.03)

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

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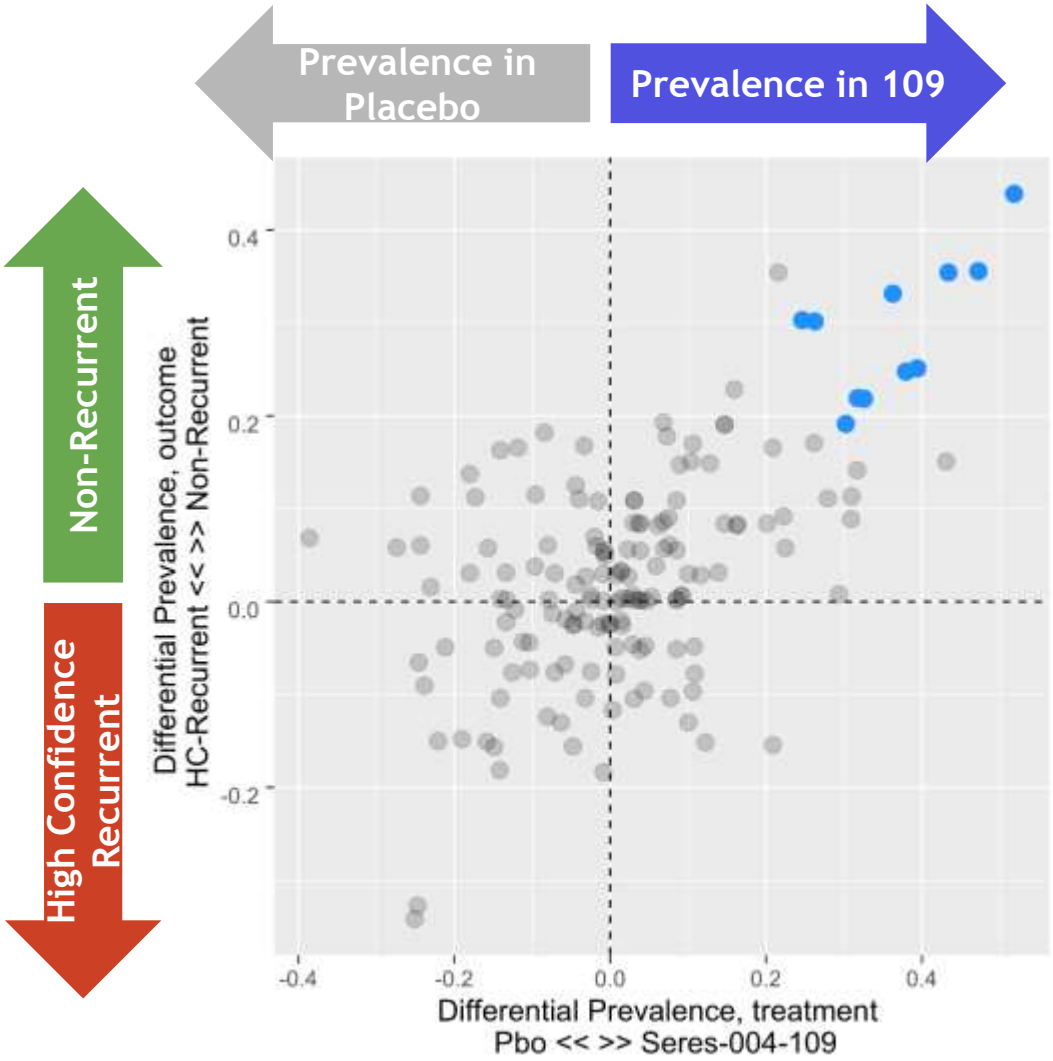
Dose

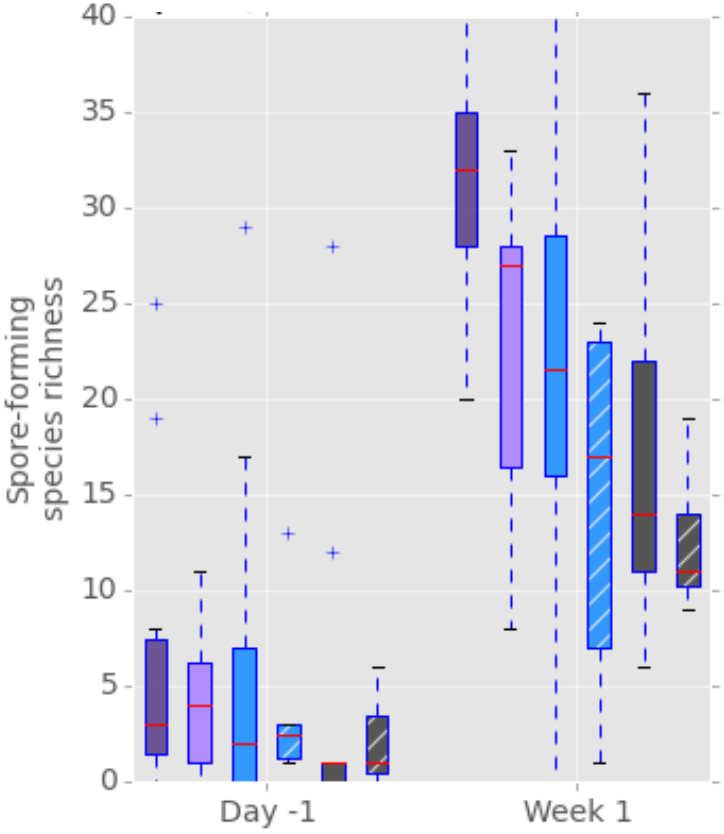
Increased prevalence of engrafted SER-109 strains is correlated with non-recurrence

- 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

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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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