Fecal Transplant and Microbiota Therapies

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NEW YORK SOCIETY FOR GASTROENTEROLOGY AND ENDOSCOPY
The Spring Course
BEST OF DDW 2022
June 4, 2022
NYSGE New York Society for Gastroenterology and Endoscopy

Clostridioides difficile: epidemiology

- **Main Risk factors**:
  - Advanced age (>65), antibiotics, contact with healthcare, IBD, solid organ transplant recipients

- **Most common cause of health-care- associated infection in the U.S.**
  - Adjusting for PCR use – total decrease by 26%
  - 35% community acquired and increasing

- **Colonization**
  - >50% of healthy infants and 4-10% of healthy adults
  - 20% of inpatients >2d
  - 15-30% of patients in long term care facilities

Lessa FC. N Engl J Med 2015; Cohen SH. Inf Cont and Hosp Epidem 2010; Ma GK Annals Int Med 2017

Diagnosis: How to test?

- **Glutamate dehydrogenase (GDH):**
  - Enzyme produced by all *C. difficile* strains
  - Highly sensitive, rapid initial screening test (but non-specific, detects non-toxigenic strains)
- **Toxin A & B Enzyme Immunoassay (EIA)**
  - Detects free toxin but high threshold (assay dependent)
  - Specific but not as sensitive (false negatives/risk of underdiagnosis)
- **C diff PCR** gene for toxin B
  - Rapid, inexpensive
  - Very sensitive, less specific (false positives/risk of overdiagnosis)

Diagnosis: How to test?

- **2 step testing**
  - (1) **GDH or PCR**→ Negative = NOT CDIFF
    GDH or PCR→ Positive → Proceed to **Toxin EIA**
  - (2) **Toxin EIA** negative→ Not Cdiff, colonized, false negative, early infection
    Toxin EIA positive→ Cdiff
  - Don’t believe your GDH result? Check PCR
  - No single commercial test can be used as a stand alone
  - CLINICAL CONTEXT

Furuva-Kanamori et al BMJ Inf Dis 2015 Wadwa A. et al. Alimen Pharmacol Ther 2016

Microbial therapeutics

- **VE303 (Vedanta)**- Oral defined bacterial consortium
- **CP101 (Finch)**- Oral one-time dose of donor-derived entire microbial community
- **RBX2660 (Rebiotix/Ferring)**- 150 mL donor-derived entire microbial community enema
- **Vancomycin vs Fidaxomicin**

VE303 Strains and Mechanisms of Action

VE303 Strain Identity

Cluster	Closest Relative as Determined by Whole-Genome Sequencing[a]
XIVa	*Enterocloster bolteae*
IV	*Anaerotruncus colihominis*
XIVa	*Sellimonas intestinalis*
XIVa	Clostridium_Q *symbiosum*
XIVa	*Blautia* sp001304935
XIVa	Dorea_A *longicatena*
XVII	Clostridium_AQ *innocuum*
IV	*Flavonifractor* sp000508885

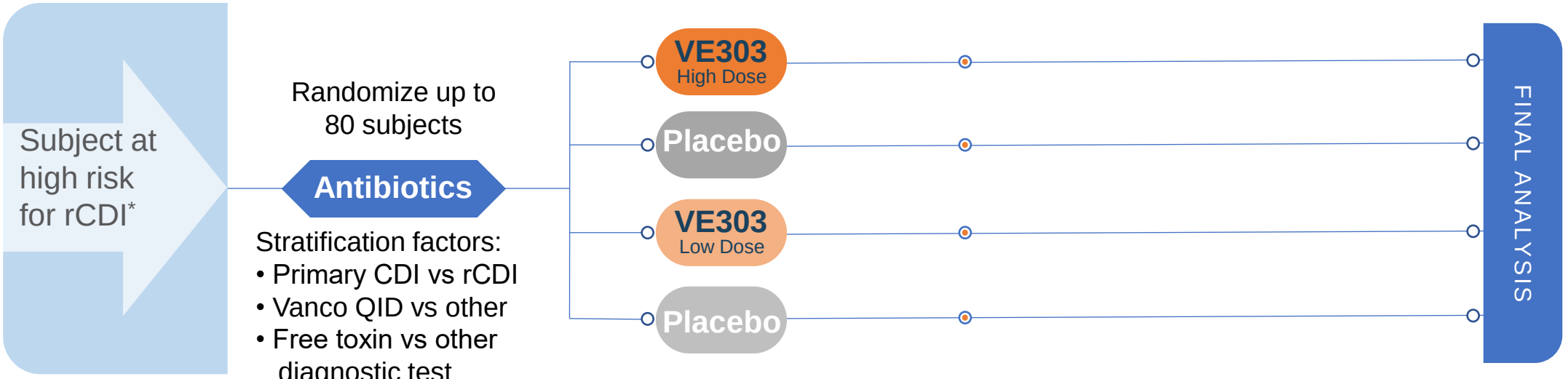
Putative Mechanisms of Action

1. Conversion of primary bile acids to secondary bile acids, which may promote *C. difficile* resistance[1,2]
2. Nutrient competition limits the outgrowth of pathogenic microbes, such as *C. difficile*[3,4]
3. Prevention of disease-associated inflammation caused by *C. difficile* toxins[5]
4. Short-chain fatty acid production, which has been reported to be important for maintenance of barrier function[6,7]
5. Induction of regulatory T cells, which play a role in maintaining intestinal homeostasis by controlling inflammation[8,9]
6. Direct inhibition of *C. difficile* growth in vivo

Buffie CG. Nat Rev Immunol 2013;13:790–801.; 2. Buffie CG. Nature 2015;517:205–8.; 3. Itoh K. Lab Anim 1987;21:20–5.; 4. Wilson KH. Infect Immun 1988;56:2610–4.; 5. Martz SL. J Gastroenterol 2017;52:452–65.; 6. Ghosh TS. PLoS One 2013;8:e83823.; 7. Sommer MOA. Science 2009;325:1128–31.; 8. Atarashi K. Nature 2013;500:232–6.; 9. Furusawa Y. Nature 2013;504:446–50.

VE303 Phase 2 Clinical Study Was Designed to Inform Future Development

CONSORTiUM
CLINICAL RESEARCH STUDY FOR rCDI



*≥1 rCDI episodes, or primary CDI with increased risk of recurrence

Primary Objective: Determine dose regimen(s) as indicated by the CDI recurrence rate

- **Primary Efficacy Endpoint:** % of subjects with CDI recurrence through Week 8
- **Secondary Efficacy Endpoint:** % of subjects with CDI recurrence through Week 4, 12, or 24

Louie et al. DDW 2022.

VEV303 CDI Recurrences and Absolute Risk Reductions Through Week 8

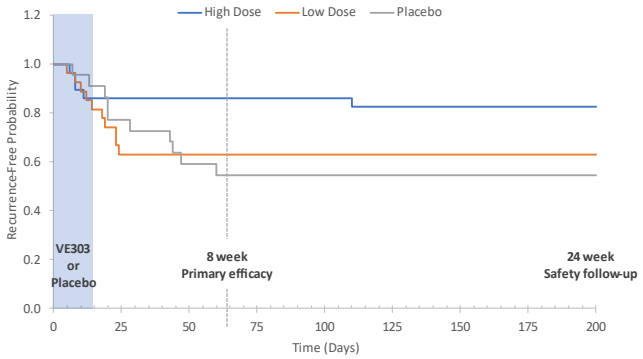
Definition of CDI Recurrence	VE303 High Dose (N=29)	VE303 Low Dose (N=27)	Placebo (N=22)	Adjusted Absolute Risk Reduction	
				High Dose vs Placebo (%, 90% CI)	Low Dose vs Placebo (%, 90% CI)
Toxin-Positive Analysis (n, %)	4 (13.8)	9 (33.3)	5 (22.7)	11.0% (–9, 27)	–6.8% (–32, 10)
Sensitivity I (n, %)	4 (13.8)	10 (37.0)	8 (36.4)	**21.1% (3, 42)**	3.1% (–23, 22)
Sensitivity II (n, %)	4 (13.8)	10 (37.0)	10 (45.5)	**30.5% (11, 52)**	9.9% (–15, 32)

Sensitivity II: Odds Ratio of CDI Recurrence Up to Week 8			Number Needed to Treat
	Odds Ratio (exact 90% CI)	P value (one-sided)	
VE303 High Dose vs Placebo	0.192 (0.048, 0.712)	0.0077	3.1

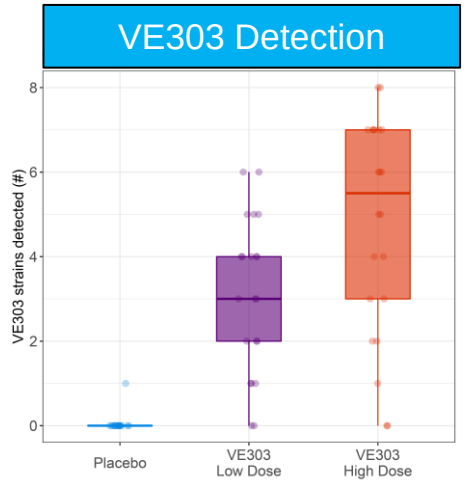
Louie et al. DDW 2022.

VE303 Strain Colonization and Microbiome Recovery Provide a Rationale for Clinical response of the VE303 High Dose

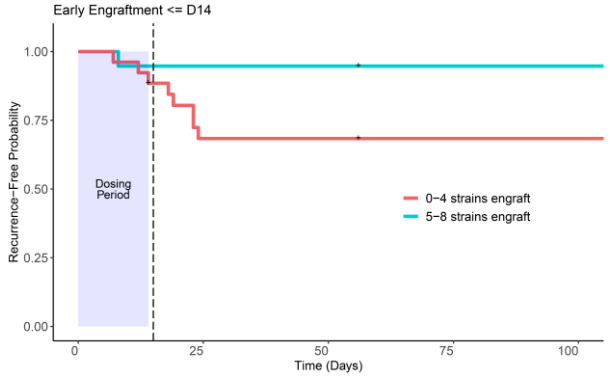
VE303 high dose prevented recurrence in subjects at high risk of rCDI



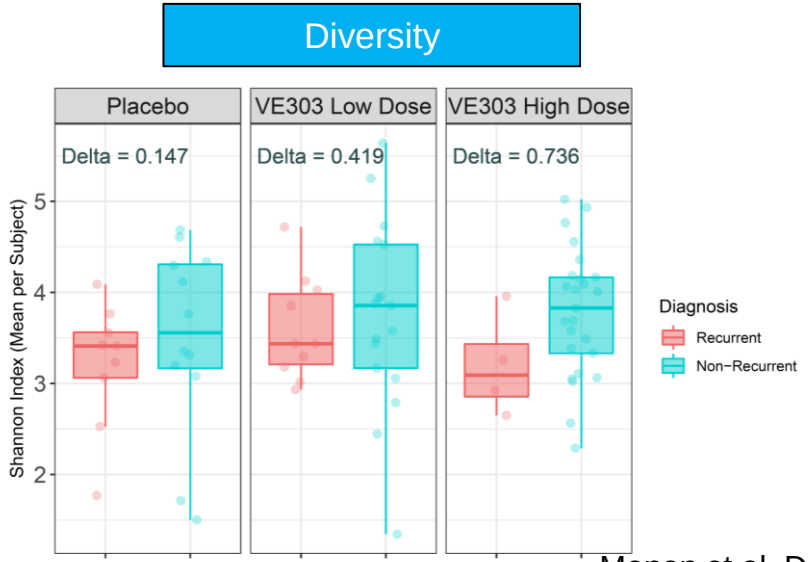
VE303 dosing led to effective, dose-dependent strain colonization



Subjects with high vs low VE303 strain engraftment had higher recurrence-free probability

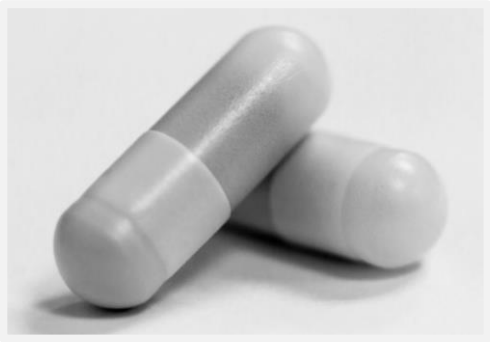


Higher VE303 dosing was associated with faster host microbiome recovery, which correlates with clinical cure

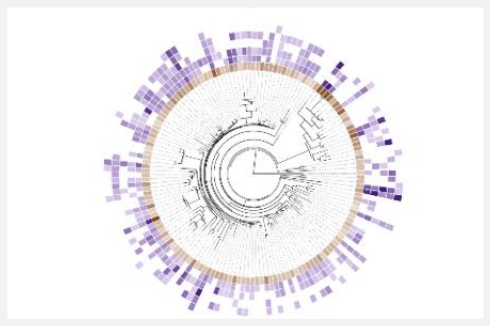


Menon et al. DDW 2022.

CP101 is an investigational orally-administered microbiome therapeutic designed to prevent recurrent CDI



- **CP101 is a donor-derived microbiome therapeutic that delivers a diverse microbial community**
- In PRISM3, a RCT, CP101 prevented recurrence in participants with first CDI recurrence and those with multiple recurrences

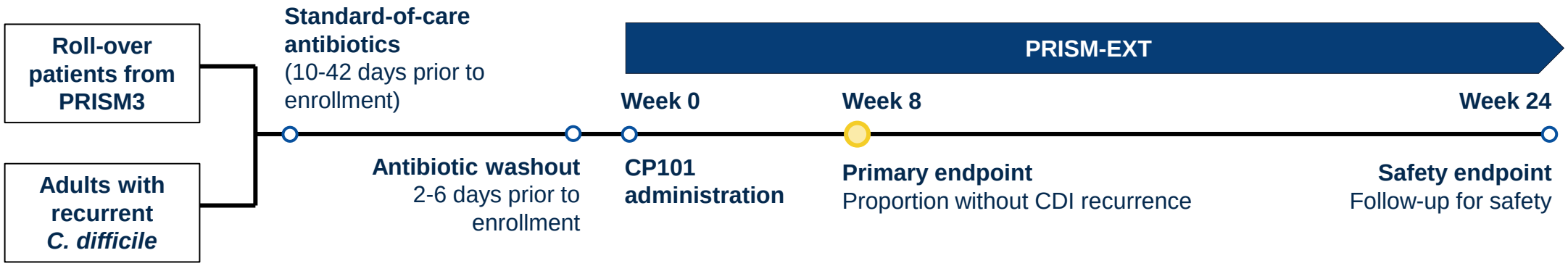


- Designed to **increase microbiome diversity associated with a healthy gut,** which is depleted in patients with recurrent CDI

- **One-time, oral** administration
- **No bowel prep** required
- **cGMP manufacturing process**

Allegretti et al. DDW 2022.

PRISM-EXT, an open-label trial of CP101 for the prevention of recurrent CDI

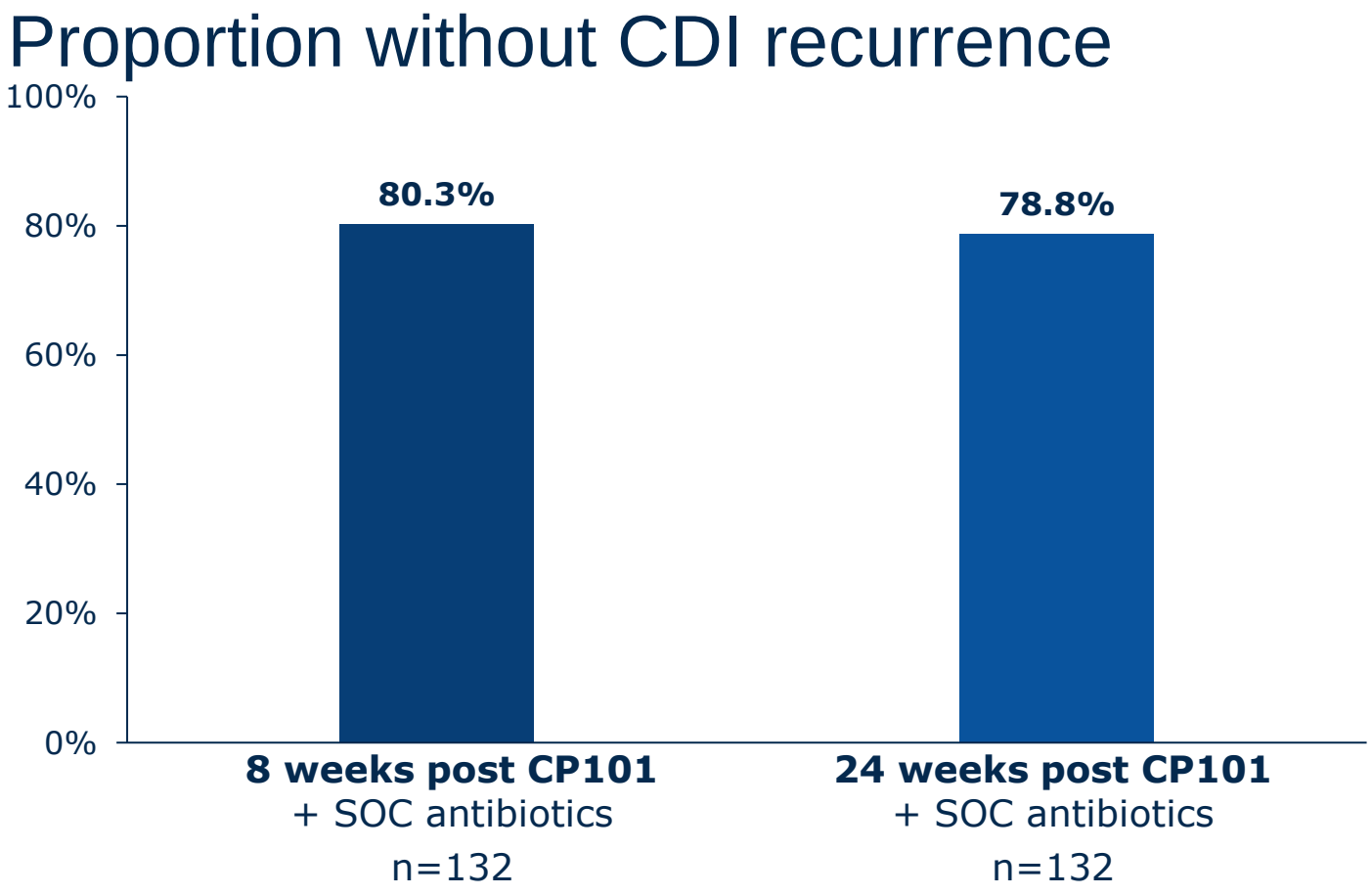


Design elements	• 51 sites across the U.S. and Canada
Key inclusion criteria	• Recurrent CDI including **first CDI recurrence** • Qualifying CDI episode diagnosed by **Toxin EIA-based testing** OR **PCR-based testing**
Primary endpoints	• Proportion of participants without CDI recurrence through Week 8 • Incidence of adverse events through Week 8
Secondary endpoints	• Proportion of participants without CDI recurrence through Week 24 • Incidence of adverse events through Week 24

83% of CDI diagnosed by PCR in US

Allegretti et al. DDW 2022.

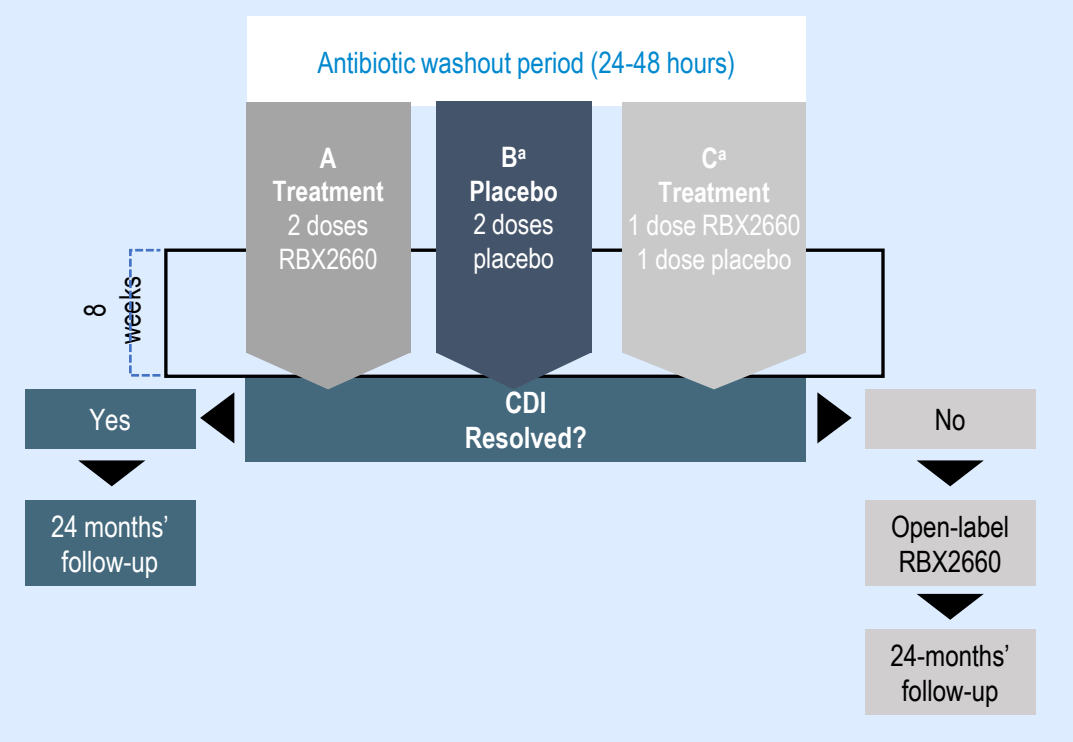
A large proportion of participants did not experience CDI recurrence in the PRISM-EXT study on CP101



Allegretti et al. DDW 2022.

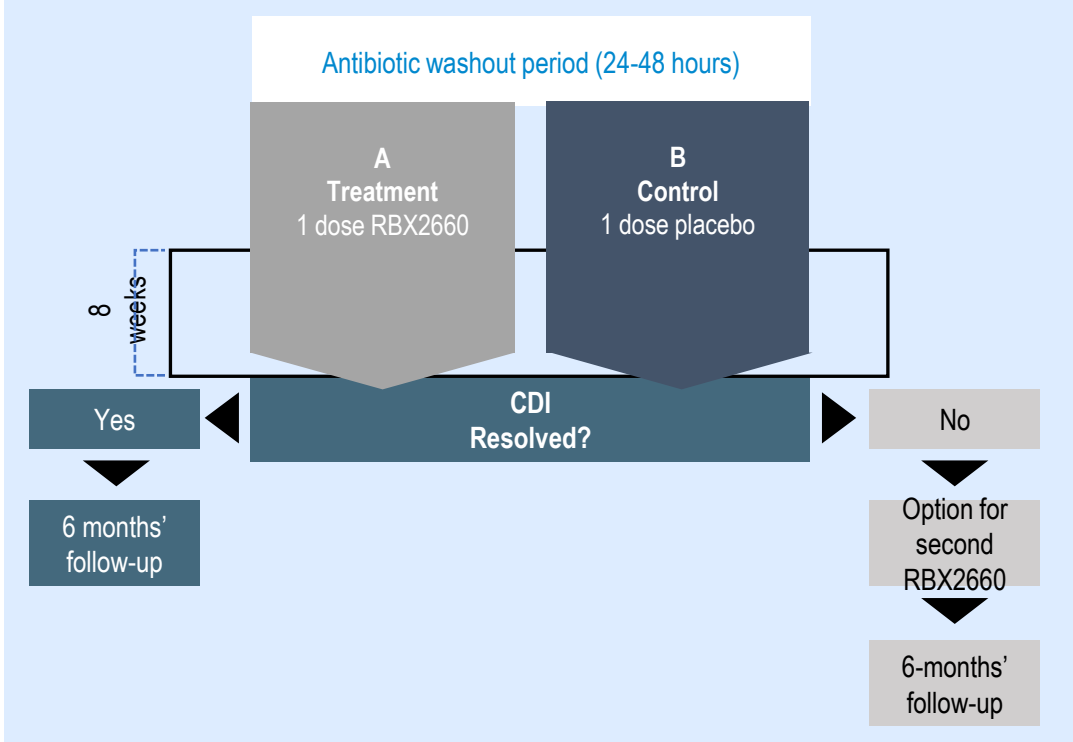
RBX 2660: PUNCH CD2 Study

- ≥2 instances of recurrence of CDI
- 2 doses of RBX2660, placebo, or RBX2660 followed by placebo, administered 7 ± 2 days apart



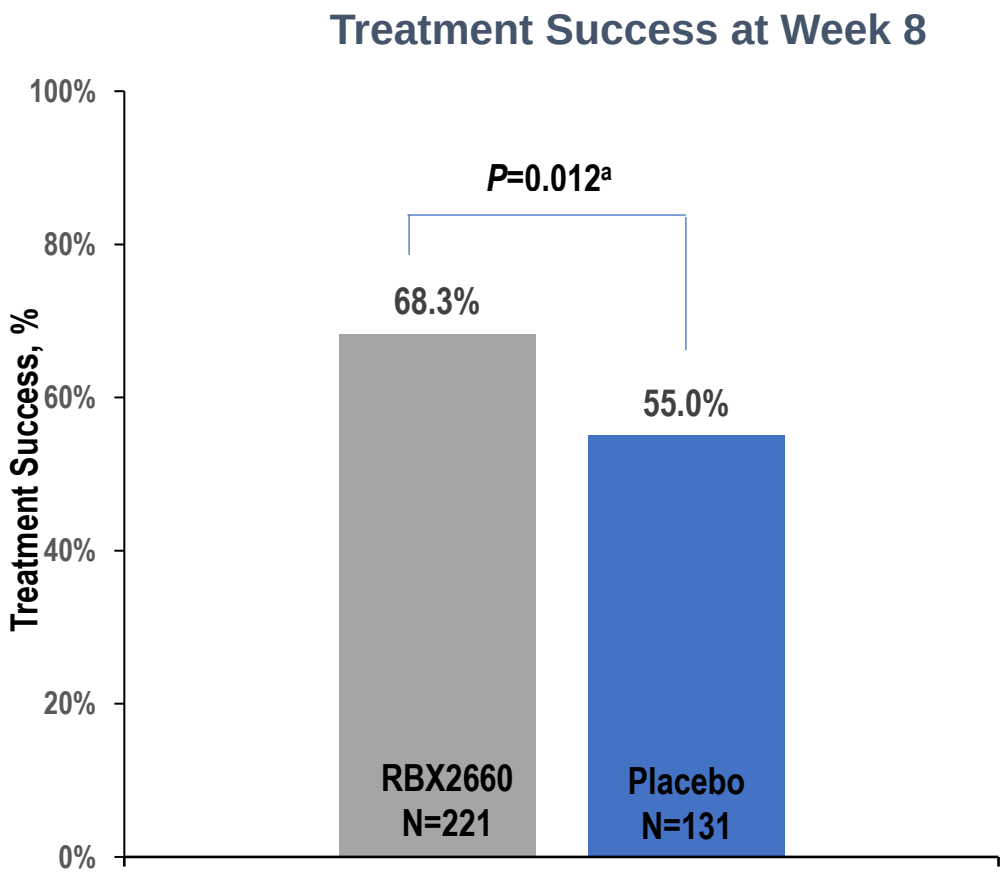
PUNCH CD3 Study

- ≥1 instance of recurrence of CDI
- 267 received blinded treatment (2 RBX2660:1 placebo)
- If blinded treatment unsuccessful, open-label RBX2660



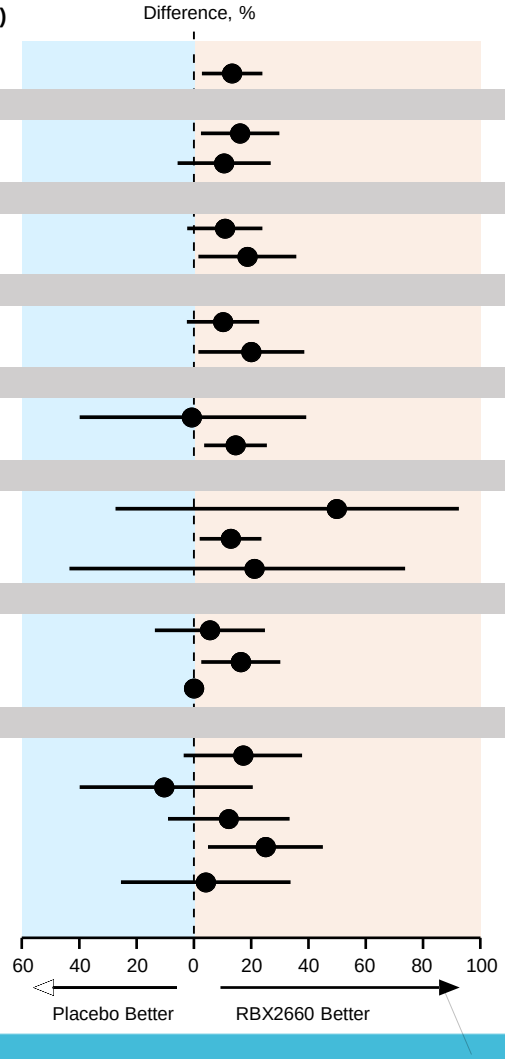
Feuerstadt et al. DDW 2022.

In a Pooled Analysis, the Rate of Treatment Success in the RBX2660 Group Was Greater Than in the Placebo Group for All Participants



Subgroup Analyses of Treatment Success Within 8 Weeks of Blinded Treatment

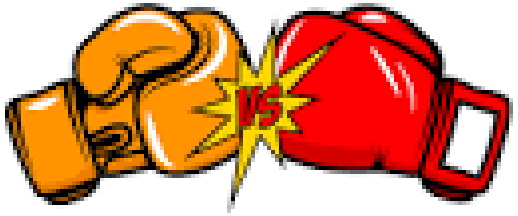
Subgroups	Placebo n/N (%)	RBX2660 n/N (%)	Difference, %	Difference (95% CI)	*P* Values
All participants	72/131 (55.0)	151/221 (68.3)		13.4 (2.9-23.9)	
Age, years					**0.5587**
<65	44/79 (55.7)	82/114 (71.9)		16.2 (2.5-29.9)	
≥65	28/52 (53.8)	69/107 (64.5)		10.6 (−5.7 to 26.9)	
Number of CDI episodes					**0.5490**
≤3	50/83 (60.2)	91/128 (71.1)		10.9 (−2.3 to 24.0)	
>3	22/48 (45.8)	60/93 (64.5)		18.7 (1.6-35.8)	
Sex					**0.4071**
Female	52/90 (57.8)	100/147 (68.0)		10.2 (−2.4 to 22.9)	
Male	20/41 (48.8)	51/74 (68.9)		20.1 (1.6-38.7)	
Race					**0.6442**
Other than White	7/10 (70.0)	9/13 (69.2)		−0.8 (−40.0 to 39.3)	
White	65/121 (53.7)	142/208 (68.3)		14.6 (3.6-25.5)	
Ethnicity					**0.7541**
Hispanic or Latino	3/6 (50.0)	3/3 (100.0)		50.0 (−27.3 to 92.8)	
Not Hispanic or Latino	68/122 (55.7)	142/207 (68.6)		12.9 (2.0-23.7)	
Unknown	1/3 (33.3)	6/11 (54.5)		21.2 (−43.5 to 73.9)	
Antibiotic duration (prior CDI)					**0.4466**
≤14 days (Vanco)	23/40 (57.5)	41/65 (63.1)		5.6 (−13.7 to 24.9)	
>14 days (Vanco)	40/76 (52.6)	87/126 (69.0)		16.4 (2.6-30.2)	
Unknown	1/2 (50.0)	0 (0)			
Site geography					**0.4011**
Outside of US	17/34 (50.0)	39/58 (67.2)		17.2 (−3.5 to 37.9)	
Eastern US	10/15 (66.7)	18/32 (56.3)		−10.4 (−40.0 to 20.6)	
Southern US	18/28 (64.3)	39/51 (76.5)		12.2 (−9.0 to 33.4)	
Northern US	17/38 (44.7)	37/53 (69.8)		25.1 (5.0-45.1)	
Western US	10/16 (62.5)	18/27 (66.7)		4.2 (−25.5 to 33.8)	



- [a]Pearson chi-square test.

Feuerstadt et al. DDW 2022.

Fidaxomicin vs. Vancomycin



- Examined sustained response and CDI recurrence within 4- and 8-weeks after initial treatment with ***fidaxomicin*** vs. ***vancomycin*** among Medicare beneficiaries with CDI

- Sustained response: clinical resolution (no additional CDI treatment or hospitalization before or within one day after abx completion) and no evidence of CDI recurrence.

- CDI recurrence was measured among patients with clinical resolution as any evidence of a new CDI treatment or CDI-related hospitalization within 4- or 8-weeks after the initial prescription fill.

Dubberke et al. DDW 2022.

Table. Clinical Outcomes among Propensity-Score Matched Medicare Beneficiaries with CDI Initiating Fidaxomicin vs. Vancomycin for an Initial or Recurrent CDI Episode with Regression Controlling for Unbalanced Variables

	Fidaxomicin	Vancomycin	Difference	p-value (clustered)
Initial CDI Episode				
All patients with initial CDI episode	**N = 190**	**N = 190**		
Sustained response (4 weeks)	71.7%	58.2%	13.5%	0.0058
Sustained response (8 weeks)	63.2%	50.0%	13.2%	0.0114
Among patients with a clinical resolution	**N = 141**	**N = 141**		
CDI Recurrence (4 weeks)	20.6%	29.0%	-8.4%	0.101
CDI Recurrence (8 weeks)	31.3%	38.9%	-7.6%	0.1893
Recurrent CDI Episode				
All patients with recurrent CDI episode	**N = 67**	**N = 67**		
Sustained response (4 weeks)	75.1%	45.1%	30.1%	0.0002
Sustained response (8 weeks)	66.5%	38.9%	27.6%	0.0012
Among patients with a clinical resolution	**N = 40**	**N = 40**		
CDI Recurrence (4 weeks)	*	*	-10.3%	0.292
CDI Recurrence (8 weeks)	*	*	-13.3%	0.255

* Per CMS policy, results based on cell sizes < 11 and/or exact values for cell sizes ≥11 that may permit calculation of a cell size < 11 cannot be displayed.

Dubberke et al. DDW 2022.

Treatment

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

McDonald et al. CID; 2018; 1-48.

Key Points

- Diagnosis of *C. difficile* should be based on the clinical picture
  - Know your lab's testing methods: PCR or multistep/EIA (more specific)
- Fidaxomicin may reduce recurrence when used early
- FMT is the most effective therapy for recurrent disease
- Microbial therapeutics coming: SER-109 (Seres) and RBX2660 (Rebiotix/Ferring)
  - Others in study likely to be effective: VE303, CP101
  - Perhaps efficacy in other disease states: IBD, IBS, extra-intestinal