Speed Dating - New CDI Agents

IDAC Sunday May 7, 2023

Ellie JC Goldstein MD

Director

RM Alden Research Laboratory

Conflicts of Interest 2023

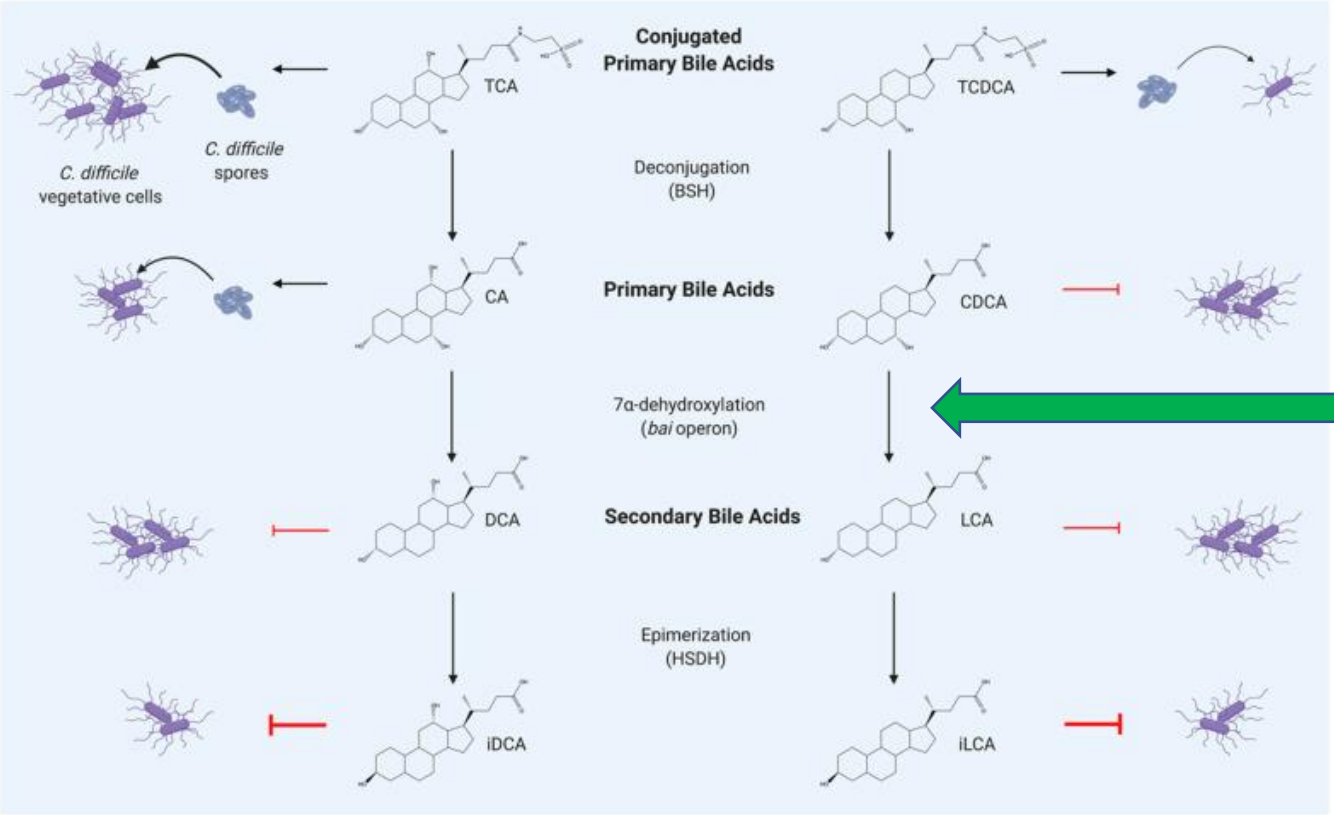
- **Advisory Boards:**
- **Acurx Pharmaceuticals LLC,**
- **Bio K +,**
- **Merck Pharmaceuticals,**
- **Rebiotix**
- **Shionogi Pharma,**
- **Summit LLC**
- **Symbiotix**
- **Speakers Bureau: Merck, Shionogi**

New CDI Agents

- **Ridinilazole (SMT-1998)**
- **Ibezapolstat (ACX-362E)**
- **Non-toxogenic *C difficile (NTCD-M3)***
- **Reboyta (RBX 2660)**
- **SER 109**
- **VE303**

Why does *C. difficile* require dysbiosis to cause infection?

Answer: Bile acids!



Primary bile acids: BAD (promote C diff germination)

Healthy colon concentration: usually very low

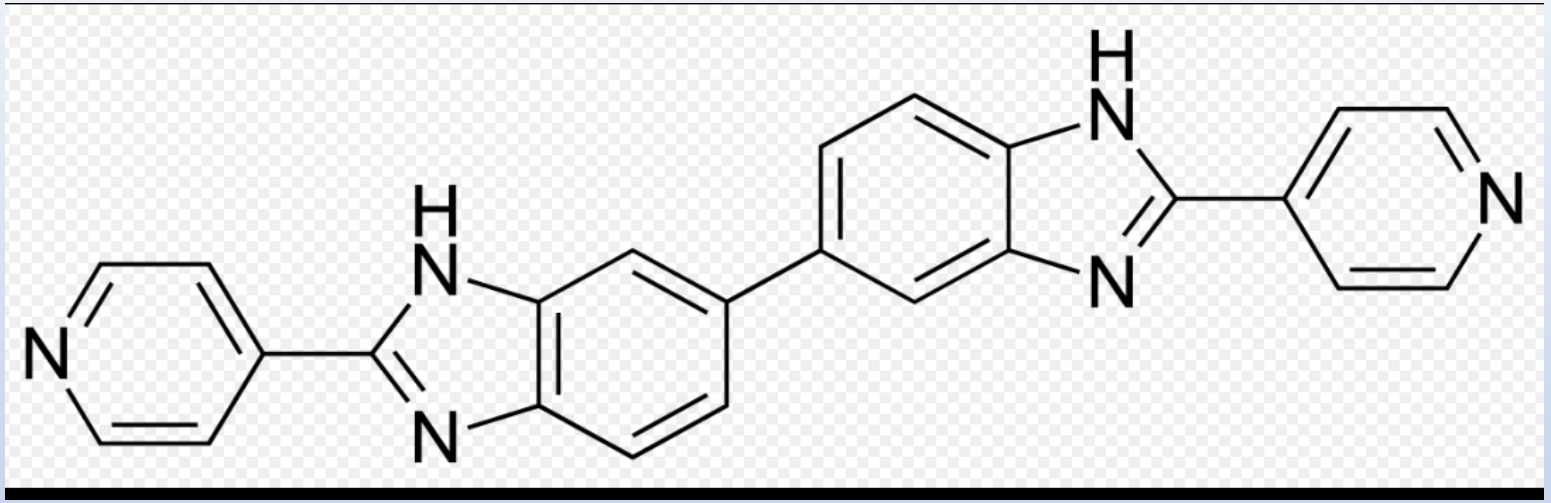
Bile acids are converted by specific gut microbiota

Secondary bile acids: Good (inhibit C diff growth)

Healthy colon concentrations: usually high

Most important taxa responsible for converting primary to secondary bile acids: Clostridiales

Ridinilazole



- **Non absorbable**
- **Does not act through cell wall inhibition**
- **Nor via lipid, protein, RNA or DNA synthesis**
- **Likely impairs cell division- elongates cells and inhibits sporulation**
- **Narrow spectrum**

Less Microbiome change compared to vancomycin

Table 1
In vitro minimum inhibitory concentrations (MICs) of ridinilazole, fidaxomicin, vancomycin and metronidazole for distinct ribotypes of *Clostridium difficile*.

Ribotype/Drug	MIC (μg/mL)			Reference
	Range	MIC_{50}	MIC_{90}	
Ribotype 001 ($n = 10$)				
Ridinilazole	0.06–0.125	0.125	0.125	[58]
Fidaxomicin	0.008–0.06	0.03	0.06	
Vancomycin	0.5–4	1	4	
Metronidazole	0.125–1	1	1	
Ribotype 002 ($n = 8$)				
Ridinilazole	0.125–0.25	0.25	NR	[60]
Fidaxomicin	0.06–0.25	0.25	NR	
Vancomycin	1–2	1	NR	
Metronidazole	0.25–0.5	0.5	NR	
Ribotype 005 ($n = 3$)				
Ridinilazole	0.25	0.25	NR	[60]
Fidaxomicin	0.06–0.25	0.25	NR	
Vancomycin	2	2	NR	
Metronidazole	0.5	0.5	NR	
Ribotype 014 ($n = 8$)				
Ridinilazole	0.125–0.25	0.125	NR	[60]
Fidaxomicin	0.06–0.5	0.25	NR	
Vancomycin	1–2	1	NR	
Metronidazole	0.25–0.5	0.5	NR	
Ribotype 027 ($n = 11$ [58]; $n = 11$ [60])				
Ridinilazole	0.25–0.5	0.25	0.25	[60]
	0.125–0.25	0.125	0.125	[58]
Fidaxomicin	0.5–1	0.5	0.5	[60]
	0.03–0.06	0.06	0.06	[58]
Vancomycin	1–8	2	4	[60]
	0.5–4	1	2	[58]
Metronidazole	2–8	2	8	[60]
	1–2	2	2	[58]
Ribotype 054 ($n = 4$)				
Ridinilazole	0.125–0.25	0.25	NR	[60]
Fidaxomicin	0.125	0.125	NR	
Vancomycin	1–2	1	NR	
Metronidazole	0.5	0.5	NR	
Ribotype 106 ($n = 10$ [58]; $n = 3$ [60])				
Ridinilazole	0.25	0.25	NR	[60]
	0.125–0.25	0.125	0.125	[58]
Fidaxomicin	0.5	0.5	NR	[60]
	0.03–0.125	0.06	0.125	[58]
Vancomycin	1	1	NR	[60]
	0.5–4	1	2	[58]
Metronidazole	0.5	0.5	NR	[60]
	1–2	2	2	[58]

$MIC_{50/90}$, MIC for 50% and 90% of the organisms, respectively; NR, not reported.

Ridinilazole

Menlo Park, CA, July 14, 2022 (GLOBE NEWSWIRE)

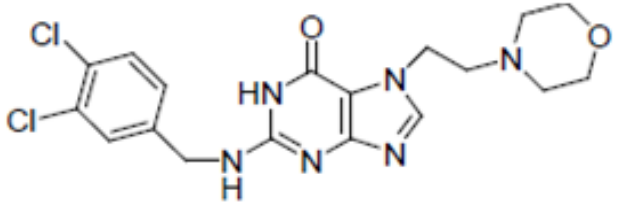
Summit and the US FDA held a Type C meeting during which Summit discussed certain data from the Ri-CoDIFy Phase III clinical trial with the agency. The FDA and Summit discussed a possible pathway in which to advance ridinilazole forward with the goal of achieving marketing authorization. This pathway would involve reasonable efforts that would likely involve at least one additional clinical trial.

759 pts randomized 1:1 ridinilazole (BID) vs vancomycin (QID) x 10D

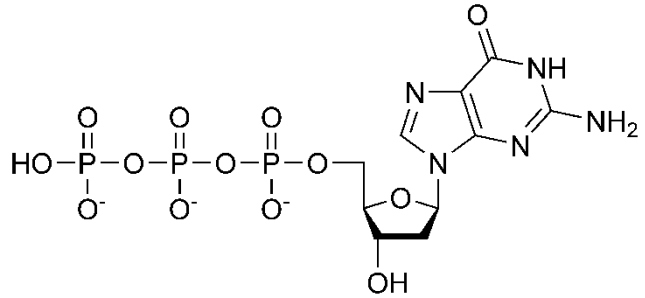
Summit has publicly disclosed that they are looking to partner in order to go through US approval

Ibezapolstat (IBZ; ACX362E)

- **A New Class of antibiotic**

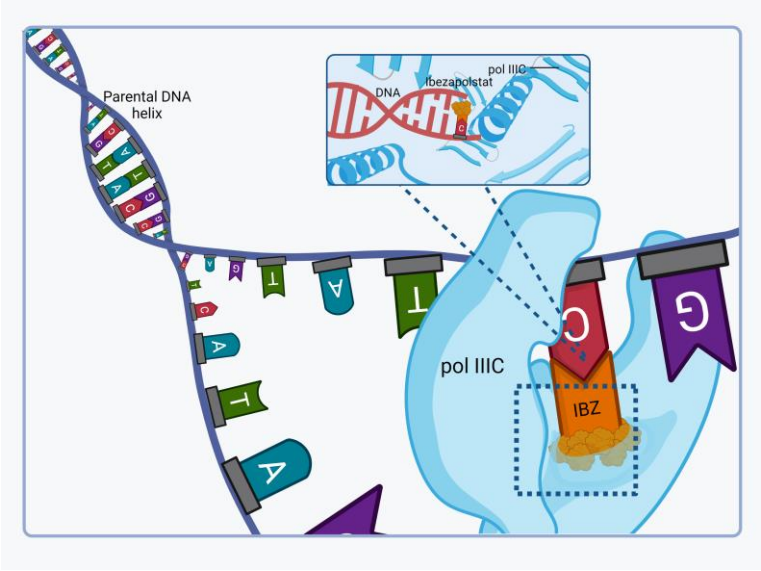


ACX-362



dGTP

- Ibezapolstat: small-molecule inhibitor of DNA pol IIIC enzyme based upon competitive inhibition of dGTP (guanosine analog)
  - DNA pol IIIC: essential for replication of low G+C content Gram-positive bacteria (Firmicutes)
  - Novel mechanism of action GPSS™ (**G**ram **P**ositive **S**elective **S**pectrum)



Xu et al. Bioorg Med Chem. 2019 Aug 1;27(15):3209-3217;
https://www.nature.com/articles/d43747-021-00149-0
Figure by BioRender created by Avalon Starr

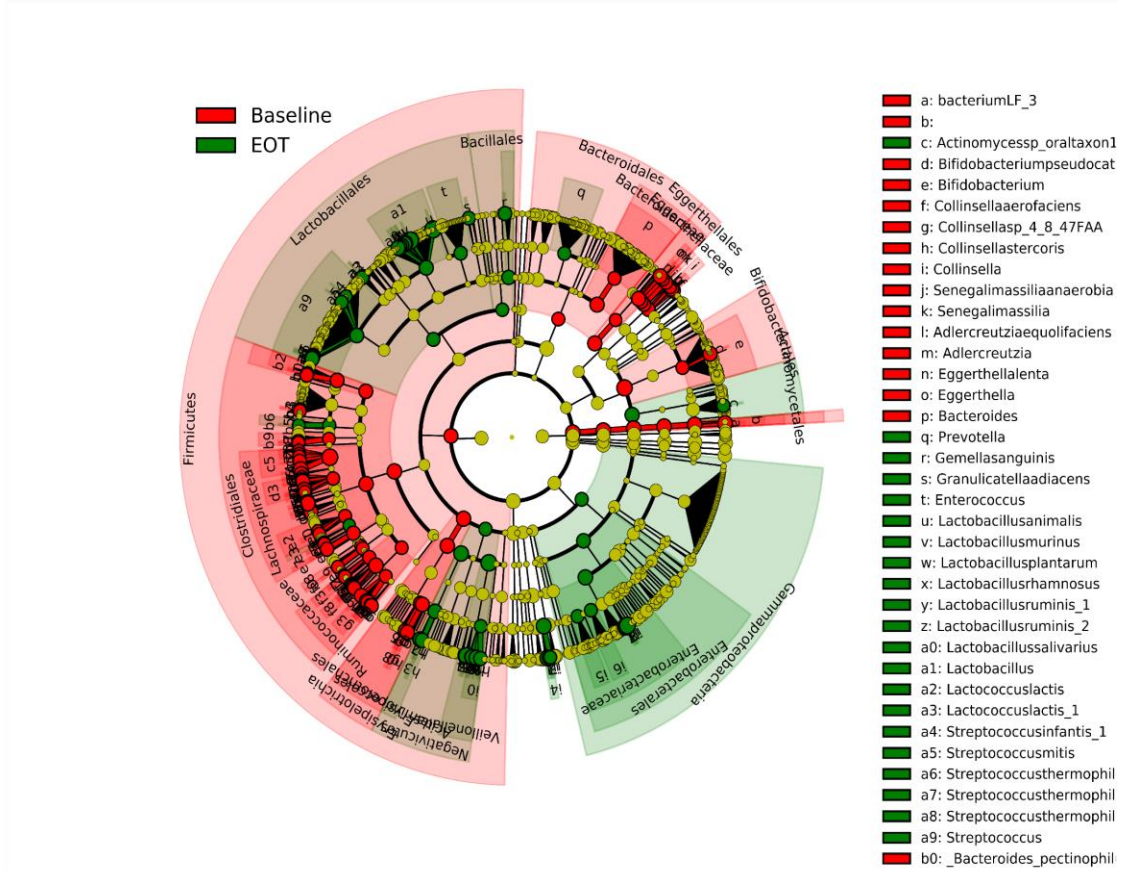
IBZ Clinical update

- Phase 1, Healthy Volunteer: Completed
  - IBZ 450 mg twice daily chosen for phase 2 studies
    - Garey et al. *J Antimicrob Chemother* 2020.
  - Microbiome evaluations predicted an anti-recurrence effects
    - *McPherson et al. *Antimicrob Agents Chemother* 2022
- Phase 2a (n=10): Completed
    - *Garey et al. Clin Infect Dis 2022
- Phase 2b (n=64): Enrolling with up to 30 US clinical sites
  - IBZ 450 mg twice daily (n=32) vs. vancomycin 125 mg PO four times daily (n=32)
  - ClinicalTrials.gov Identifier: NCT04247542

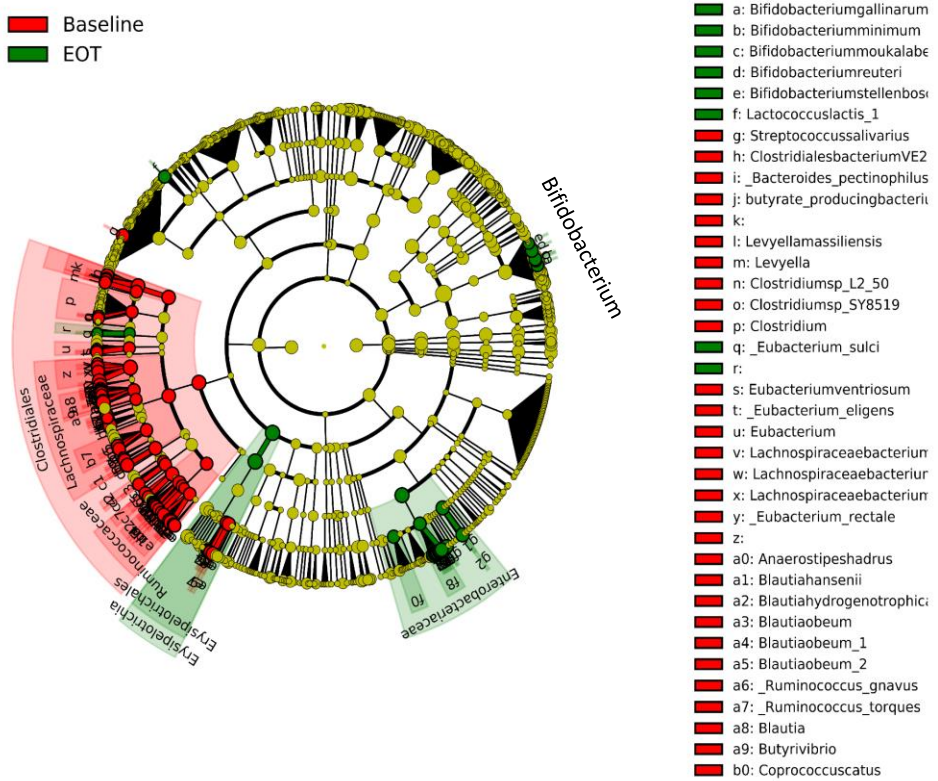
*Will focus most of our attention here along with ongoing follow-up studies

IBZ had a more selective change in Firmicutes vs. vanco

A. Vancomycin Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)



B. Ibezapolstat Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)



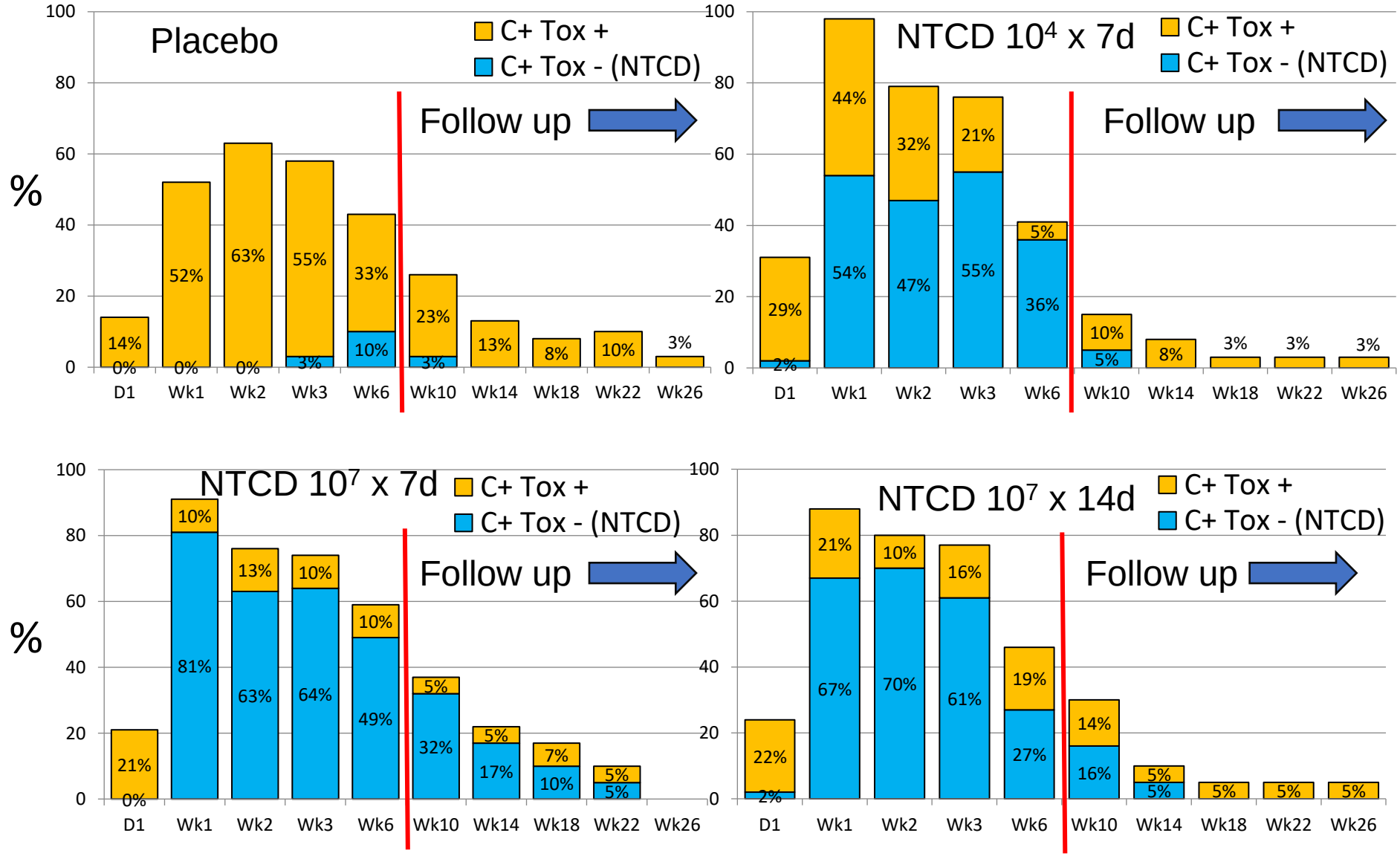
Conclusions: IBZ for the treatment of CDI

- Clinical Trial
  - IBZ: Ideal PK characteristics (high fecal concentrations / minimal systemic exposure)
  - Well tolerated in healthy volunteers and CDI patients
- Microbiome Results
  - Added value of an active comparator (vancomycin) control group in PH1 – this pioneering approach may become the new paradigm for early-phase CDI drug development
  - Metagenomics with bile acid data allowed PH1 trial prediction of CDI anti-recurrence properties
  - Beneficial effects on the fecal microbiome in CDI patients consistent and expanded from PH1 results
- Results support further development of ibezapolstat
  - Using PH1 and PH2a data, a strong hypothesis for an anti-CDI recurrence effect has been developed and is being tested in the ongoing PH2b trial

Spores of Nontoxigenic C. difficile Strain M3 for Prevention rCDI: Randomized Clinical Trial

- Dale N. Gerding, et al. JAMA 313:1739, 2015

- 168 patients who started treatment, 157 completed treatment.
- Fecal colonization: 69% of NTCD-M3 patients: 71% with 107 spores/d and 63% with 104 spores/d.
- Recurrence of CDI occurred in 13/43 (30%) placebo patients vs. 14/125 (11%) of 125 NTCD-M3 patients (P = .006)
- Lowest recurrence in 2/43 (5%) pts receiving 107 spores/d x 7 days (P = .01 vs placebo)
- Recurrence occurred in 2/86 (2%) pts who were colonized vs 12/39 (31%) pts who received NTCD-M3 and were not colonized (P < .001)



Monthly Fecal *C. difficile* Detection from Week 6 to 6 Months

Gerding DN et al JAMA 2015;313:1719, May 5, 2015, Supplementary Material

Status of NTCD M3

- **M3 is licensed to Destiny Pharma in UK who sublicensed it to Sebela Pharma in USA for Phase 3 development in USA. Manufacturing is ongoing, but Phase 3 has not yet begun because Sebela wants more Phase 2 data for fidaxomicin + M3 since fidaxomicin was not used in the original phase 2 .**
- **Personal communication Dale N Gerding MD 4-17-23**

Clinical Infectious Diseases
MAJOR ARTICLE

Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD Study

Orenstein R et al Clin Inf Dis 2016: 62:596-602 March 1

40 pts, 11 US Centers Aug-Dec 2013

6 month follow-up

4 donors

24-48 H WASHOUT Period

87.1 % Efficacy- (16 –one dose; 11- 2 doses)

Drugs. 2022; 82(15): 1527–1538.
Published online 2022 Oct 26. doi: 10.1007/s40265-022-01797-x
PMCID: PMC9607700
PMID: 36287379

Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection

CDI within 8 weeks of randomization
Bayesian analysis 2:1 randomization
267 patients: 180 RBX2660 vs. 87 Placebo
Treatment success rate: 70.6% RBX 57.5 % Placebo

90% of those with success at 8 weeks had sustained response at 6 months

REBYOTA Administration Instructions FDA Package insert

- Place carton in refrigerator (36 to 46 F) for 24 H, Use within 5 Days (including thaw time); 150 ml
- Administer 24 to 72 H after last dose Abx
- Patient in L side or knee to chest position
- Hold rectal tube in place with one hand entire time
- Other hand pinch clamp and slowly raise bag for gravity flow; NO IV Pole
- Up to 15 minutes Admin time

microorganisms

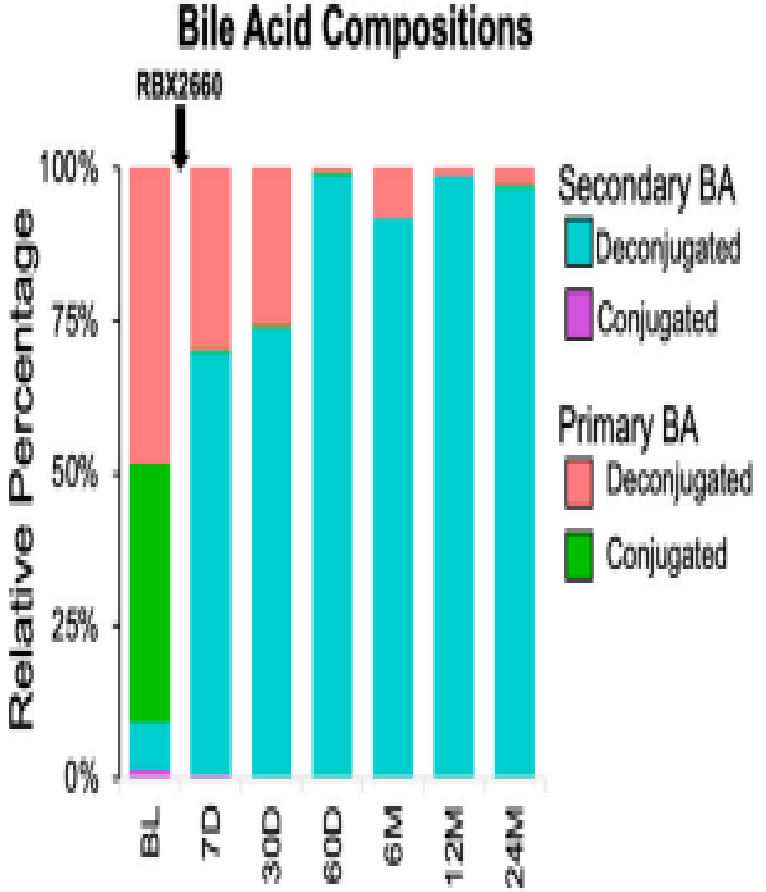
MDPI

Article

Human Fecal Bile Acid Analysis after Investigational Microbiota-Based Live Biotherapeutic Delivery for Recurrent *Clostridioides difficile* Infection

Romeo Papazyan et al. Microorganisms 2023;11:135

After RBX2660 administration,
there was a significant drop in primary Bas
concurrent with increased secondary BAs
that sustained through 24 months post-RBX2660



Most important taxa responsible for converting primary to secondary bile acids: Clostridiales

Clinical Infectious Diseases

MAJOR ARTICLE

SER-109, an Investigational Microbiome Drug to Reduce Recurrence After *Clostridioides difficile* Infection: Lessons Learned From a Phase 2 Trial

89 subjects enrolled (67% female; 80.9% diagnosed by PCR). rCDI rates were lower in the SER-109 arm than placebo (44.1% vs 53.3%) but did not meet statistical significance.

Early engraftment of SER-109 was associated with nonrecurrence (P < .05) and increased secondary bile acid concentrations (P < .0001)

A higher dose of SER-109 and requirements for toxin testing were implemented in the current Phase 3 trial.

SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection

Feuerstadt P. et al; NEJM 2022;Jan 20- 386:220-229

Phase 3, double-blind, randomized, placebo-controlled trial in which patients who had had three or more episodes of *C. difficile* infection (inclusive of the qualifying acute episode) received SER-109 or placebo (four capsules daily for 3 days) after standard-of-care antibiotic treatment.

*** 281 patients screened, 182 were enrolled.**

*** 3 x 10^7 cfu**

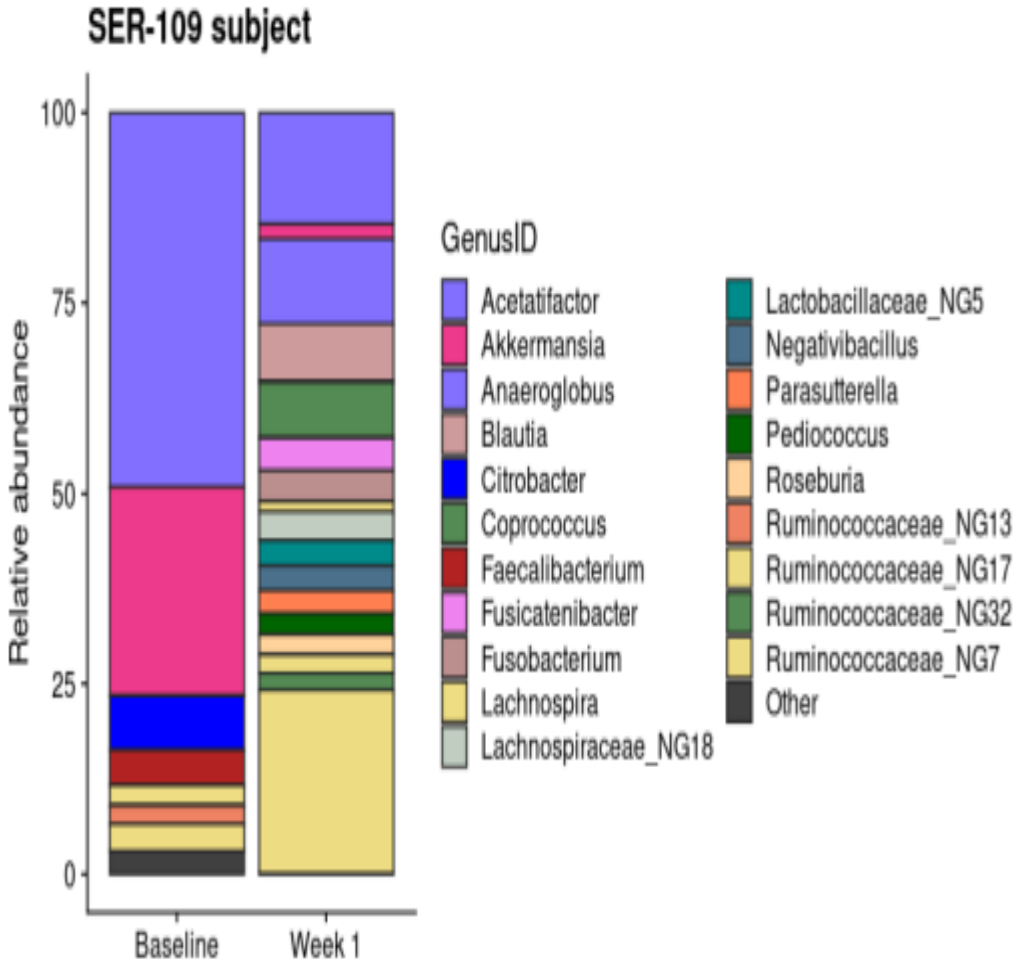
*** rCDI- 12% in the SER-109 group and 40% in the placebo group** (relative risk, 0.32; 95% confidence interval [CI], 0.18 to 0.58; P<0.001 for a relative risk of <1.0; P<0.001 for a relative risk of <0.833). (**8 weeks post Rx**)

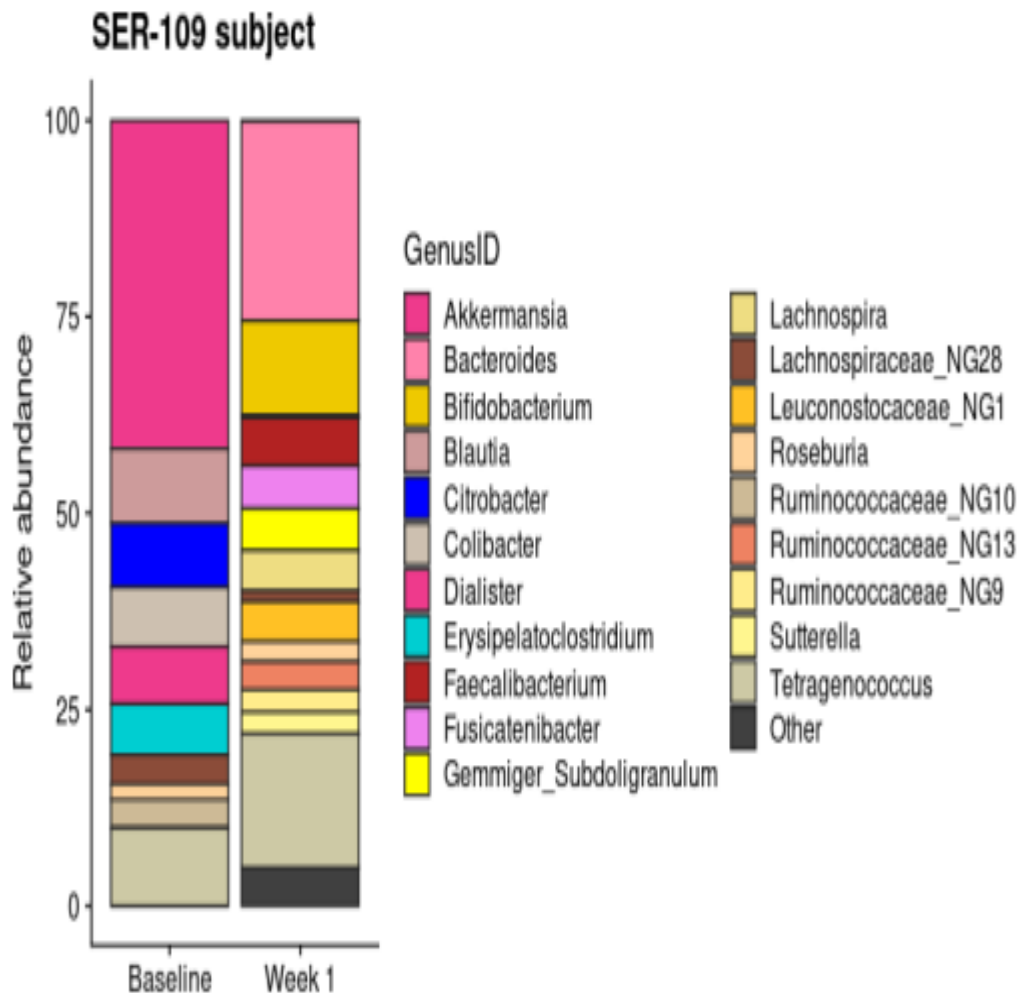
SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection

Feuerstadt P. et al; NEJM 2022;Jan 20- 386:220-229

- Stratified according to age (<65 or ≥65 years) and antibiotic received for *C. difficile* infection (vancomycin or fidaxomicin) before randomization
- Because vancomycin and fidaxomicin can persist for up to 5 to 7 days after discontinuation, 10 ounces of magnesium citrate was administered the night before treatment to limit inactivation of SER-109 dose species (i.e., species of bacteria present in SER-109)
- **CHARACTERIZATION OF SER-109**
- four donors underwent an extensive health examination,

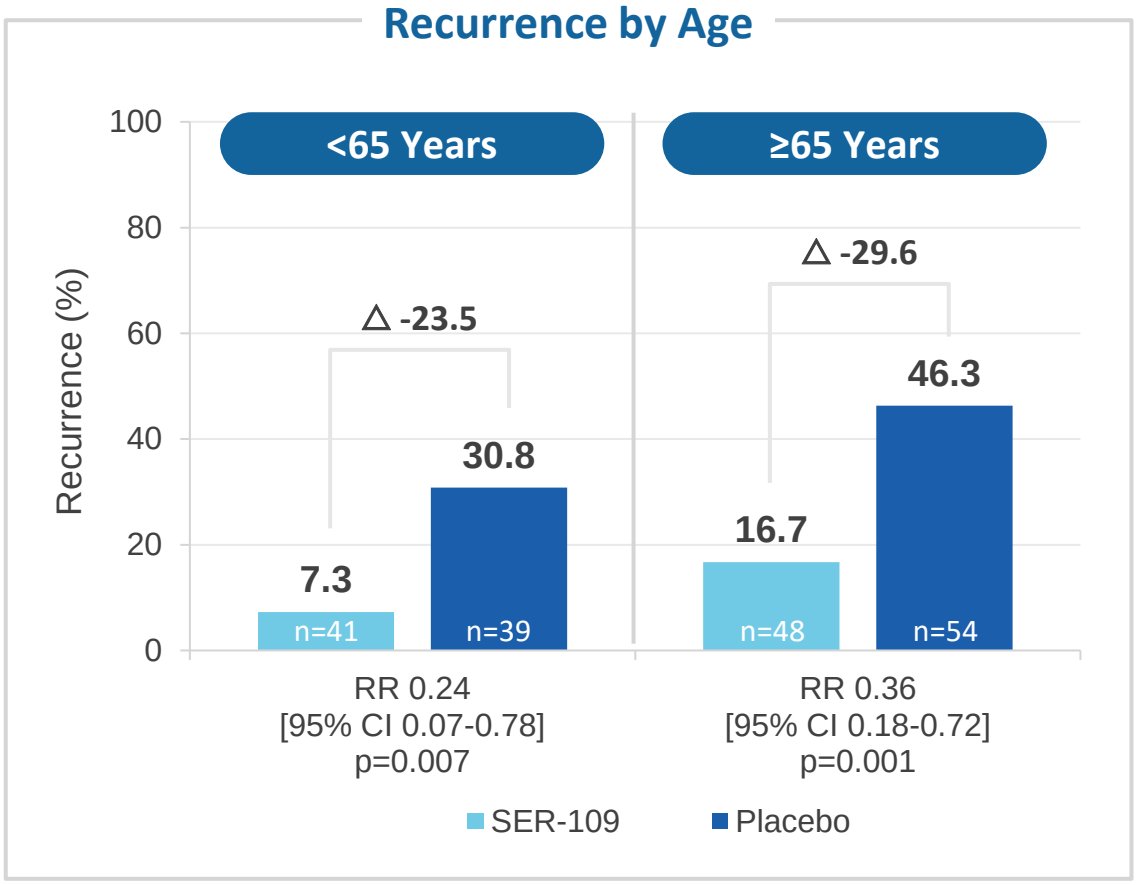
Representative SER-109 and placebo genus-level taxonomic profiles at baseline and one week post-treatment

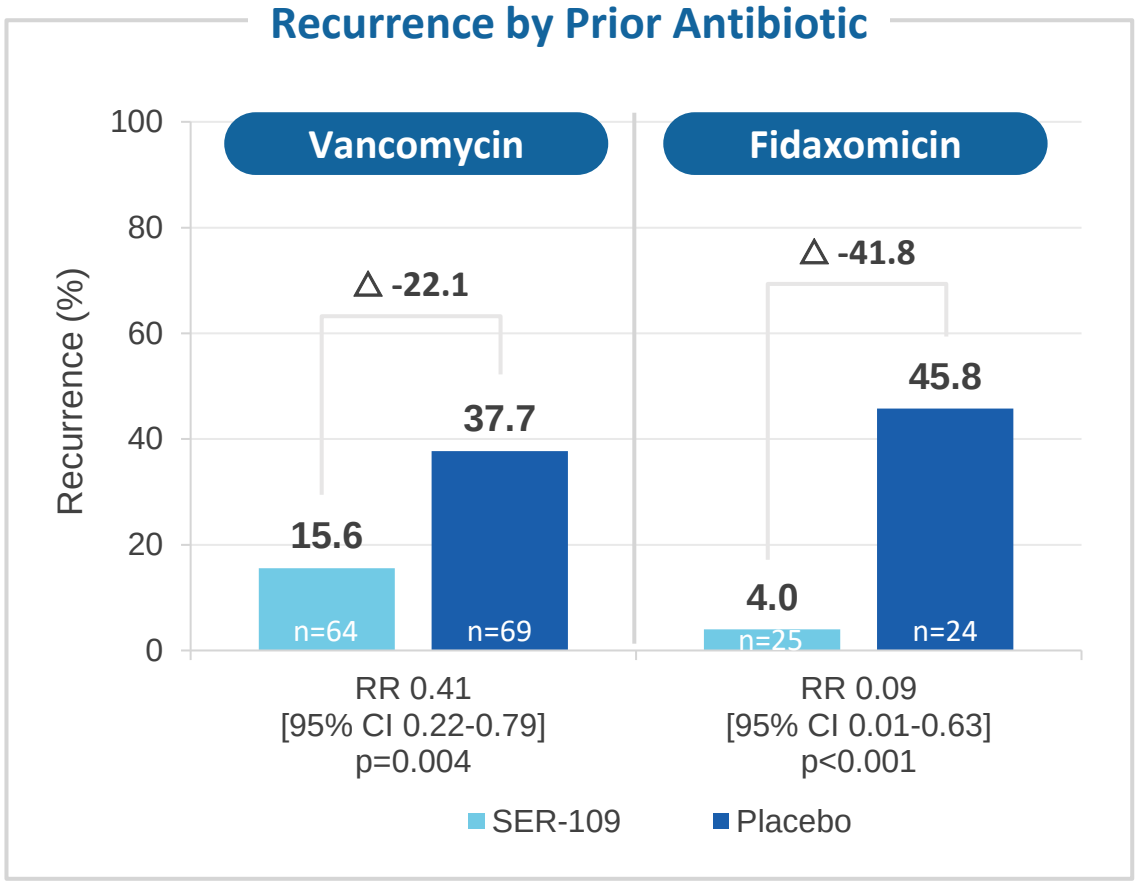




SER-109 subject

Recurrence was Significantly Lower at Week 8 with SER-109 vs Placebo in Both Age-stratified Groups and when Stratified by Antibiotic





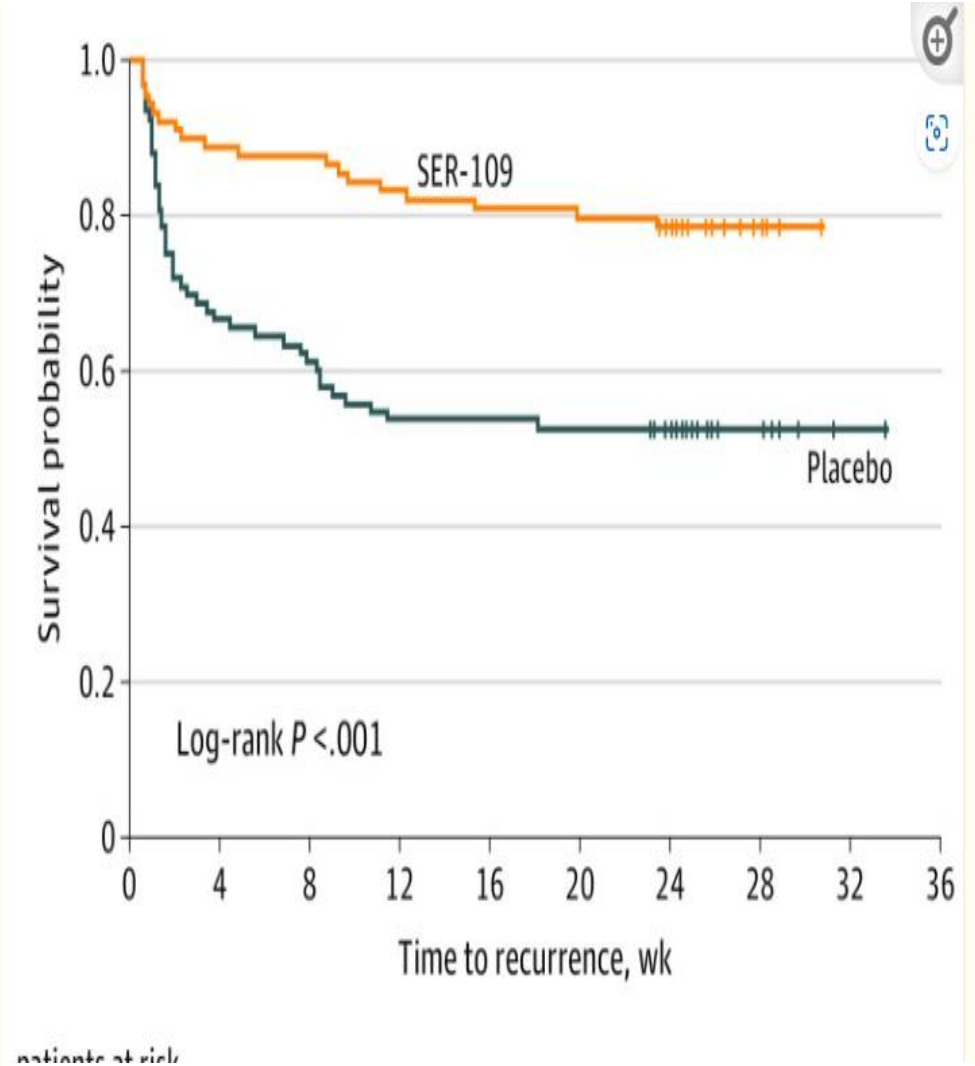
Berenson, et al. SHM Annual Meeting 2021. Abstract #974338.

Extended Follow-up of SER-109 through 24 weeks for rCDI

Cohen S, T Louie et al. JAMA 2022 Nov 22; 328(20): 2062–2064.

Cumulative Recurrent *Clostridioides difficile* Infection Rates, Rate Differences, and Relative Risks at Weeks 4, 8, 12, and 24[a]

Time point[b]	No. (%) SER-109 (n = 89)	Placebo (n = 93)	Rate difference (95% CI)[c]	*P* value	Relative risk (95% CI)[d]	*P* value
4 wk	10 (11.2)	31 (33.3)	−22.1 (−33.4 to −10.1)	<.001	0.35 (0.19 to 0.67)	<.001
8 wk	11 (12.4)	37 (39.8)	−27.4 (−38.9 to −14.8)	<.001	0.32 (0.18 to 0.58)	<.001
12 wk	16 (18.0)	43 (46.2)	−28.3 (−40.3 to −14.8)	<.001	0.40 (0.24 to 0.65)	<.001
24 wk	19 (21.3)	44 (47.3)	−26.0 (−38.4 to −12.2)	<.001	0.46 (0.30 to 0.73)	<.001



JAMA | Preliminary Communication

VE303, a Defined Bacterial Consortium, for Prevention of Recurrent *Clostridioides difficile* Infection
A Randomized Clinical Trial

Louie T, Y Golan et al. 4-15-23 doi:10.1001/jama.2023.4314 NTC 03788434

Phase II trial randomized. Double blind dose ranging trial

To define efficacy 8 strains of commensal *Clostridium* spp.

5 strains-cluster XIVa, 2 strains-cluster IV; 1 strain - cluster XVII

Dose: 8×10^9 cfu/ml vs 1.6×10^9 cfu/ml vs placebo

Orally once daily x 14 days

79 pts with High Risk for relapse

8 week Relapse rate: 13.8% vs 37% vs 45.5%

eTable 1. VE303 Strain Identity

Strain	Cluster Designation	Closest Relative as Determined by Whole-Genome Sequencing[a]
VE303-01	XIVa	*Enterocloster bolteae*
VE303-02	IV	*Anaerotruncus colihominis*
VE303-03	XIVa	*Sellimonas intestinalis*
VE303-04	XIVa	Clostridium_Q *symbiosum*
VE303-05	XIVa	*Blautia* sp001304935
VE303-06	XIVa	Dorea_A *longicatena*
VE303-07	XVII	Clostridium_AQ *innocuum*
VE303-08	IV	*Flavonifractor plautii*

[a] Whole-genome sequence assignment according to genome taxonomy database release 207 (https://gtdb.ecogenomic.org/; April 2022).

Thank you Any Questions?