Role of Live Biotherapeutic Products (LBPs) in the Treatment of *Clostridioides difficile*

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2023 ICHP ANNUAL MEETING

Disclosures

The presenter does not have any conflicts or financial disclosures in relation to the content of this presentation.

The faculty mentor is a current consultant to Ferring Pharmaceuticals. Any relevant conflicts have been resolved.

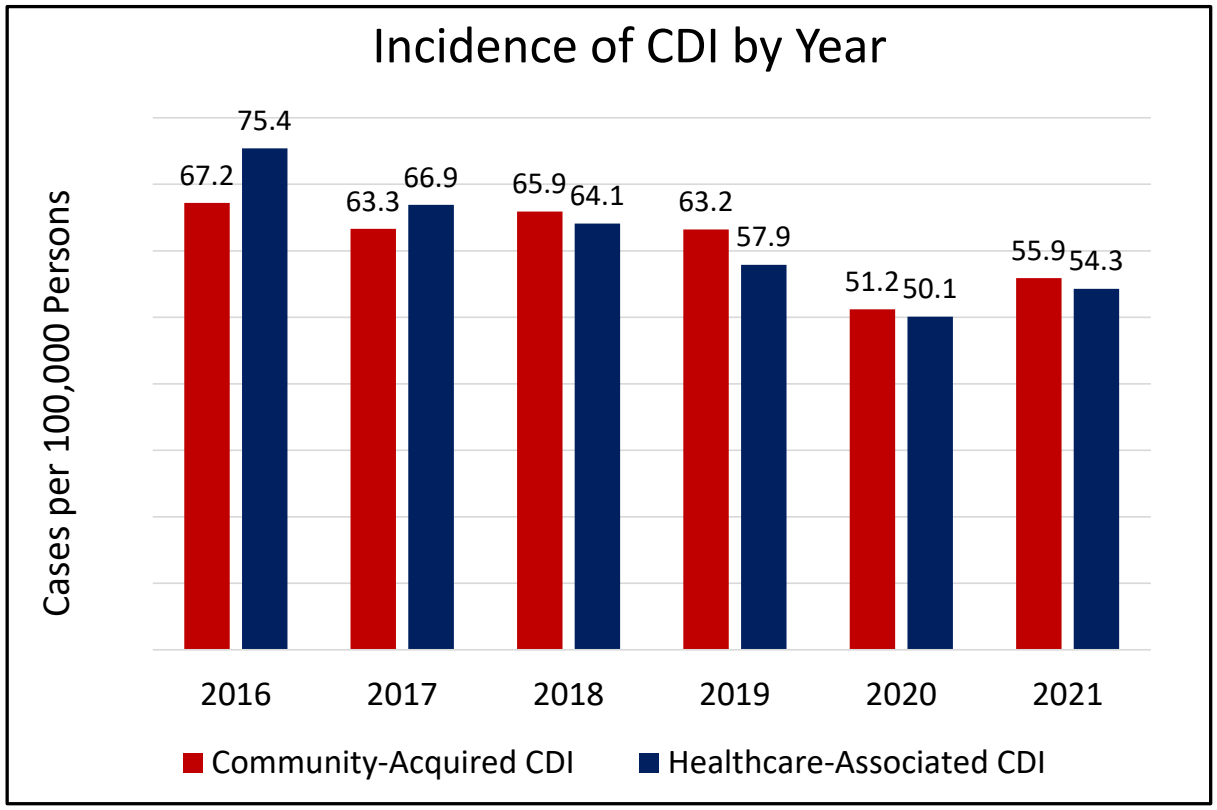
Objectives

1. Explain the mechanism of Live Biotherapeutic Products (LBPs) and their role in the management of *Clostridioides difficile* (C. diff.) infections
2. Review the safety and efficacy data of historical and present Fecal Microbiota Transplants (FMTs)
3. Describe the literature supporting new FDA-approved LBPs

Clostridioides difficile Infection (CDI) and the Role of Live Biotherapeutic Products

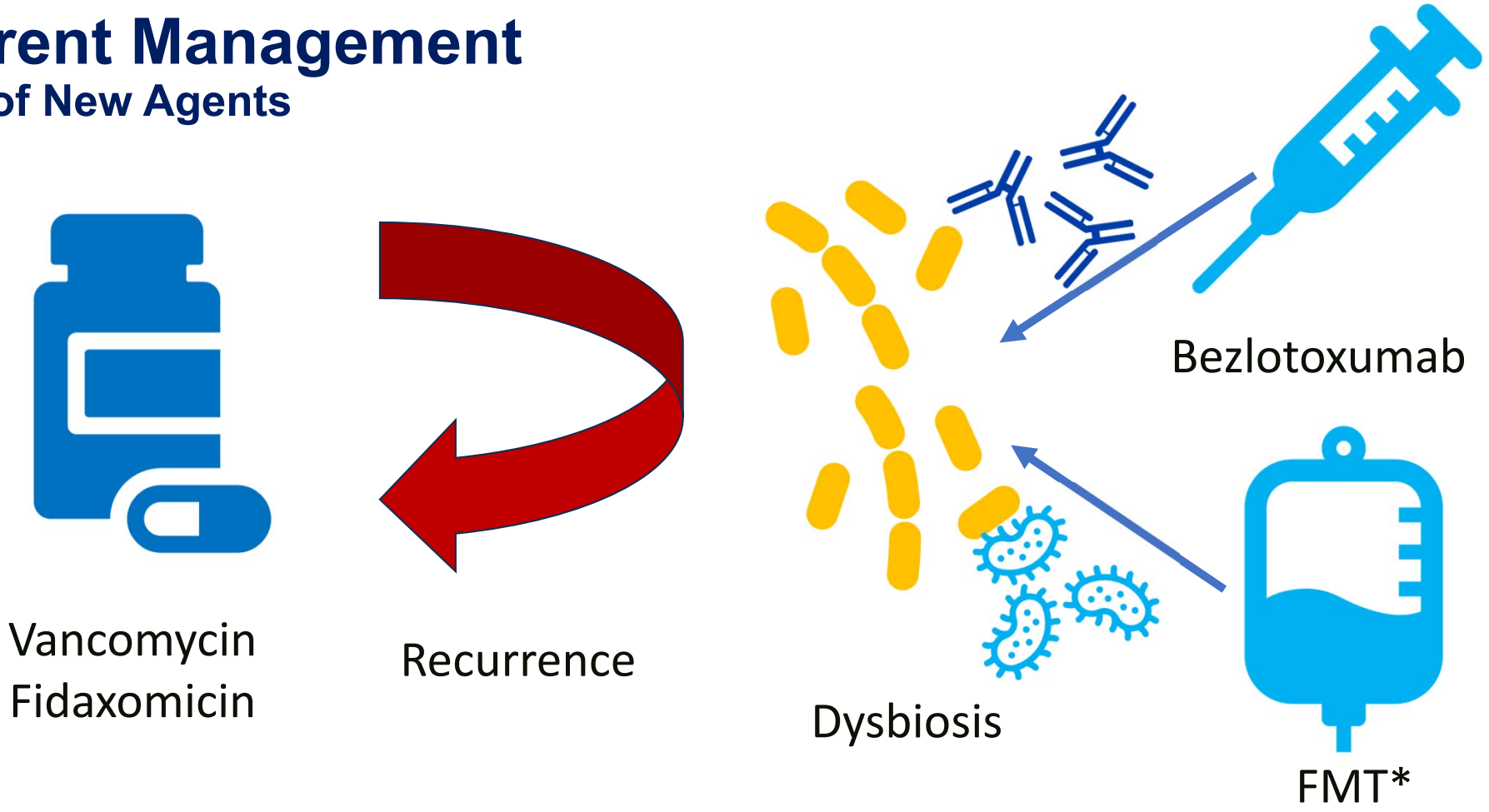
Epidemiology

- CDC Emerging Infections Program
  - Data from 10 counties
  - Population of 12.2 million people
  - ~12% recurrence rate
- CDC threat report (2017):
  - 223,900 hospitalized cases
  - 12,800 deaths



CDC. Antibiotic Resistance Threats in the United States, 2019.
CDC. *Clostridioides difficile* Infection (CDI) Tracking, 2022.

Current Management
Role of New Agents



*FMT: Fecal Microbiome Transplantation

What are Live Biotherapeutic Products?

- Transfer of fecal material
  - Transplants he[illegible]thy m[illegible]es to infe[illegible]d patie[illegible]
  - Clini[illegible]
- [illegible]
- [illegible]
  - Ful[illegible]echanism under investigation
  - Ideal methods to be determined

LBP = FMT

LBP = FMT

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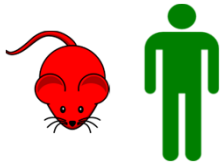
Tennant M. *The Yale Global Health Review.* December 1, 2016.

Mechanisms of Fecal Microbiome Transplantation

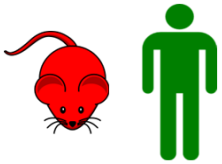
Why it Works



- Successful restoration of microbiome
  - Recipient diversity index matching donors
  - Recipient species colonization matches donors

= human data

= mouse data



Microbiome regulates local growth factors

- Deconjugating 1º bile acids into 2º bile acids
- Bacteriotoxins with G+ activity

Microbiome regulates cytokine expression

- Responsible for local immune regulation
- Reduces proinflammatory cytokines

Hernández Del Pino RE, et al. *Journal of Leukocyte Biology*. 2021;109(1):195-210
Leffler DA, Lamont JT. *N Engl J Med*. 2015;372(16):1539-1548
Littmann ER, et al. *Nat Commun.* 2021;12(1):755
Lozupone et al. *ISME J* **5**, 169–172 (2011).

When poll is active respond at **PollEv.com/ichp3** Send **ichp3** to **22333**

1. You are counseling a patient in clinic with recurrent CDI about potentially using an LBP. The patient asks you to describe how the therapy works. The best response is:

0

0%	0%	0%	0%
LBPs introduce Bacteroides spp. depleted by CDI which will outcompete C. diff. for resources.	LBPs are used instead of antibiotic therapy and cause the innate immune system to attack C. diff.	LBPs replace a variety of commensal bacteria, creating an environment to prevent C. diff. overgrowth.	LBPs are used for initial infection as they prevent C. diff. spores from attaching to the gut lumen.

Safety and Efficacy Data of FMT Products

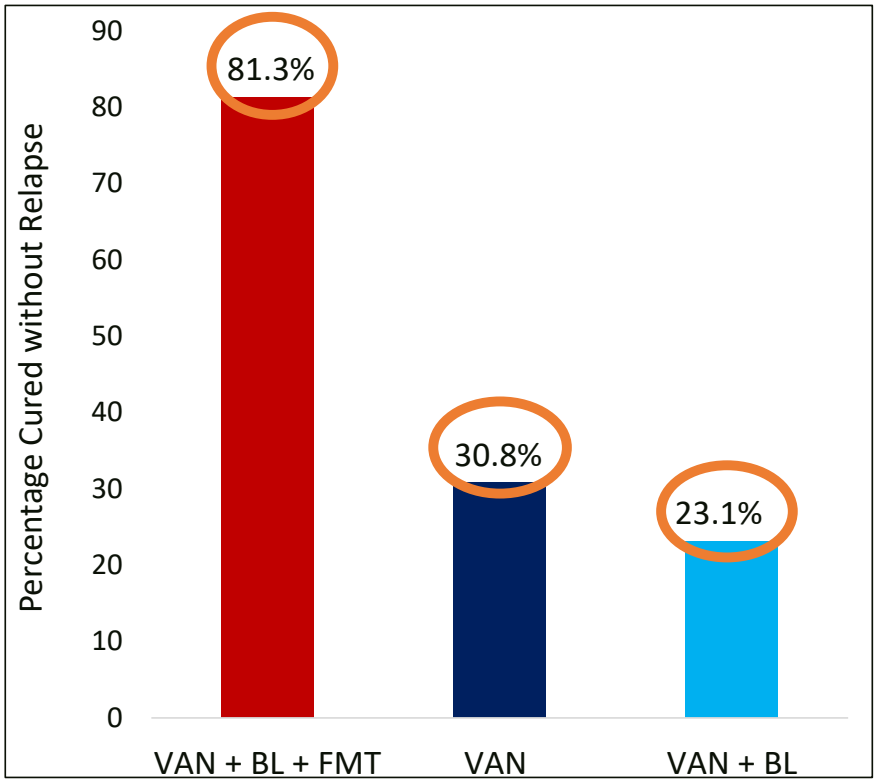
Fecal Microbiome Transplantation
Clinical Success

- ≥18 years old
- Relapse after ≥1 treatments
- *C. difficile* toxin (+)

Randomization
Double-blinded

- Vancomycin + BL + FMT
- Vancomycin
- Vancomycin + BL

Primary Outcome: Cure Without Relapse at 10 weeks

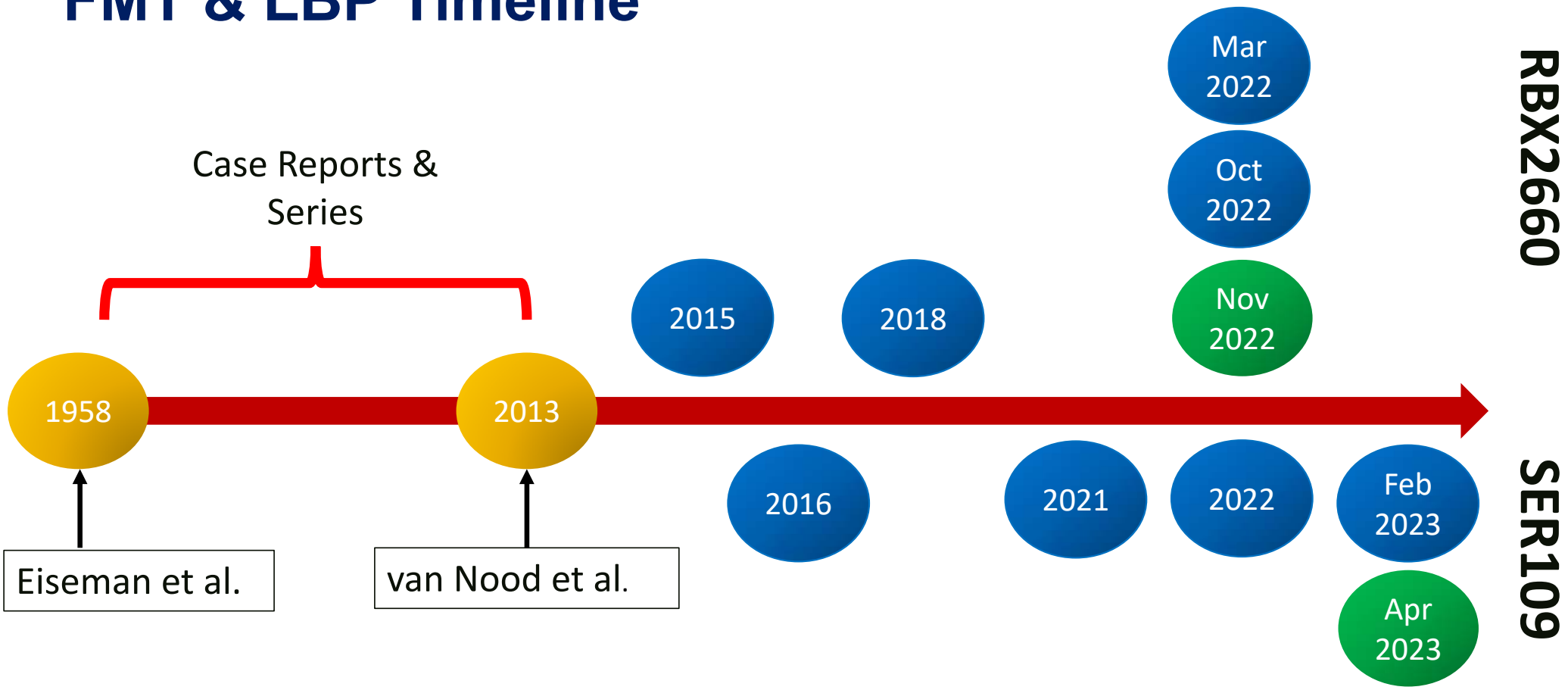


Key Takeaways
First RCT Evaluating FMT
High Efficacy vs. Antibiotic Therapy

VAN: Vancomycin 500 mg po QID x 4 days
BL: Bowel lavage
FMT: Fecal microbiome transplantation

van Nood E, et al. *N Engl J Med.* 2013;368(5):407-415.

FMT & LBP Timeline



Eiseman B, et al. Surgery. 1958;44(5):854-859
van Nood E, et al. *N Engl J Med.* 2013;368(5):407-415

FMT Modern Efficacy
Systematic Review and Meta-analysis

Baunwall et al. 2020

- 45 studies: RCT and cohort
- 8w cure: 84% single dose (80-88%)
- 8w cure: 91% repeat dose (89-94%)

Pomares Bascuñana et al. 2021

- 15 studies: RCT, cohort, and cases within 5 years
- Effectiveness: 82% (75%-89%)

Baunwall SMD, et al. *EClinicalMedicine*. 2020;29-30:100642
Pomares Bascuñana RÁ, et al. *Lett Appl Microbiol*. 2021;73(2):149-158.

Safety Data
Reports from 50 Publications

Gastrointestinal

Abdominal pain, bloating, diarrhea, nausea, flatulence

Systemic

Fever

Procedural

Nasal irritation, sore throat, bowel perforation, GI bleed, aspiration

Autoimmune

IBD disease flare, rheumatoid arthritis, peripheral neuropathy

Infectious

Peritonitis, pneumonia, diverticulitis, appendicitis, bacteremia, UTI

Pathogen Transmission

Norovirus, Cytomegalovirus, multi-drug resistant organisms

DeFilipp Z, et al. *N Engl J Med*. 2019;381(21):2043-2050
Li YT, et al. *Aliment Pharmacol Ther*. 2016;43(4):445-457.
Wang S, et al. *PLoS ONE*. 2016;11(8):e0161174.

Donor Screening

- Human immunodeficiency virus
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Syphilis
- Norovirus
- Rotavirus
- Adenovirus
- Ova and parasites

- *Clostridioides difficile*
- Vancomycin-resistant enterococci
- Methicillin-resistant *Staphylococcus aureus*
- ESBL and CRE genes
- Shiga-toxin *E. coli*
- *Vibrios*
- *Salmonella*
- *Listeria*
- SARS-CoV-2 (after 12/01/2019)

ESBL = Extended-Spectrum Beta Lactamase Inhibitor
CRE = Carbapenem Resistant *Enterobacterales*
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

Carlson PE. *Cell Host & Microbe*. 2020;27(2):173-175.

When poll is active respond at **PollEv.com/ichp3** Send **ichp3** to **22333**

2. A physician colleague asks you about what historical data exists for FMTs. The best response is:

0

0%	0%	0%	0%
FMT data from clinical trials have shown high efficacy and safety.	FMT data are restricted to case reports making it difficult to assess efficacy and safety.	FMT data from clinical trials have shown high efficacy but frequent serious adverse events.	FMT data are restricted to case reports but have shown variable efficacy and high safety.

Newly Approved Therapy: RBX2660

Fecal microbiota, live-jslm

Rebyota™

Product Description – RBX2660

- 50g stool/150 mL PEG/NS enema
- $1x10^8$ – $5x10^{10}$ CFU/mL mixed culture
  - $1x10^5$ Bacteroides CFU
- Standardized donors
- Frozen sample: stored from -60 °C to -90 °C
- Administer within 72 hours of last antibiotic dose

Drugs.com. *Rebyota Images.* Accessed online March 2023.
Rebyota. Package insert. Ferring Pharmaceuticals, Inc. 2022.

Clinical Trials - Overview

Excluded

- Immunocompromised, gastrointestinal comorbidity, alternative pathogen or diagnosis
- *Not applicable to PUNCH CD3 OLS*

Demographics

- ~65 years old
- ~2/3 female
- >90% white
- ~90% vancomycin lead-in

Adverse Events

- 69.7% RBX2660 vs 60.2% placebo
- None life-threatening
- No pathogen-traced infections
- Study discontinuation <1%

Aggregate Clinical Trial Data

Participants (%) N=620	Doses of RBX2660
324 (52.3%)	1
270 (43.5%)	2
14 (2.3%)	3
12 (1.9%)	4

Braun T, et al. *Open Forum Infect Dis*. 2021;8(Suppl 1):S611.

Clinical Trials – PUNCH CD2
Efficacy of RBX2660 vs Placebo

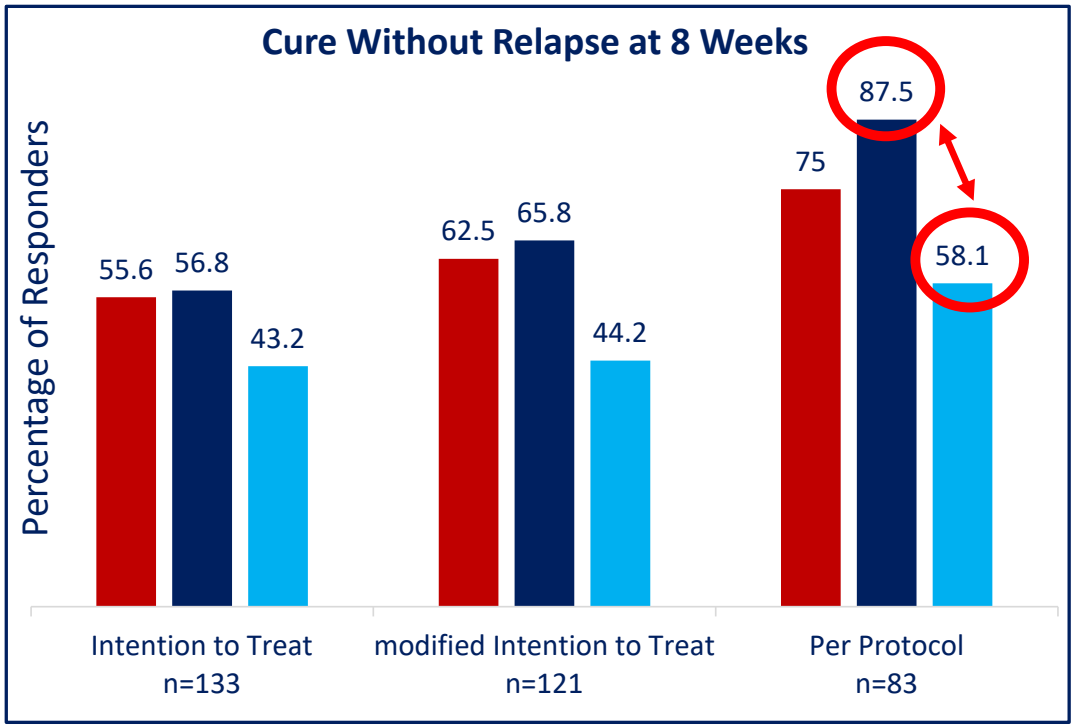
- ≥18 years old
- Relapse after ≥2 treatments
- *C. difficile* (+)
- Antibiotic treatment course

2 doses RBX2660

1 dose RBX2660 + 1 dose Placebo

2 doses Placebo

Randomization
Double-blinded



Key Takeaways

Not All Patients Need 2 Enemas

Long Term Safety Data

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Dubberke ER, et al. *Infect Dis Ther*. 2023;12(2):703-709.

Clinical Trials - PUNCH Open Label

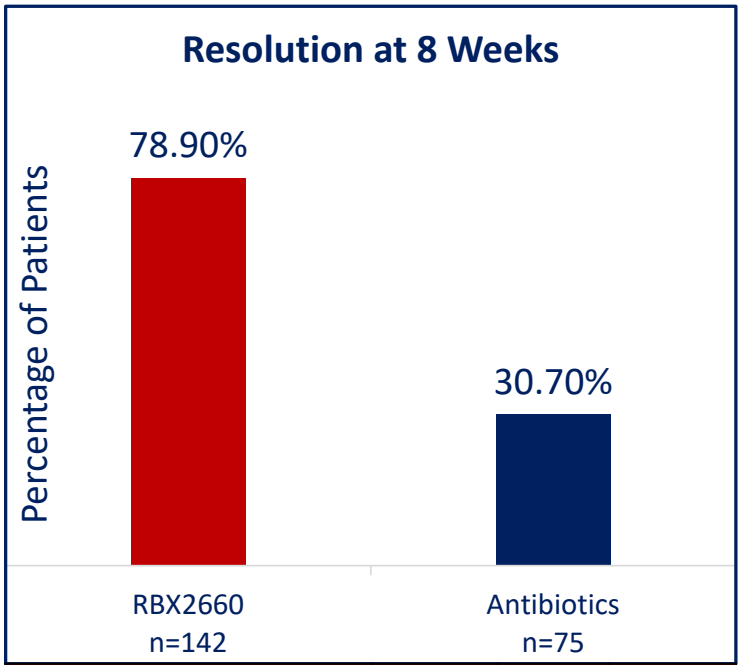
RBX2660 vs Historical Control

- ≥18 years old
- Relapse after ≥2 treatments
- *C. difficile* (+)
- Antibiotic treatment course

2 doses RBX2660

Antibiotics (historical)

Not Randomized



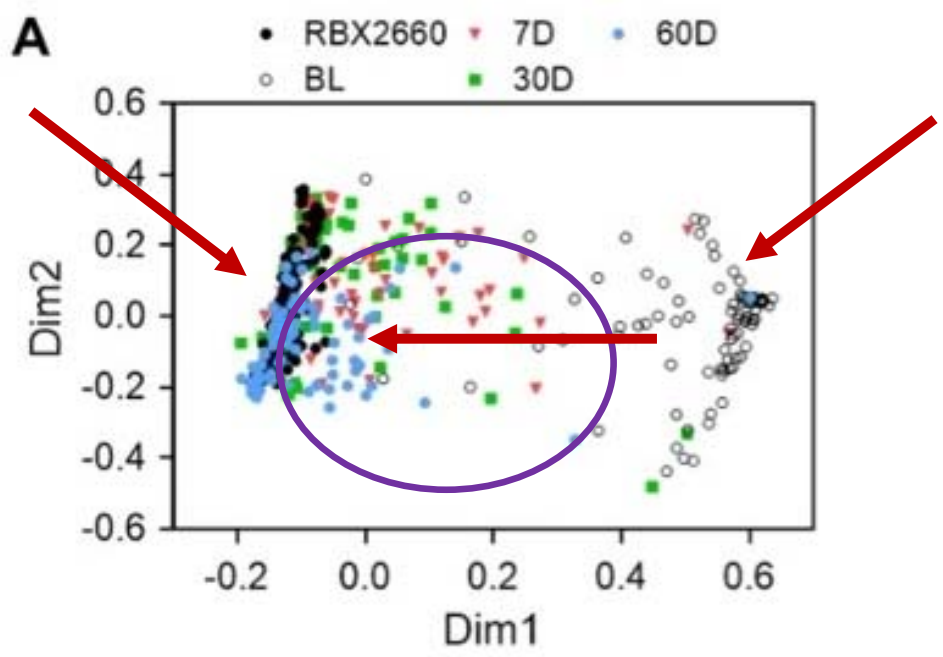
	6m	12m	24m
Sustained Clinical Response	97%	95%	91%

Key Takeaways

Long Term Sustained Response
Long Term Safety Data
High Efficacy vs. Antibiotics

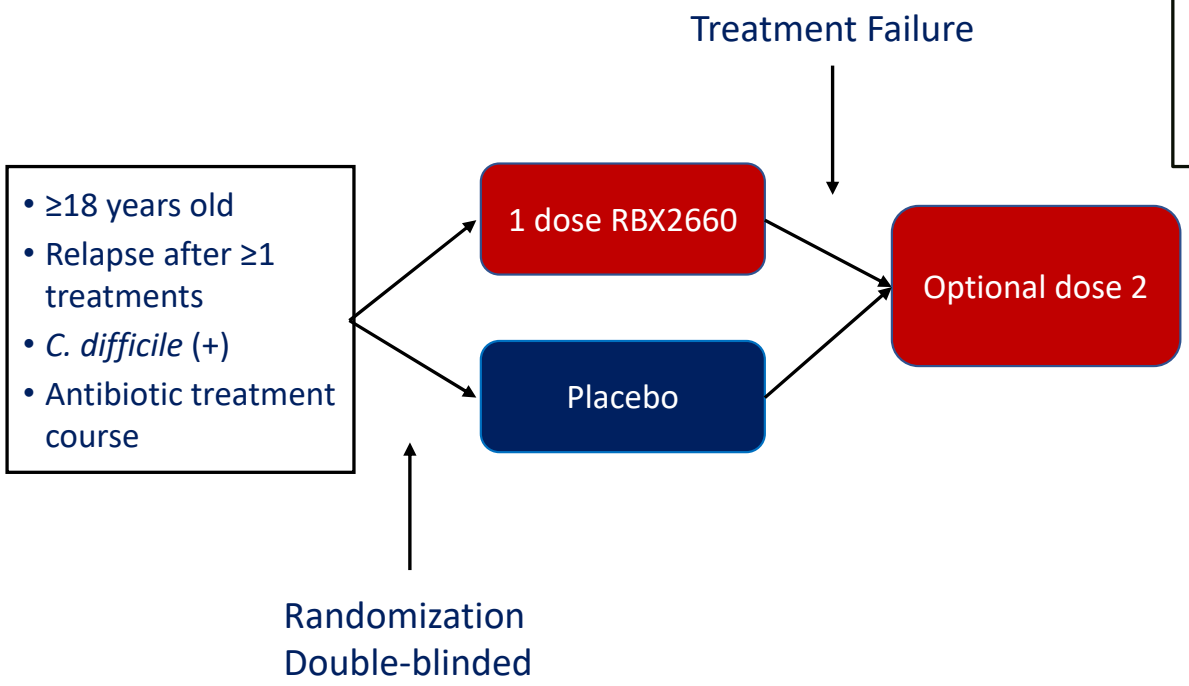
Orenstein R, et al. *BMC Infect Dis*. 2022;22(1):245.

Clinical Trials – PUNCH Open Label
Similarity of Stool Cultures



Treatment Responders
n = 105

Clinical Trials – PUNCH CD3
Efficacy of RBX2660 vs Placebo



1° Outcome: Posterior probability of success

Bayesian modeling including PUNCH CD-2

Cutoff per FDA requirement 0.97503 (α = 0.025)

2° Outcomes

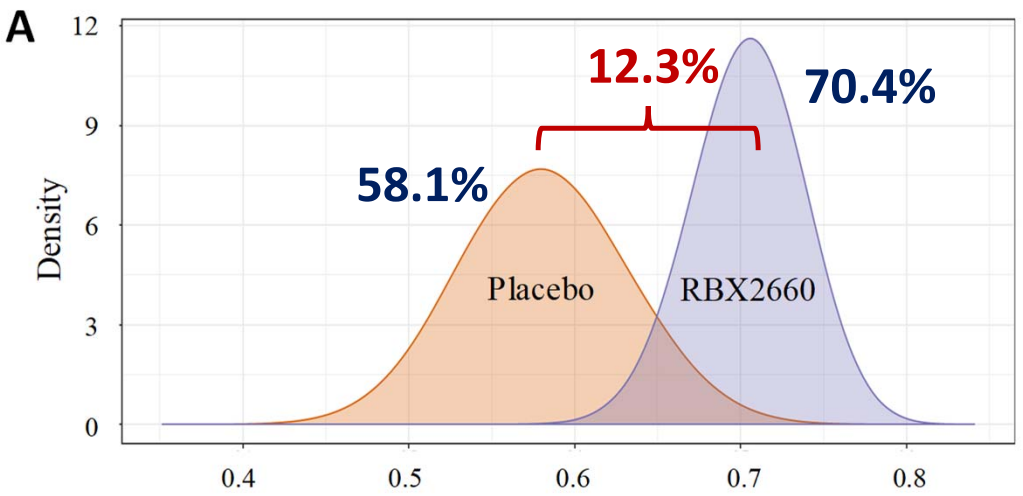
Overall RBX2660 response	83.6%
Placebo arm response	62.5%
Sustained response in both arms	90%

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

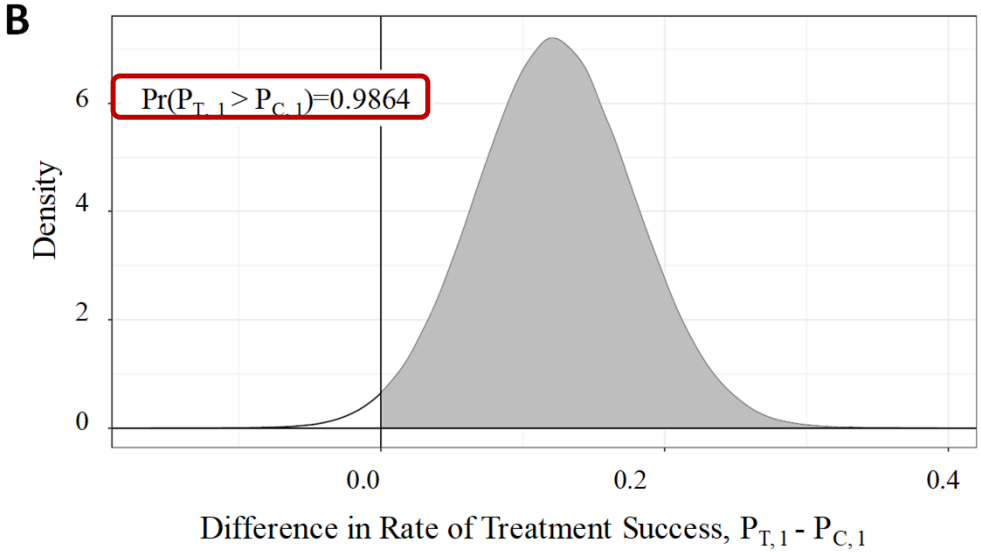
Clinical Trials – PUNCH CD3

Primary Outcome

Posterior Distribution of Success Rate for mITT



Difference in Rate of Treatment Success



Key Takeaways

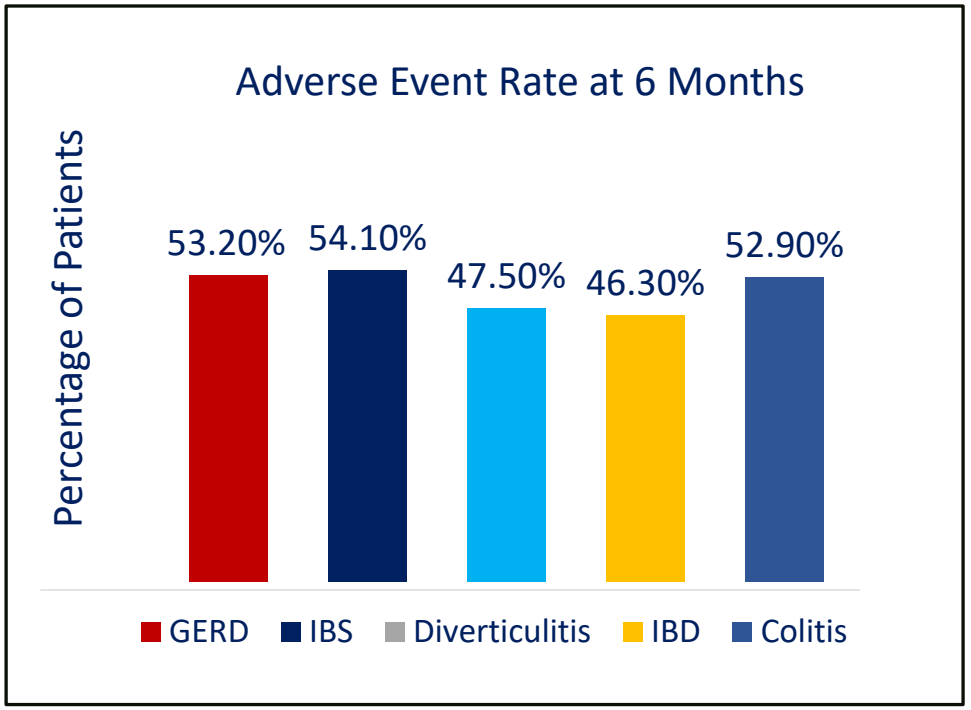
Efficacy Significantly Better Than Placebo
Resulted in Drug Approval

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

Interim Results – PUNCH CD3 OLS
Single Dose in Previously Excluded Comorbidities

- ≥18 years old
- Relapse after ≥1 treatments
- *C. difficile* (+)
- Antibiotic treatment course

→ One dose of RBX2660



Key Takeaways

Expected Safety in GI Comorbidities

Expected Efficacy in GI Comorbidities

Khanna S, et al. *Am J Gastroenterol*. 2022;117(10S):e96-e96.

Newly Approved Therapy: SER109

Fecal microbiota spores, live-brpk

Vowst™

Product Description – SER109

- 4 oral capsules daily x 3 days
- $1x10^6$ – $3x10^7$ spore CFU / capsule
  - Phyla *Firmicutes* Spores
  - Non-spore removal: ethanol and filtration
- Shelf life: 36 months at 2-25°C
- Administration
  - 10 oz Magnesium citrate night before
  - 2-4 days after last antibiotic dose

Drugs.com. *Vowst Images*. Accessed online July 2023.
US FDA. Summary Basis for Regulatory Approval. April, 2023.
Vowst. Package insert. Seres Therapeutics, Inc. 2023.

Clinical Trials - Overview

Excluded

- Immunocompromised, gastrointestinal comorbidity, alternative pathogen or diagnosis
- Concomitant loperamide, cholestyramine, diphenoxylate/atropine

Demographics

- ~65 years old
- ~2/3 female
- >90% white
- ~80% vancomycin lead-in

Adverse Events

- One hypersensitivity reaction
- No serious adverse events drug-related
- No pathogen-traced infections

Trial Name and Population	Treatment Related Adverse Event Rate
Khanna et al (N = 30)	50%
ECOSPOR (n = 59)	55%
ECOSPOR III (n = 89)	51%
ECOSPOR IV (N = 263)	53.6%

Khanna, et al. *The Journal of Infectious Diseases*. 2016;214(2):173-181.
McGovern BH, et al. *Clinical Infectious Diseases*. 2021;72(12):2132-2140
Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229.
Sims, M. *JAMA Netw Open.* 2023;6(2):e2255758.

Clinical Trials - ECOSPOR

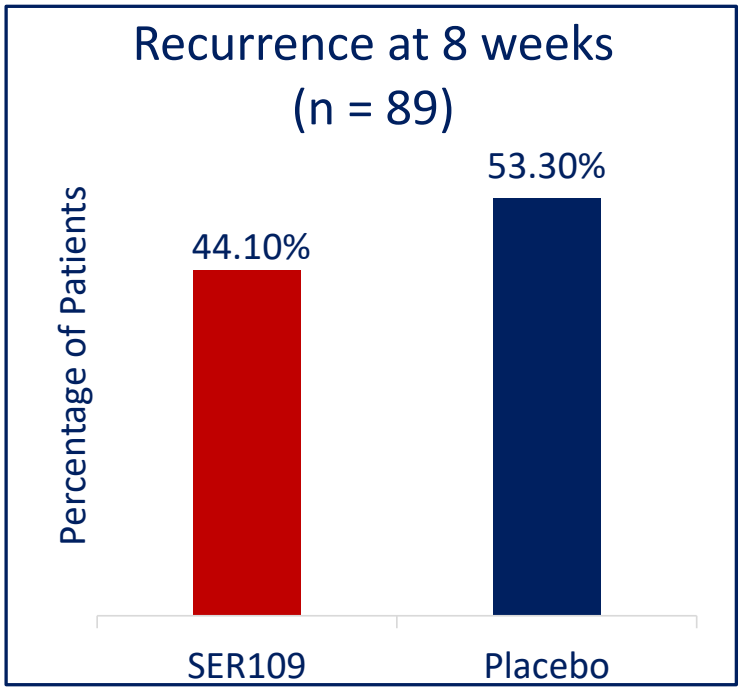
SER109 vs Placebo

- ≥18 years old
- Relapse after ≥1 treatment
- *C. difficile* (+)
- Antibiotic treatment course
- 10 oz Magnesium citrate bowel prep

→ 4 capsules SER109

→ Placebo

Randomization
Double-blinded



Outcome	Risk Ratio
1 dose SER109 vs Placebo	**1.2 (0.8-1.9)**

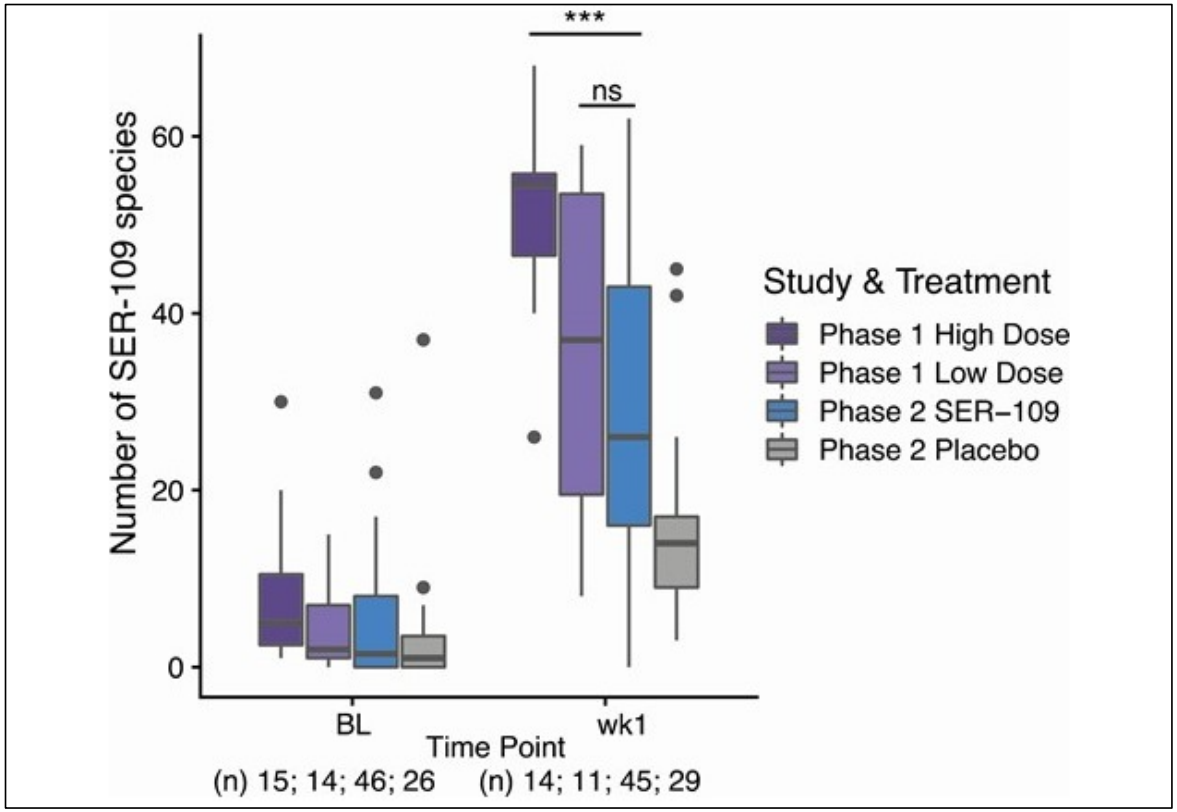
Key Takeaways

Dose-Response Relationship
Long Term Safety Data

McGovern BH, et al. *Clinical Infectious Diseases*. 2021;72(12):2132-2140.

Clinical Trials - ECOSPOR

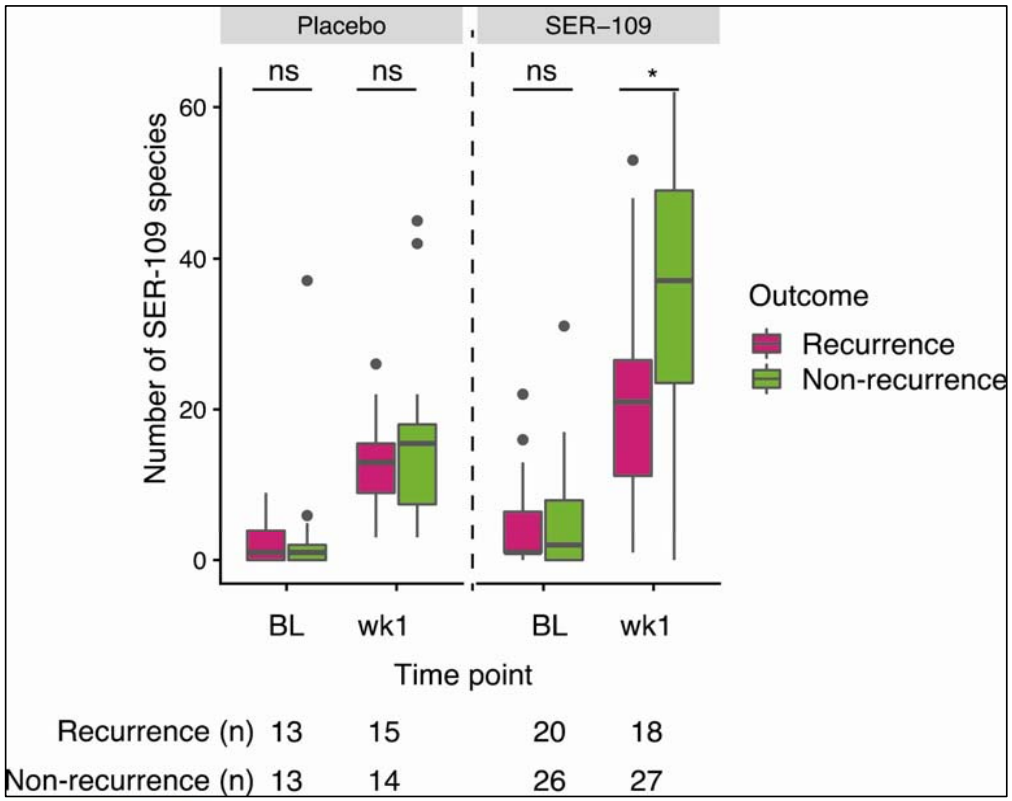
Dose vs Engraftment Post-hoc



McGovern BH, et al. *Clinical Infectious Diseases*. 2021;72(12):2132-2140.

Clinical Trials - ECOSPOR

Engraftment vs Recurrence



Clinical Trials – ECOSPOR III

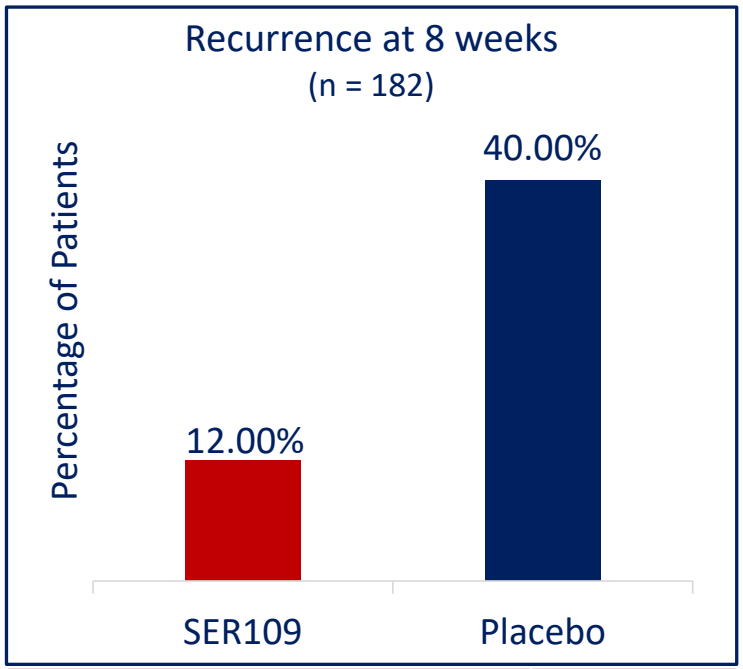
SER109 vs Placebo

- ≥18 years old
- Relapse after ≥1 treatment in 12m
- *C. difficile* **toxin** (+)
- Antibiotic treatment course
- 10 oz Magnesium citrate bowel prep

4 capsules SER109 x3 days

Placebo

Randomization
Double-blinded



Outcome	Risk Ratio
8-week Recurrence Risk SER109 vs Placebo	**0.32 (0.18-0.58)**
Sustained Clinical Response SER109	**88%**

Key Takeaways

High-Dose Efficacy Superior to Placebo
High Sustained Clinical Response

Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229.

Clinical Trials – ECOSPOR IV

Single arm

- ≥18 years old
- Relapse after ≥1 treatment
- *C. difficile* (+)
- 10-42d antibiotic treatment

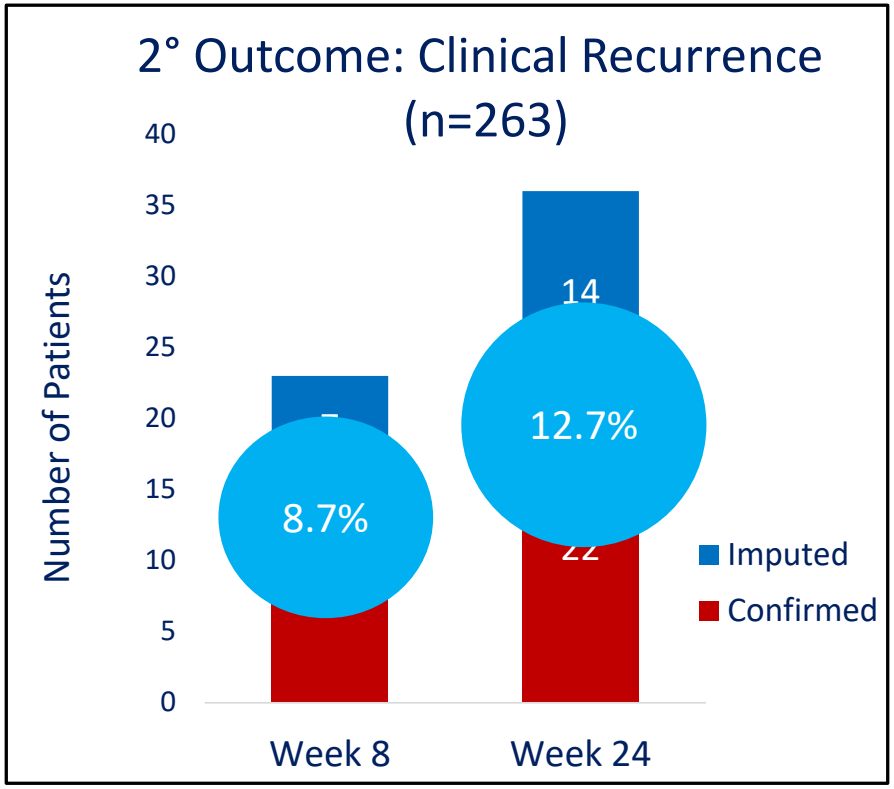
- ECOSPOR III recurrence
- *C. difficile* EIA (+)

10oz MgCt bowel prep

4 capsules daily x3 days

1° Outcome: Adverse Events up to 24 weeks

- Overall 53.6% (141/263)
- 1 hypersensitivity reaction



Key Takeaways

Short Term Safety of High Dose

Sustained Clinical Response

Sims, M. *JAMA Netw Open.* 2023;6(2):e2255758.

076 - Hunt - Role of LBPs in c Diff

Visual settings | Edit

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3. A pharmacist colleague asks you to describe the differences between RBX2660 and SER109 clinical trial data. The best response is:

0

0%	0%	0%	0%
The patient population enrolled in the PUNCH studies were older and more diverse.	The ECOSPOR studies showed a much higher sustained clinical response.	Engraftment was only studied in the ECOSPOR trials.	The PUNCH studies have published data for patients with IBD.

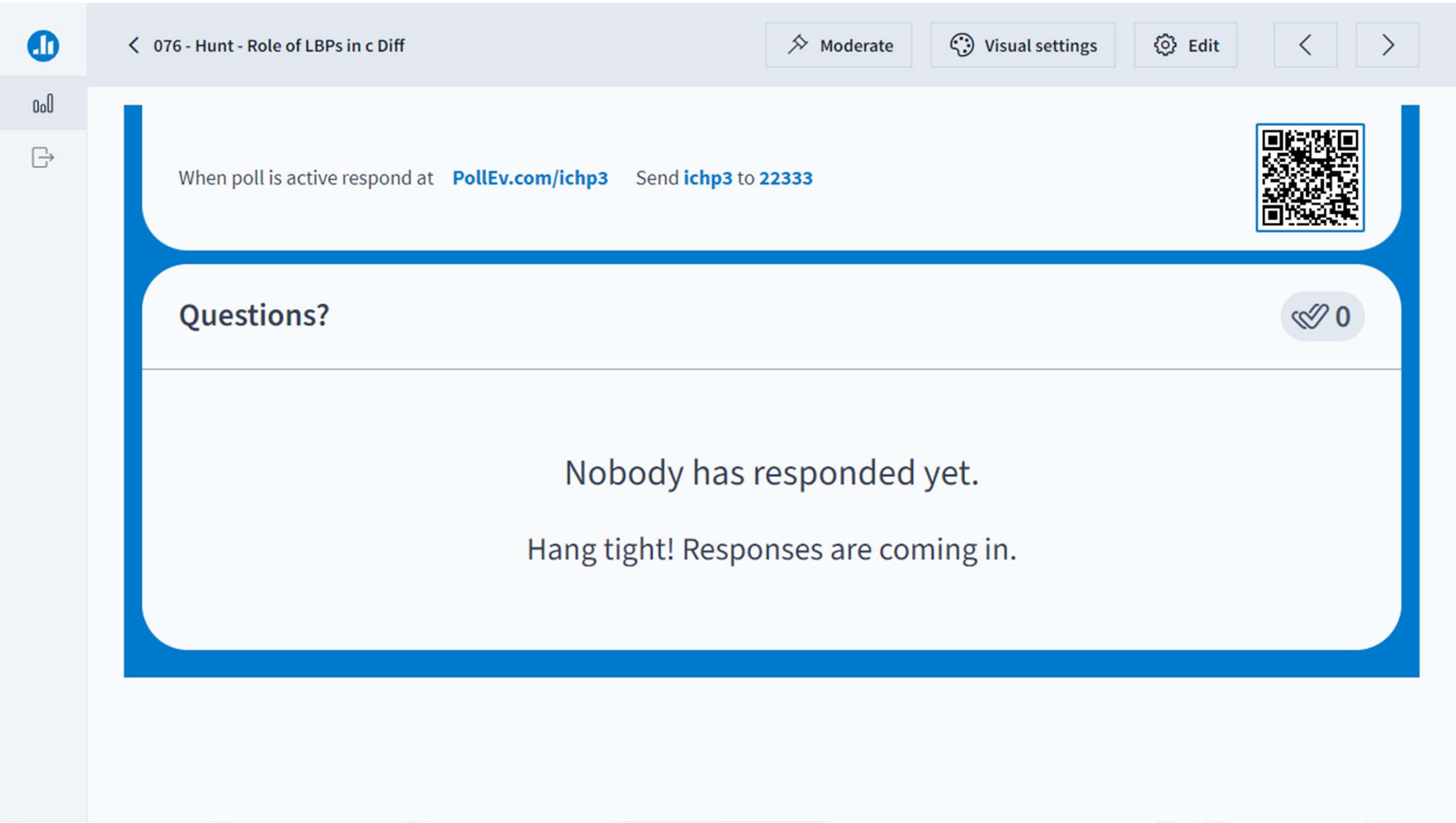
Summary: *C. difficile* and LBPs

What We Do Know

- Successful LBP engraftment resembles donor microflora and alters local colonic environment
- Clinical success is correlated with engraftment and has 90% sustained response
- LBPs remain consistently more effective than antibiotic monotherapy for the treatment of CDI
- LBPs remain consistently safe both short-term and long-term

What We Don't Know

- The full relationship between colonic microbiota, the adaptive immune response, and *C. difficile* infection
- Desirable product contents and formulation
- Why some patients are unresponsive to LBPs
- The safety of LBPs in specialty populations


076 - Hunt - Role of LBPs in c Diff
Moderate
Visual settings
Edit
When poll is active respond at PollEv.com/ichp3 Send ichp3 to 22333
Questions?
0
Nobody has responded yet.
Hang tight! Responses are coming in.

Supplemental Resources

Mechanistic Review:

Littmann, E.R., Lee, JJ., Denny, J.E. et al. Host immunity modulates the efficacy of microbiota transplantation for treatment of Clostridioides difficile infection. Nat Commun 12, 755 (2021).

Product Review:

Wang JW, Kuo CH, Kuo FC, et al. Fecal microbiota transplantation: Review and update. *Journal of the Formosan Medical Association*. 2019;118:S23-S31

Citations

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2. CDC. *Clostridioides difficile* Infection (CDI) Tracking. Atlanta, GA: U.S. Department of Health and Human Services, CDC. Last updated February 24, 2022.
3. Tennant M. Fecal Microbiota Transplantation: The Future of Feces. *The Yale Global Health Review.* December 1, 2016. Accessed online March 8th, 2023. https://yaleglobalhealthreview.com/2016/12/01/fecal-microbiota-transplantation-the-future-of-feces/
4. Hernández Del Pino RE, Barbero AM, Español LÁ, Morro LS, Pasquinelli V. The adaptive immune response to *Clostridioides difficile* : A tricky balance between immunoprotection and immunopathogenesis. *Journal of Leukocyte Biology*. 2021;109(1):195-210.
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6. Littmann, E.R., Lee, JJ., Denny, J.E. *et al.* Host immunity modulates the efficacy of microbiota transplantation for treatment of *Clostridioides difficile* infection. *Nat Commun* **12**, 755 (2021). https://doi.org/10.1038/s41467-020-20793-x
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10. Pomares Bascuñana RÁ, Veses V, Sheth CC. Effectiveness of fecal microbiota transplant for the treatment of *Clostridioides difficile* diarrhea: a systematic review and meta-analysis. *Lett Appl Microbiol*. 2021;73(2):149-158.

Citations

11. Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. *EClinicalMedicine*. 2020;29-30:100642

12. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. Grivennikov S, ed. *PLoS ONE*. 2016;11(8):e0161174.

13. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *e. Coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med*. 2019;381(21):2043-2050

14. Yang L, Li W, Zhang X, et al. The evaluation of different types fecal bacteria products for the treatment of recurrent Clostridium difficile associated diarrhea: A systematic review and network meta-analysis. *Front Surg*. 2022;9:927970.

15. Carlson PE. Regulatory considerations for fecal microbiota transplantation products. *Cell Host & Microbe*. 2020;27(2):173-175

16. Drugs.com. *Rebyota 150 mL single dose Images.* Updated February 12, 2023. Accessed online March 4th, 2023. https://www.drugs.com/imprints/medicine-34078.html

17. Rebyota. Package insert. Ferring Pharmaceuticals, Inc. 2022

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