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Microbiome Restoration: Getting One Step Closer Every Day!

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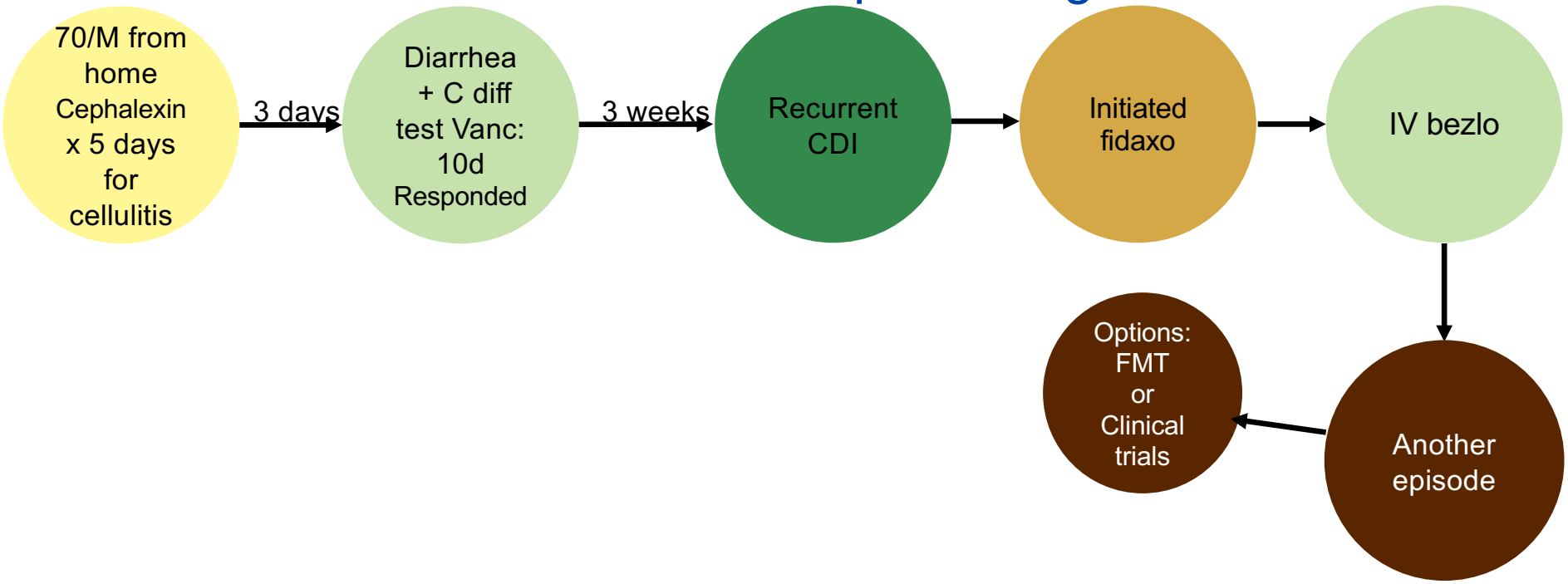
Learning Objectives

- Describe data for microbiome restoration for recurrent *C difficile* infection
- Adverse events with microbiota-based therapies
- Standardized microbiota-based therapies

The One Where *C difficile* keeps coming back…



Preparing and managing patients before FMT

- Step1: Start an antibiotic to bring active symptoms under control
  - Diarrhea improves in 3-5 days
  - Risk of recurrence after 3 episodes is ~60%
- Step2: Discuss recurrence prevention: Restore microbiome
  - Initiate referral to a center / specialist performing microbiome restoration
    - Fecal microbiota transplantation (FMT)
    - Clinical trials of microbiome restoration therapies
  - Majority of patients will be discharged prior to getting FMT
- Step3: Prescribe enough antibiotic until specialist appointment
  - Vancomycin 4 times a day for 10-14 days
  - Taper down vancomycin to lowest effective dose either once a day or once every other day

Voth E, Khanna S. Expert Rev Anti Infect Ther. 2020 Apr;12:1-8.

Fecal microbiota transplantation is the cornerstone of the management of recurrent C difficile

FMT for CDI – What is Well-known?

- Efficacy >85% to prevent recurrence
- Superior to oral vancomycin
- Fresh or frozen has similar efficacy
- No donor effect on efficacy
  - Screening and recruitment standardization needed
- Few recipient contraindications
- More adverse events are being reported
  - Long term follow up data needed
- FDA guidance on FMT is still in draft phase

FMT for Recurrent CDI Before and During COVID-19

FMT is dependent on procurement of stool from well-screened healthy donors

- General health and infection screening
  - Health & exposure questions
- Stool tests for donors
  - Enteric pathogens
  - Multi-drug resistant infections
- Blood tests for transmissible viral infections
  - HIV, viral Hepatitis, syphilis
- Serious adverse events due to transmission of infectious agents from asymptomatic donors
  - ESBL bacteremia
  - EPEC & STEC transmission
- Screening for COVID-19 is a challenge in this era

Voth E, Khanna S. Expert Rev Anti Infect Ther. 2020 Apr 12:1-8.
Khanna S, Pardi DS Am J Gastro 2020

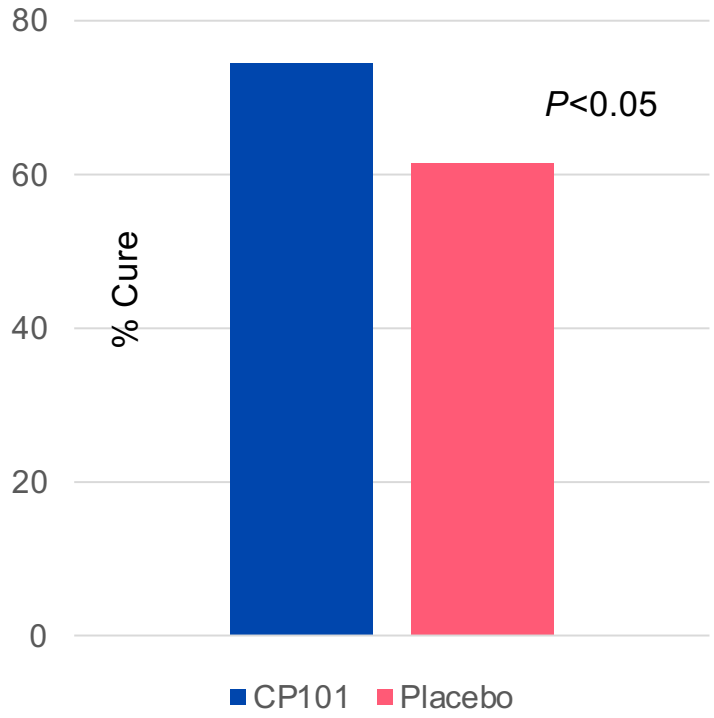
There is a need for Standardization of microbiome based therapies

Microbiome Restoration Therapies

- Capsule: donor derived
  - CP101
  - RBX7455
  - SER-109
- Capsule: synthetic
  - VE303
- Enema: donor derived
  - RBX7455

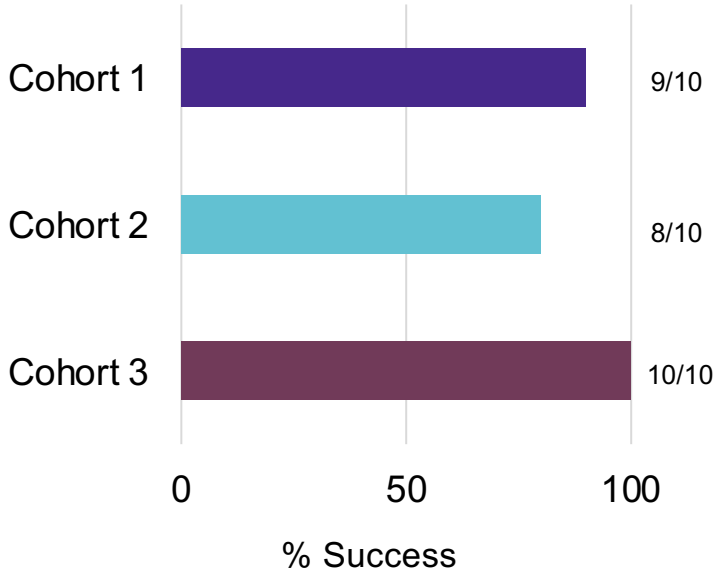
CP101: Efficacious in Phase II

- Full spectrum microbiota
  - Manufacturing and formulation details not available
- Efficacy, safety, and tolerability in adults with recurrent CDI
  - 206 patients at 51 sites
- Phase II double-blind, placebo-controlled, two doses
- Primary outcomes:
  - Proportion of patients with no CDI recurrence at 8 and 24 weeks
  - Adverse events



RBX7455 Efficacious in Phase I

- Lyophilized, room temperature
- At least one recurrence after a primary episode
- Prospective, single-center, open-label phase I, dose-finding, investigator-initiated trial
  - 3 arms – 10 patients per arm
    1. 4 capsules BID x 4 days
    2. 4 capsules BID x 2 days
    3. 2 capsules BID x 2 days



Khanna S et al CID 2020

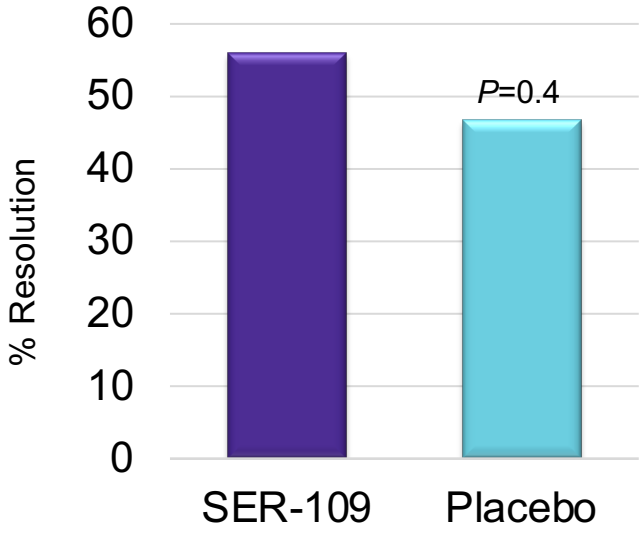
Ser-109 (*Ecobiotic*)

- Standardized, microbiota product, ~50 species of Firmicutes spores
  - Derived from donor stool – standard screening
  - Frozen at −80°C & ~150 g homogenized in saline
- Slurry centrifuged & bacterial supernatant combined with equal 100% ethanol at room temp x 1 hour
  - Reduces risk of pathogen transmission
- Pelleted by centrifugation, washed with saline, suspended with sterile glycerol
  - Filled into capsules stored at −80°C
- Spore concentration & lack of residual gram-negatives

Khanna S et al. *J Inf Dis.* 2016;214:173-81.

Ser-109: Efficacious in Phase I but Not in Phase II

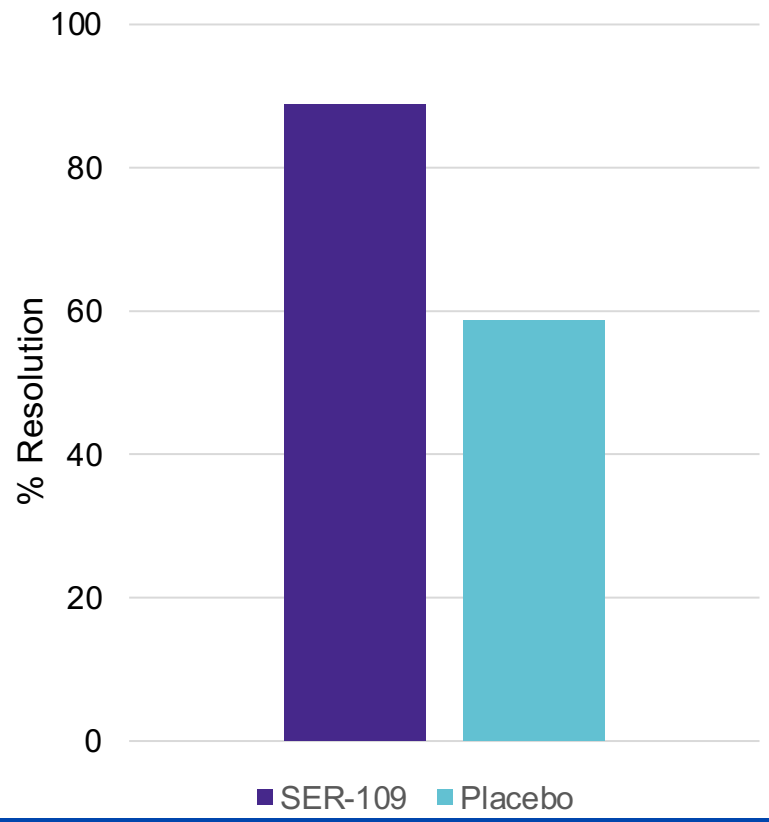
- ~50 species of Firmicutes from donor stool
  - Frozen (−80°C): suspended in saline
- 96.7% resolution rate in an open label phase I study of 30 pts
- 89 patients with ≥3 episodes
- Randomized 2:1 SER-109: placebo
  - 59 got SER-109 & 30 got placebo
- Single dose ~10^8 bacterial spores



Khanna S et al. J Infect Dis. 2016 Jul 15;214(2):173-81
McGovern BH et al. *Clin Infect Dis*. 2020 Apr 7. pii: ciaa387.

Ser-109: Efficacious in Phase III

- Multicenter, randomized, double-blind, placebo-controlled
- SER-109 in 4 capsules daily in group I or matching placebo once daily in group II: 3 days total treatment
- ≥3 CDI episodes within 9 months, inclusive of the current episode
  - Positive *C. difficile* stool toxin
  - 182 patients
- 10-21 days of antibiotics with adequate response
- Primary endpoint
  - CDI recurrence at week 8



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Lashner et al ACG 2020

The FDA has granted SER-109 both Breakthrough Therapy and Orphan Drug Designations

http://ir.serestherapeutics.com/phoenix.zhtml?c=254006&p=irol-newsArticle&ID=2280220

Enema Based Therapies: RBX2660

- Microbiota suspension
  - Derived from donor stool
  - Enema administration
- 50g stool
  - 150 mL 0.9% saline/polyethylene glycol 3350
  - ≥10^7 live organisms/ml
- Completed Phase I and II studies
- Phase III studies have been completed

Orenstein et al. *Clin Infect Dis*. 2016 Mar 1;62(5):596-602

RBX2660: Donor program

- Health & lifestyle assessment at enrollment and **every donation**
- Blood and stool tests
  - HIV
  - Hepatitis A, B, and C
  - Syphilis
  - *C. difficile*, VRE
  - Norovirus, rotavirus, adenovirus
  - Ova and parasites
  - *Vibrio*, *Listeria* and enteric pathogens

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VRE = vancomycin-resistant *Enterococcus*

Orenstein et al. *Clin Infect Dis*. 2016 Mar 1;62(5):596-602

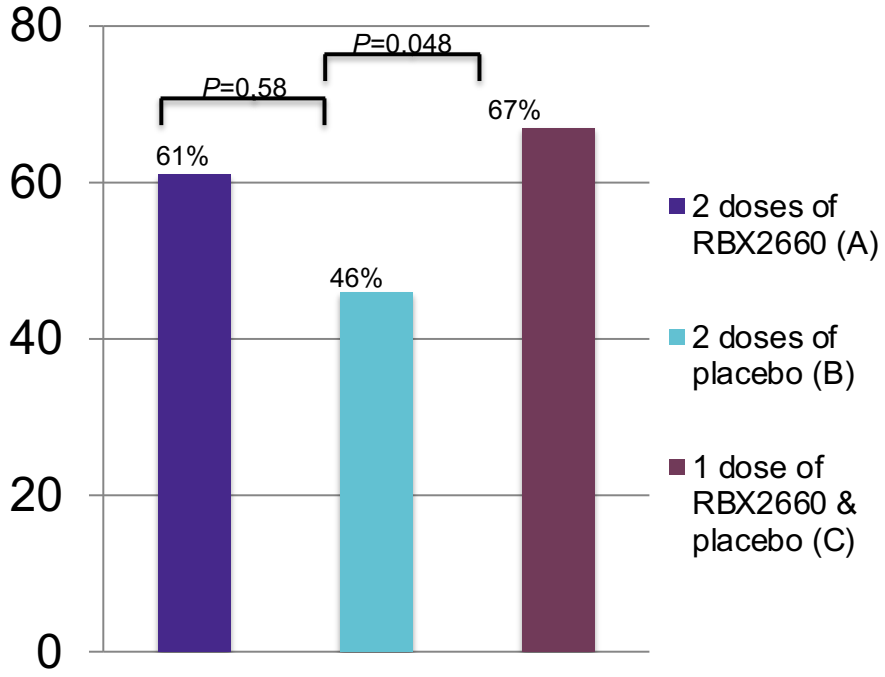
RBX2660: Donor program & processing

- Stool donations pooled with samples from same donor
- Subjected to repeat stool testing at least every 45 days
- Stored frozen at ≤−80°C after processing
- Thawed prior to shipment
- Stored at room temp for up to 2 days
- Units traceable to specific donors and recipients

Orenstein et al. *Clin Infect Dis*. 2016 Mar 1;62(5):596-602

Enema Based Therapy: RBX2660 is More Effective than Placebo*

- Microbiota suspension from donor stool as enema
- 50 g stool in 150 mL diluent
  ≥10^7 organisms/ml
- Double-blinded RCT: Phase II
- Patients with recurrent CDI
- Three or more episodes
- Enemas after standard antibiotic treatment

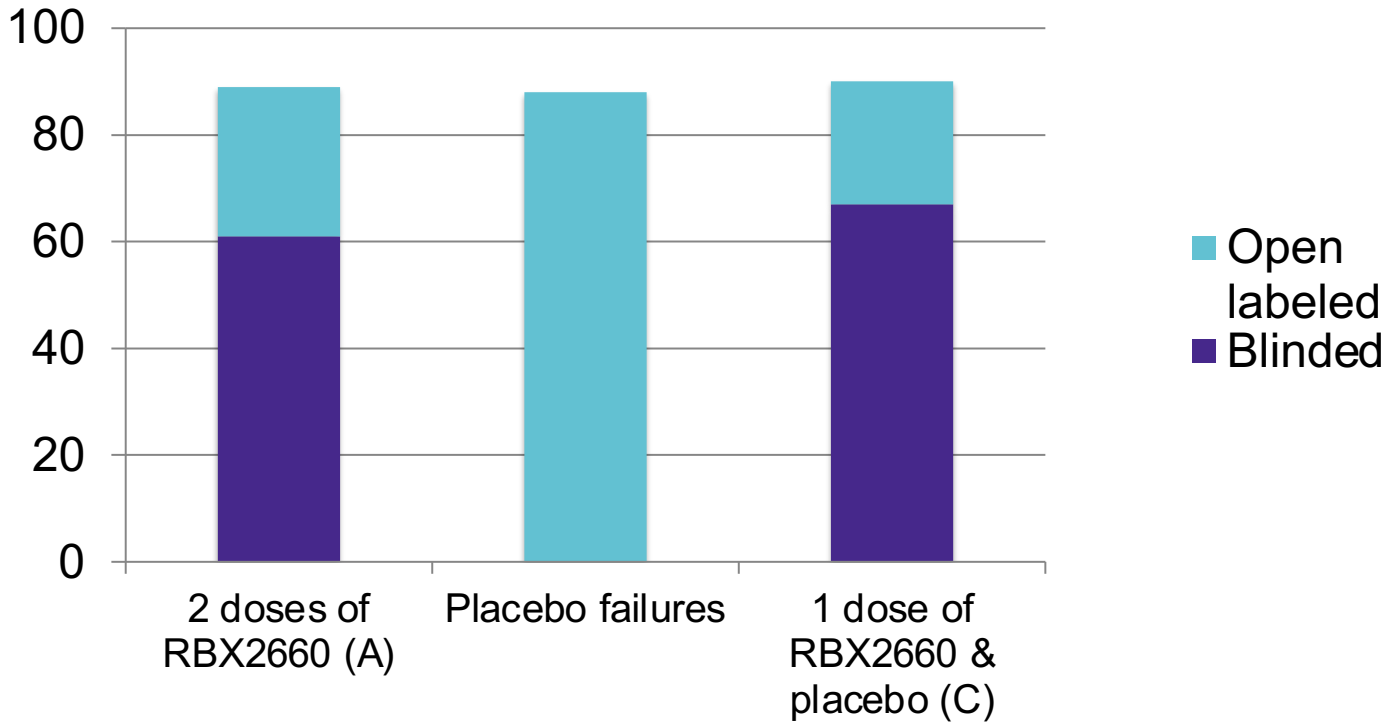


* Secondary endpoint

RCT = randomized controlled trial

Dubberke E et al. *Clin Infect Dis*. 2018 Sep 28;67(8):1198-1204.

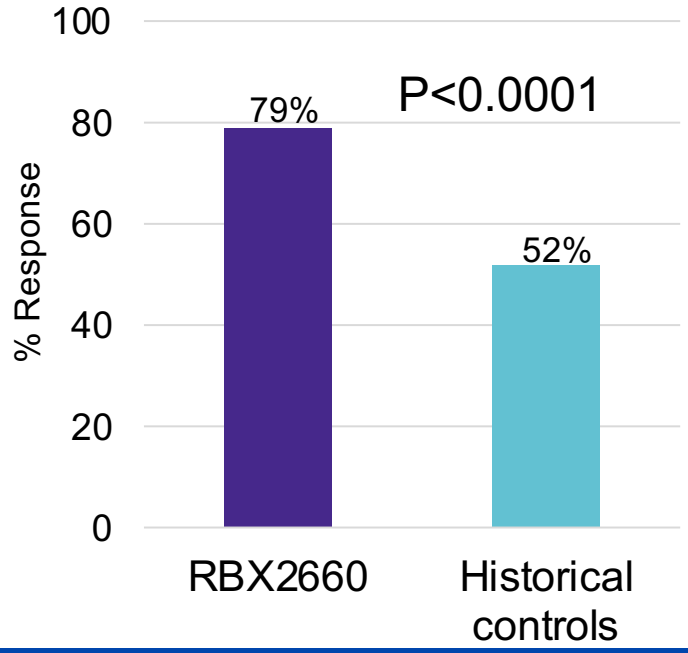
Overall Success With at Least 1 dose of RBX2660 (Blinded and Open-label): 88.6%

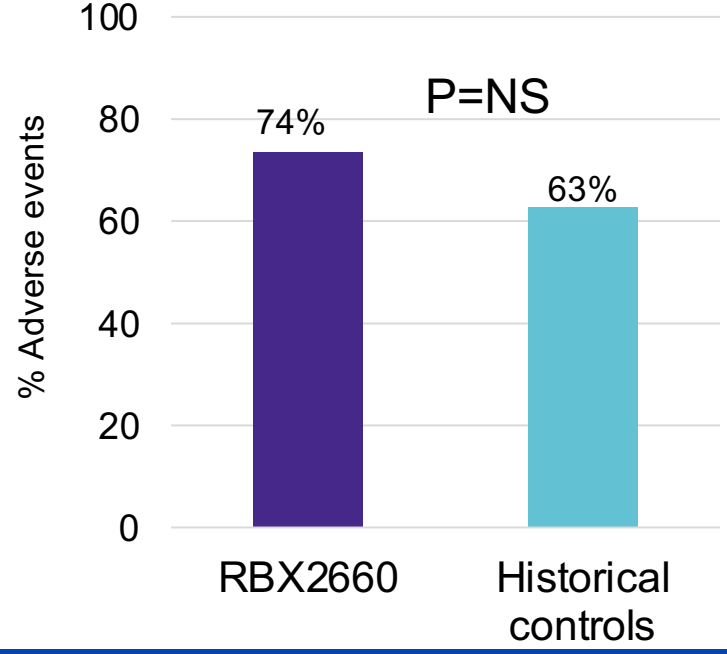


Dubberke E et al. *Clin Infect Dis*. 2018 Sep 28;67(8):1198-1204.

RBX2660: Open-label vs Historical Controls Safety and Efficacy

- Prospective, multicenter, open-label Phase II
  - 132 RBX2660 at 29 & 110 controls at 4 centers





Orenstein et al. ID Week 2017.

RBX2660: Phase III trial (PUNCH CD III)

- 2 arms: placebo vs one enema
- Patients with 2 or more episodes
- Primary outcome
  - Efficacy of RBX2660 compared to placebo at 8 weeks
- Secondary outcomes
  - Adverse events
  - Quality of life
- Interim positive Phase III results released
  - Press release May 6th, 2020

https://www.rebiotix.com/news-media/press-releases/rebiotix-announces-worlds-first-positive-pivotal-phase-3-data-investigational-microbiome-based-therapy-rbx2660/

The FDA has granted RBX2660 Breakthrough Therapy, Fast Track, and Orphan Drug Designations

http://www.rebiotix.com/news-media/press-releases/rebiotix-receives-breakthrough-therapy-designation-for-rbx2660-recurrent-c-diff/

VE303: Phase II

- ‘Rationally defined’ live bacterial consortia
- Safety and efficacy of VE303 at preventing subsequent CDI compared with placebo
- Completion of at least 1 successful course antibiotics for CDI in at high risk for recurrence or subjects with recurrent CDI.
- Randomized into 3 arms in a 1:1:1 ratio of high dose VE303, low dose VE303, and placebo

The FDA has granted VE-303 an Orphan Drug Designation

Summary

- Microbiome restoration therapies appear to be safe and effective for management of recurrent *C. difficile* infection

What Do the Next 12 Months Look Like?

- More data from CP101 and a larger Phase III trial
- A Larger trial of RBX7455
- Results from VE303 studies
- Scientific publications from RBX2660 and SER-109 studies
  - One/both of these products to get FDA approval
- FDA guidance on FMT will continue to evolve
  - Approved products would replace traditional FMT

