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Microbiome evaluation from the phase 2b, randomized, double-blind study of ibezapolstat compared with vancomycin for the treatment of *Clostridioides difficile* infection

Kevin W. Garey, M Jahangir Alam, Khurshida Begum, Jacob McPherson, Taryn A. Eubank, Jinhee Jo, Michael H. Silverman for the Ibezapolstat Phase 2 Investigator Group

July 2024 Anaerobe

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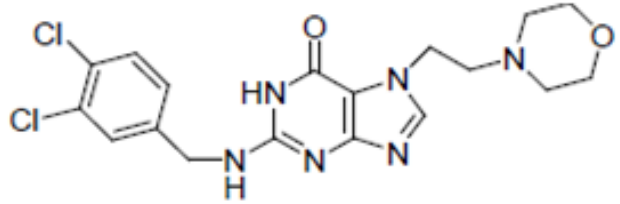
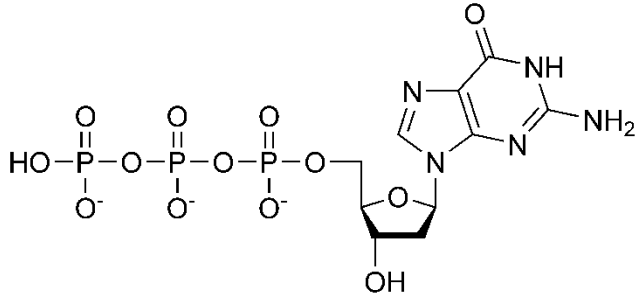
Ibezapolstat (IBZ; ACX362E)

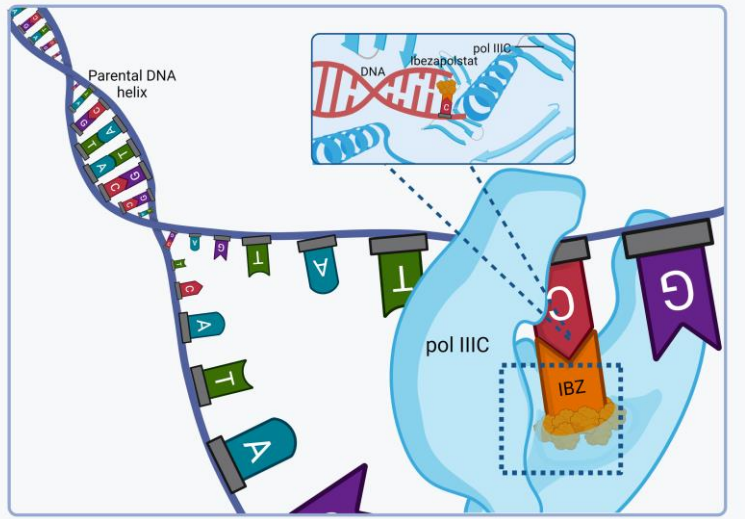


ACX-362



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)



1. Xu et al. Bioorg Med Chem. 2019 Aug 1;27(15):3209-3217

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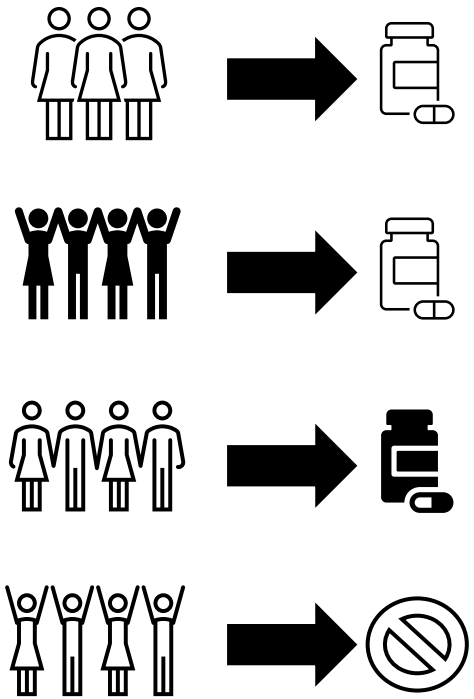
IBZ Clinical Trial Update

J Antimicrob Chemother. 2020 Dec; 75(12): 3635–3643.
Published online 2020 Sep 6. doi: 10.1093/jac/dkaa364
PMCID: PMC7662179
PMID: 32892222

A randomized, double-blind, placebo-controlled, single and multiple ascending dose Phase 1 study to determine the safety, pharmacokinetics and food and faecal microbiome effects of ibezapolstat administered orally to healthy subjects

Kevin W Garey,[d1] Khurshida Begum,[d1] Chris Lancaster,[d1] Anne Gonzales-Luna,[d1] Dinh Bui,[d1] Julie Mercier,[d2] Corinne Seng Yue,[d3] Murray P Ducharme,[d3] Ming Hu,[d1] Bradley Vince,[d2] Michael H Silverman,[d4] M Jahangir Alam,[d1] and Martin Kankam[d2]

Healthy Adult Volunteers (n=22)



Ibezapolstat 450 mg BID x 10 days

Ibezapolstat 300 mg BID x 10 days

Vancomycin 125 mg QID x 10 days

Placebo x 10 days

Stool collected daily x 13 days

Analysis:

- Adverse effects
- Pharmacokinetics in plasma and stool
- Shotgun metagenomics (Illumina NextSeq 500)

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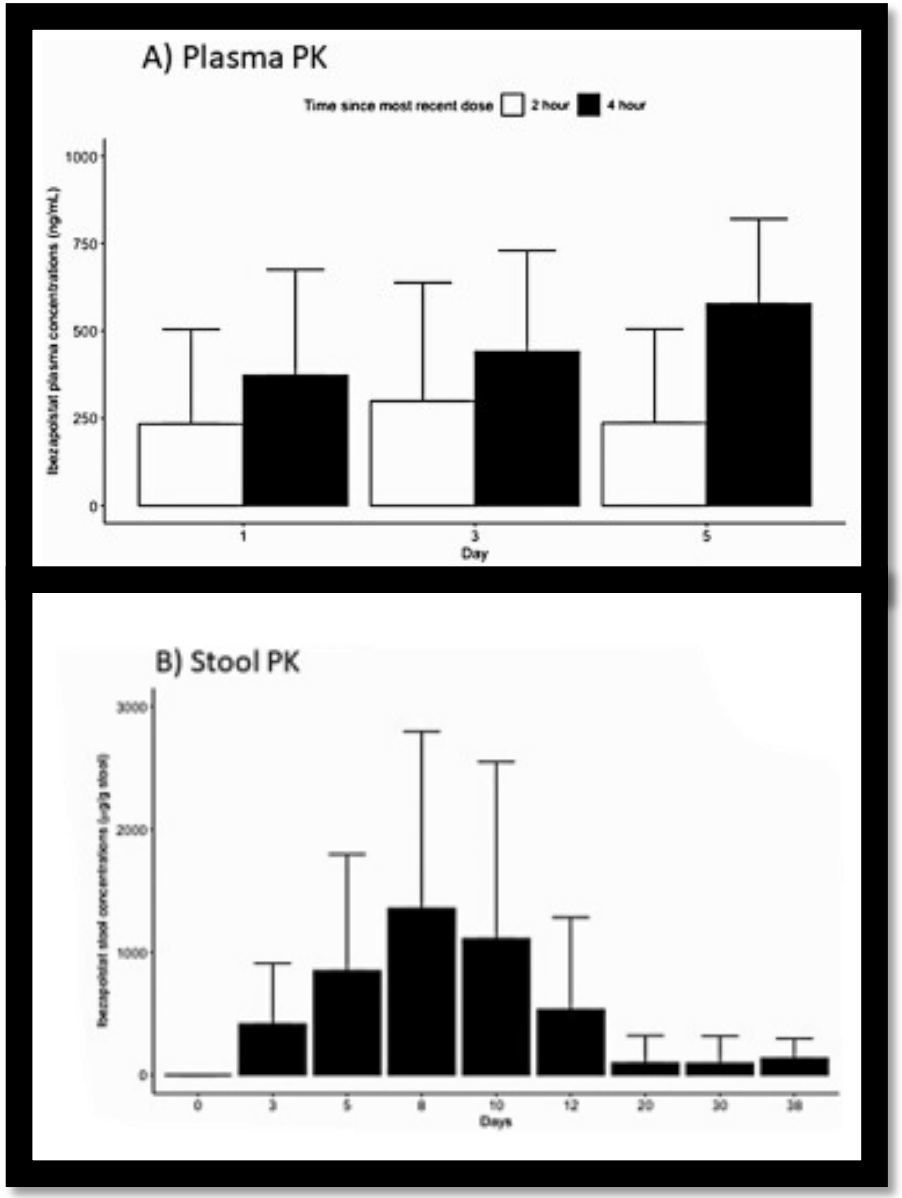
Phase 1 Results

Safe and effective for GI infections

(a)

Proportion of subjects with any drug-related adverse event (AE) in each study period

	Single ascending dose		Food effect	Multiple ascending dose	
Dose	*IBZ (n = 6)*	*Placebo (n = 2)*	*IBZ (n = 8)*	*IBZ (n = 6)*	*Placebo (n = 2)*
300	0%	50%	37.50%##	33%	50%
450	X	X	X	0%	0%
600	33%	50%	X	X	X
900	33%	50%	X	X	X
Summary	5 AE in 5 subjects	5 AE in 4 subjects	3 AE in 2 subjects	5 AE in 2 subjects	1 AE in 1 subject



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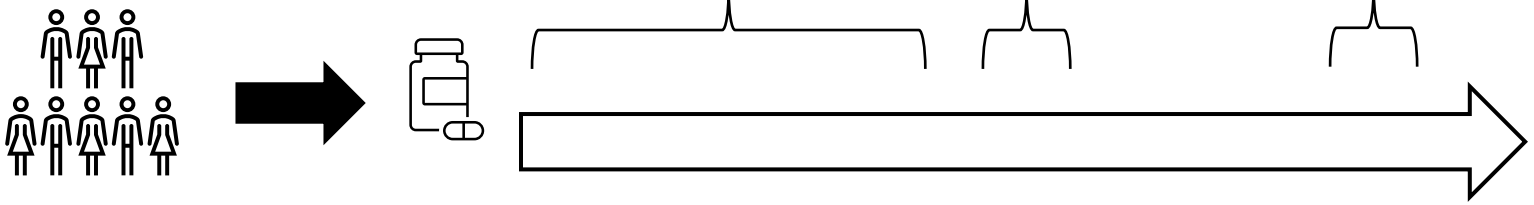
IBZ Phase 2a

Clinical Trial > Clin Infect Dis. 2022 Sep 30;75(7):1164-1170. doi: 10.1093/cid/ciac096.

Efficacy, Safety, Pharmacokinetics, and Microbiome Changes of Ibezapolstat in Adults with Clostridioides difficile Infection: A Phase 2a Multicenter Clinical Trial

Kevin W Garey [1,2], Jacob McPherson [1], An Q Dinh [2], Chenlin Hu [1], Jinhee Jo [1], Weiqun Wang [1], Chris K Lancaster [1], Anne J Gonzales-Luna [1], Caroline Loveall [1], Khurshida Begum [1], M Jahangir Alam [1], Michael H Silverman [3], Blake M Hanson [2]

CDI patients with mild/moderate disease diagnosed via toxin EIA (n=10)



Ibezapolstat 450 mg BID x 10 days

Stool collected during therapy and at follow up

10/10 patients achieved clinical cure and sustained clinical cure

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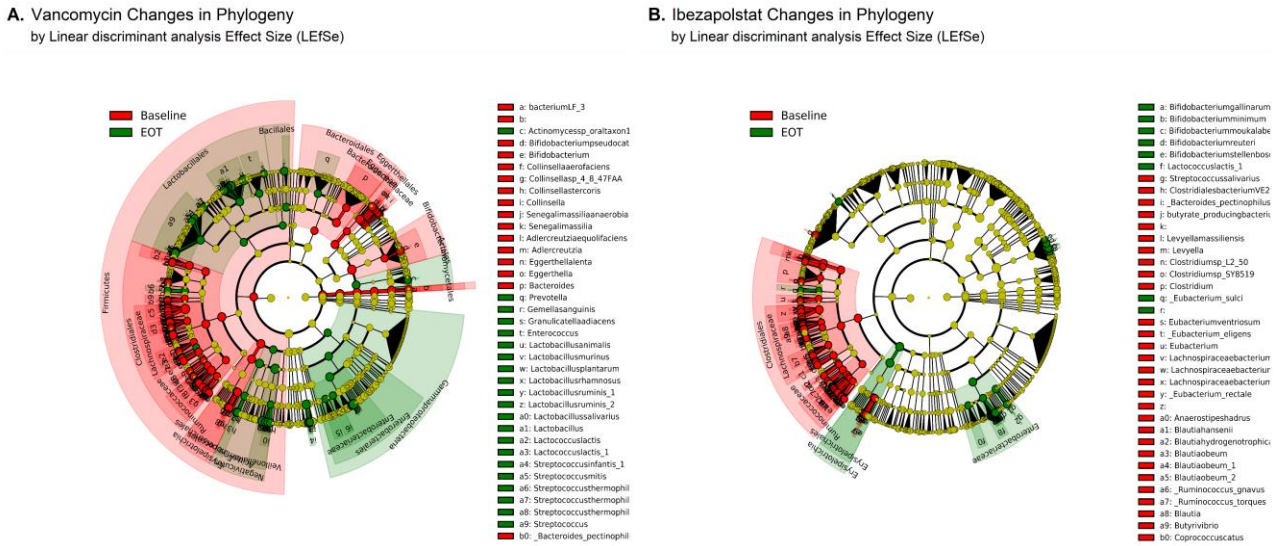
IBZ shown to have favorable effects on the microbiome

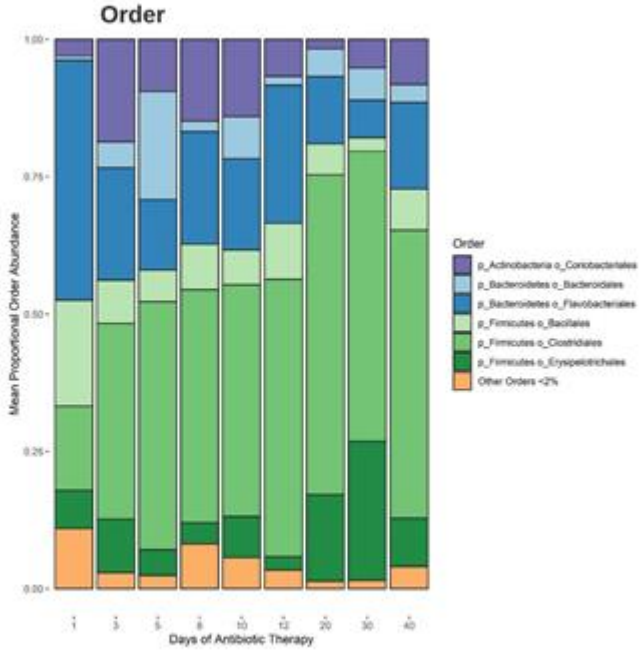
IBZ Phase 1 Healthy volunteer study in comparison with VAN



IBZ:
More narrow spectrum
Increased proportion of Actinobacteriota

McPherson et al AAC 2022

IBZ Phase 2a. Single arm, no-comparator study of CDI patients (n=10)



IBZ:
Increased proportion of Actinobacteriota
Increased proportion of Clostridiales

Garey et al CID 2022

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IBZ Phase 2b Microbiome Objectives

- Evaluate IBZ vs vancomycin (VAN) in patients with CDI for fecal microbiome effects:
    - Microbiologic eradication
    - Metagenomic proportional change
    - Quantitative changes in relative taxa

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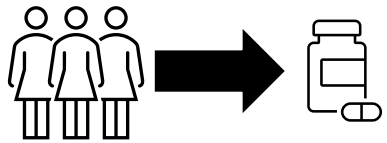
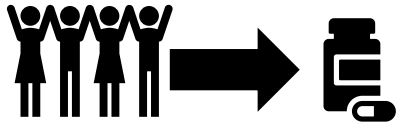
Phase 2b Study design

Patients with mild/moderate CDI diagnosed using an EIA free toxin kit



Ibezapolstat 450 mg BID X 10 days



Vancomycin 125 mg QID X 10 days

Patients followed daily for 12 days + follow-up

Outcomes Measured

Initial clinical cure (day 12 evaluation)

Sustained clinical cure (day 38)

Extended clinical cure (3 months)

Time to resolution of diarrhea (TTRD) (days 0-12)

Safety (day 38)

Microbiologic eradication (days 0-12)
anaerobic culture on CCFA

Microbiome changes (days 0-12)
qPCR and 16S rRNA

ClinicalTrials.gov ID NCT04247542

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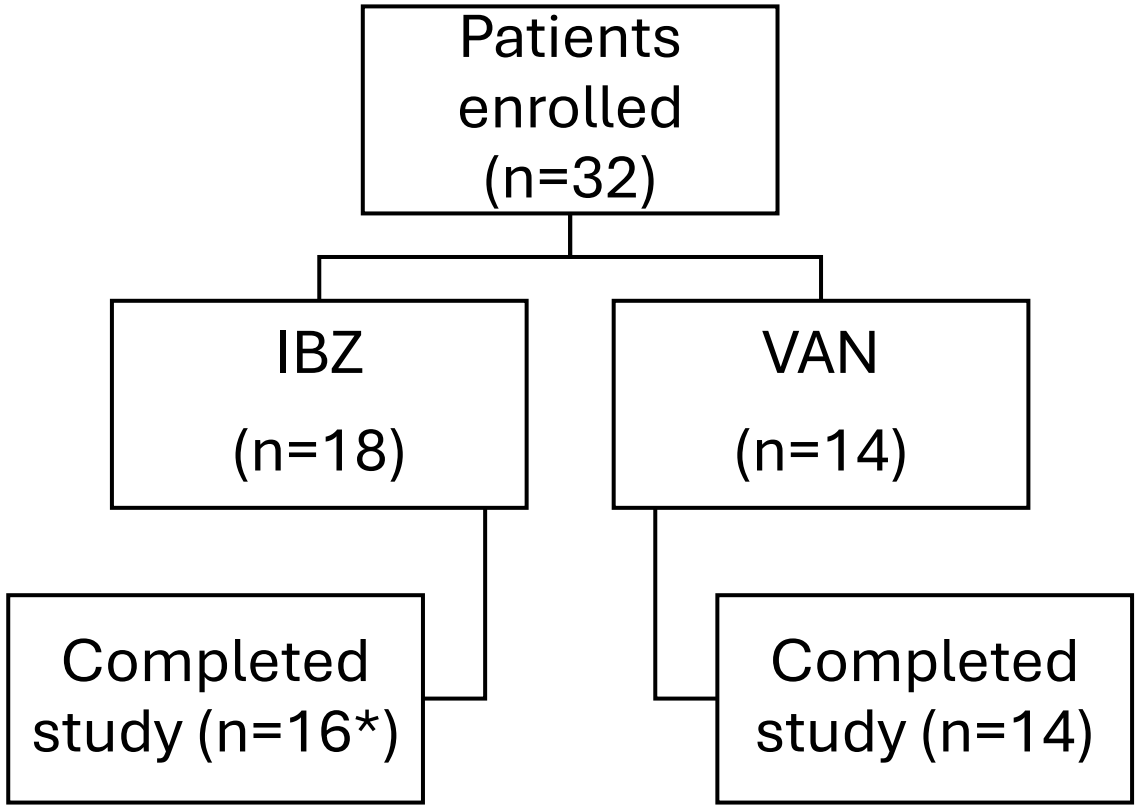
Consort Diagram



Modified intent to treat population

*One patient given IBZ withdrew consent prior to first dose; one patient given IBZ had a history of underlying irritable bowel disease and was excluded from analysis.

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Demographics and Baseline Information

	IBZ (n=16)	VAN (n=14)	*P* value
Age, years ≥75 y/o	64±13 5 (31.2%)	62±10 2 (14.3%)	0.57
Female	13 (81%)	11 (79%)	0.85
White	16 (100%)	13 (93%)	0.27
Hispanic or Latino	11 (69%)	11 (79%)	0.54
Charlson Comorbidity index	2.6±1.5	2.2±1.5	0.47
Number of UBMs at baseline Median (minimum, maximum)	6 (3-15)	6 (4-13)	
Baseline *C. difficile* ribotype strains			
F014-020	0	3	
F027	1	2	
F106	3	1	
F002	1	1	
F116	0	1	
Other	6	3	

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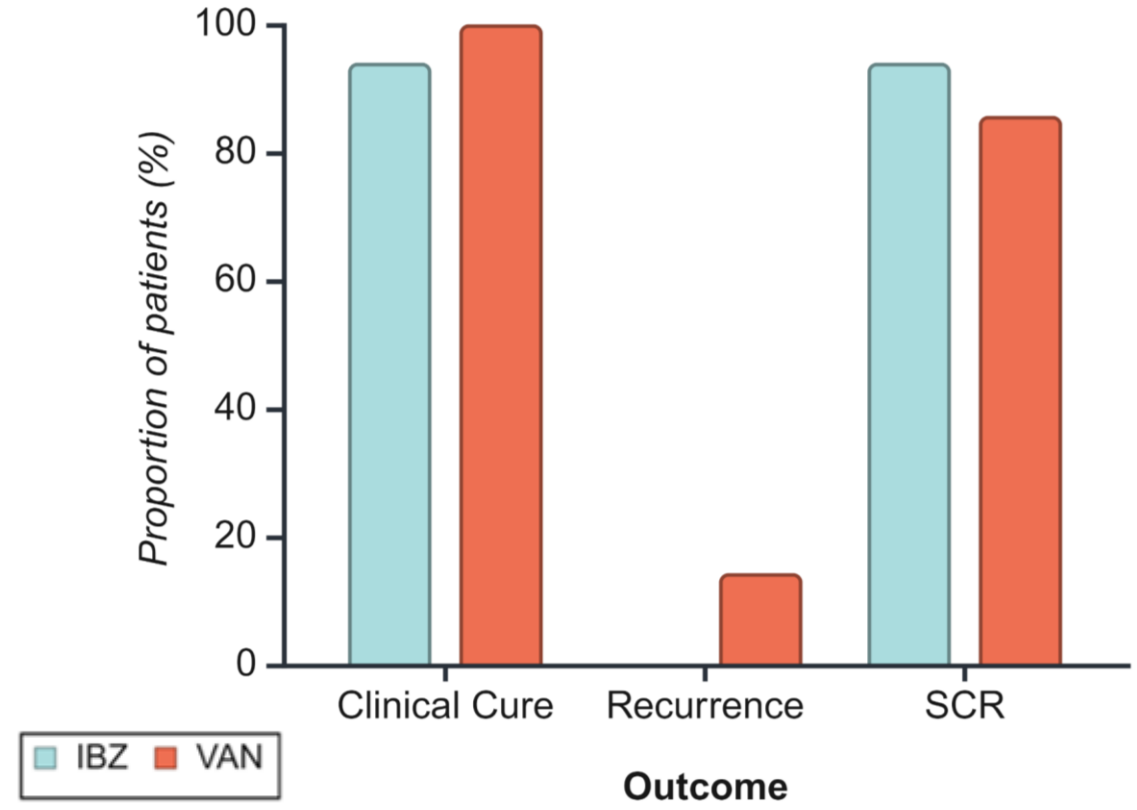
Efficacy (mIT population)



Number of events	15	14	0	2	15	12
Number of patients	16	14	16	14	16	14

Safety

	IBZ	VAN
Drug-related Serious Adverse Events	0	0
Drug-related treatment withdrawals	0	0
Moderate adverse event, possibly related	0	Headache (n=1)
Mild adverse event, possibly related	GERD (n=2) Nausea (n=1)	0

5 of 5 (100%) IBZ patients followed for three months experienced no recurrence of infection

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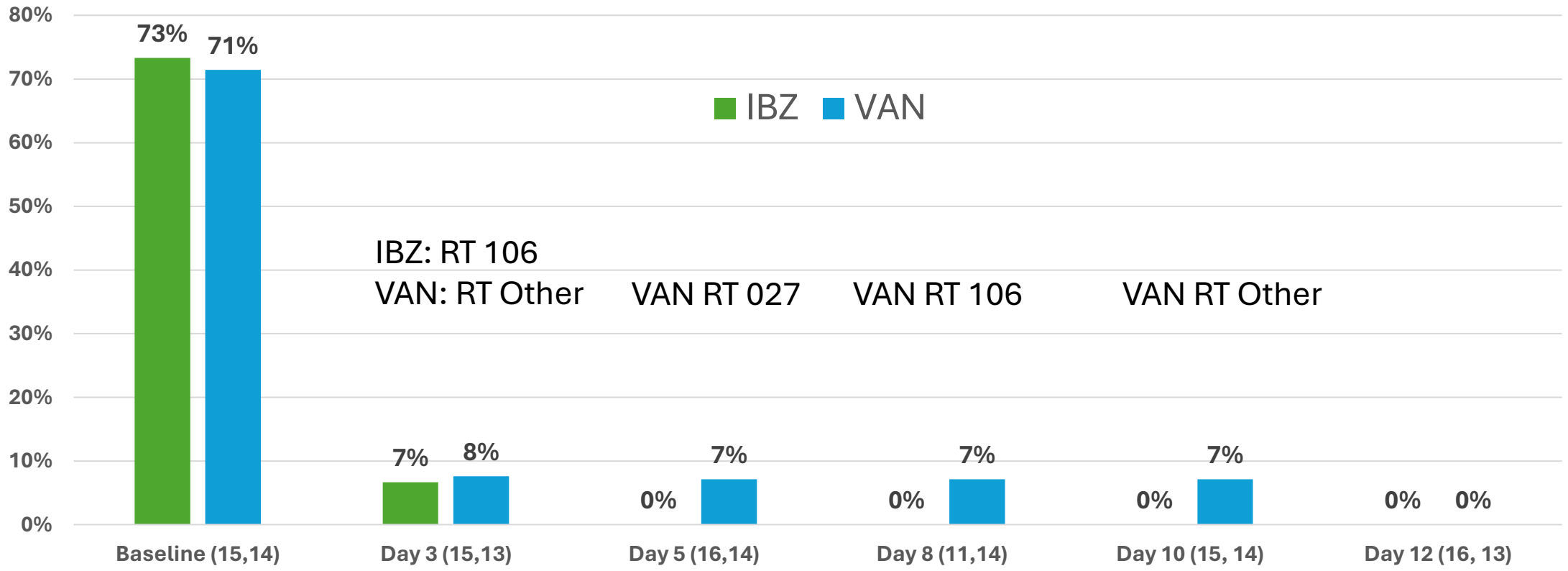
Microbiologic Eradication



IBZ: One patient with positive *C. difficile* growth past baseline
VAN: Four patients with positive *C. difficile* growth past baseline

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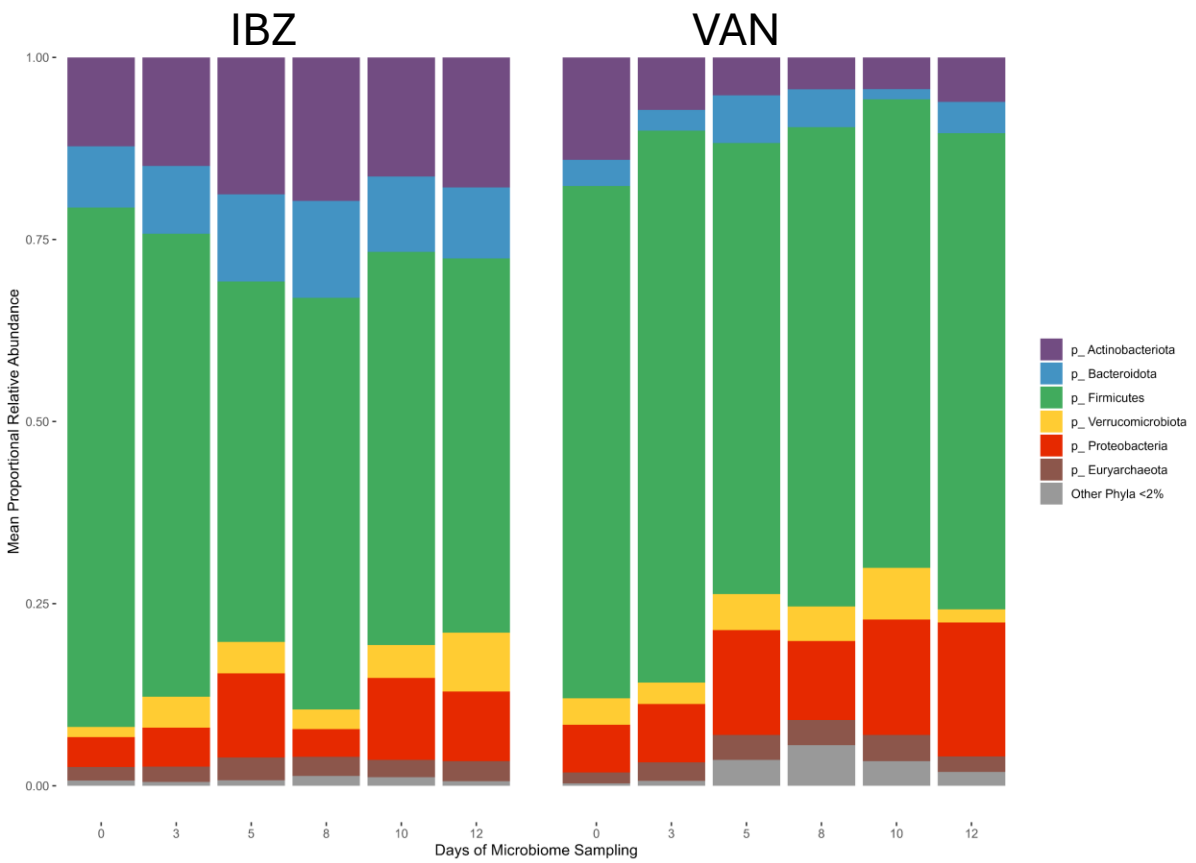
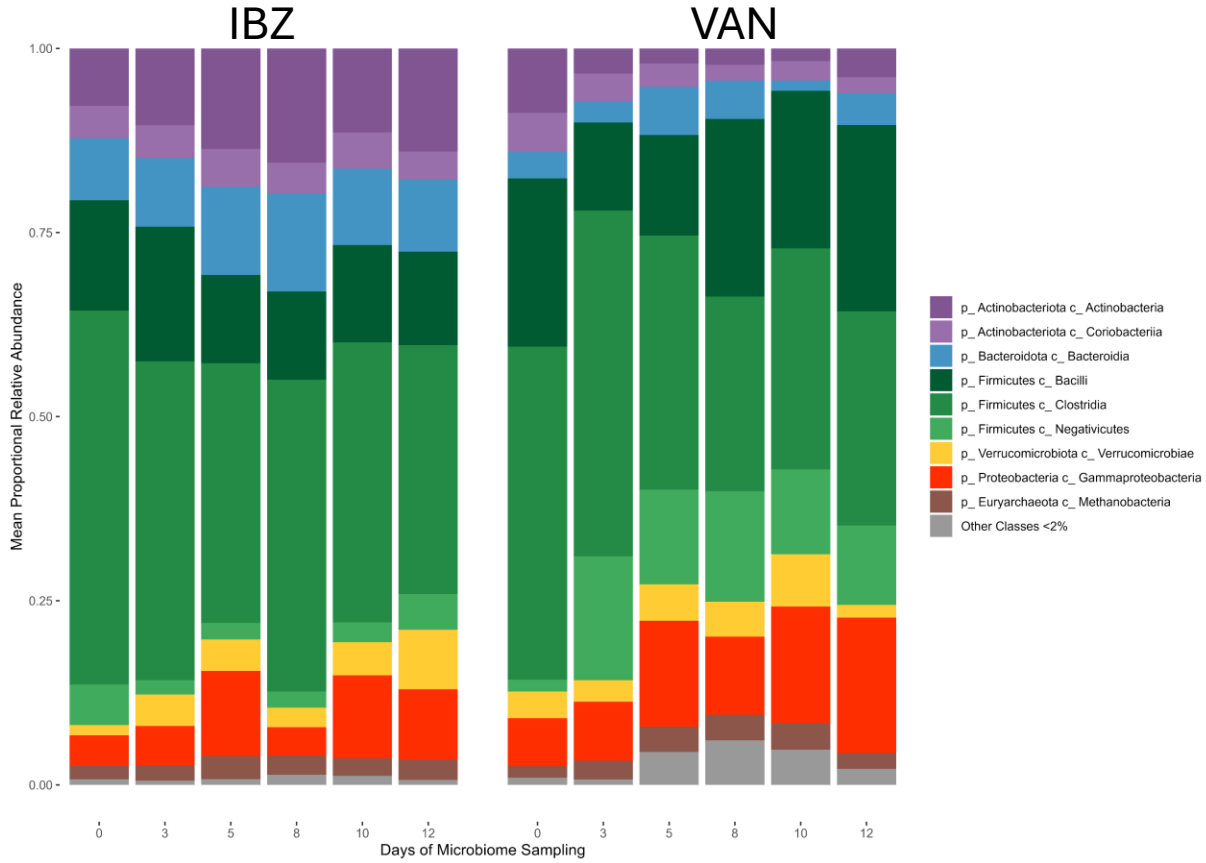
Microbiome. Favorable microbiome results were observed with IBZ

Phylum



Class



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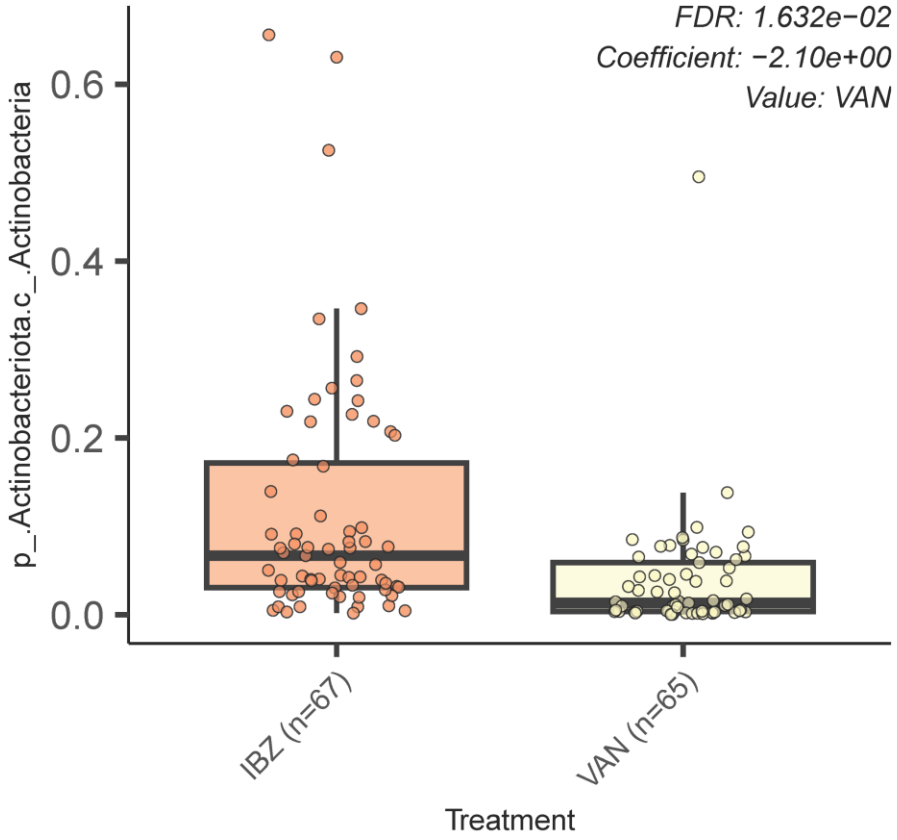
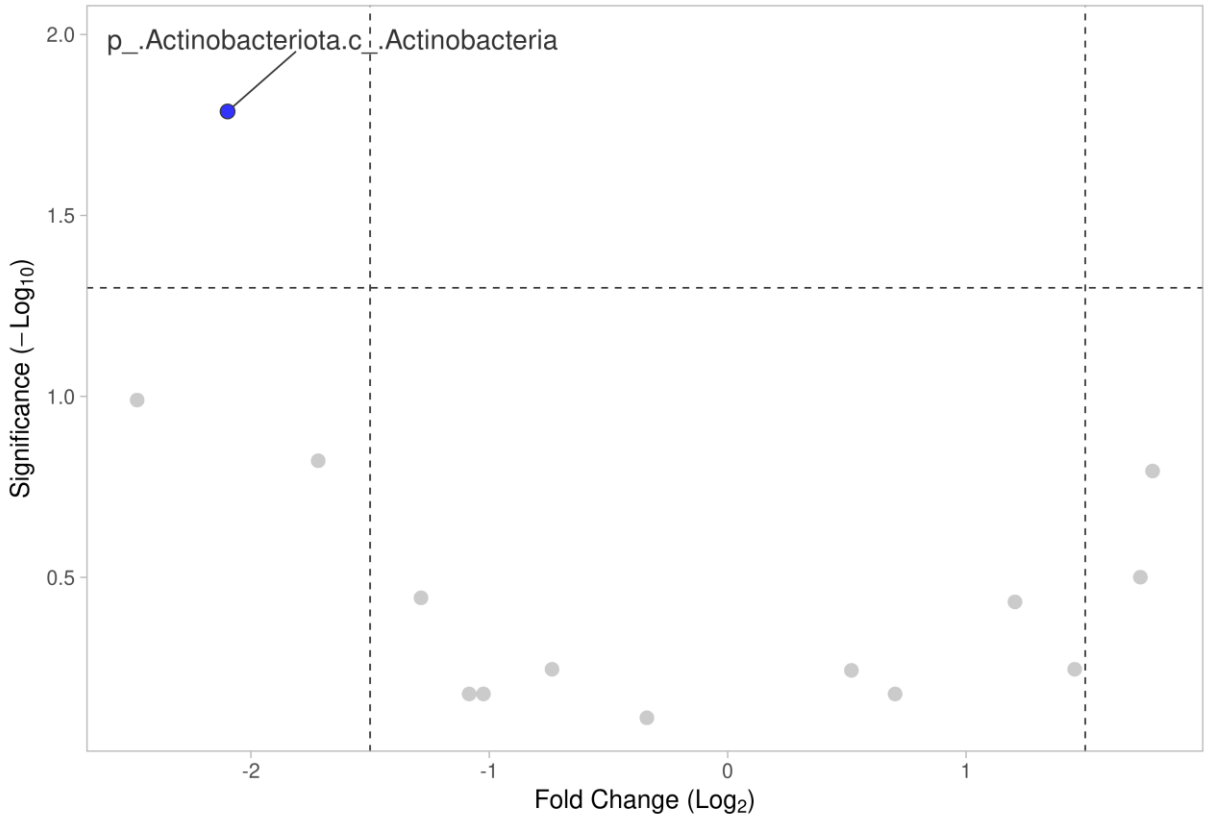
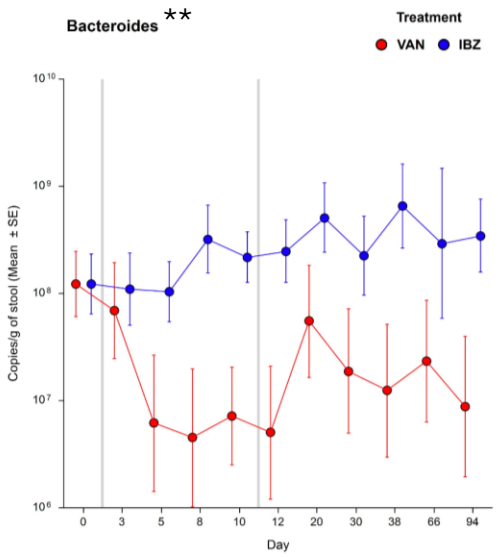
VAN caused approximately a 2-fold reduction on Actinobacteria compared to IBZ

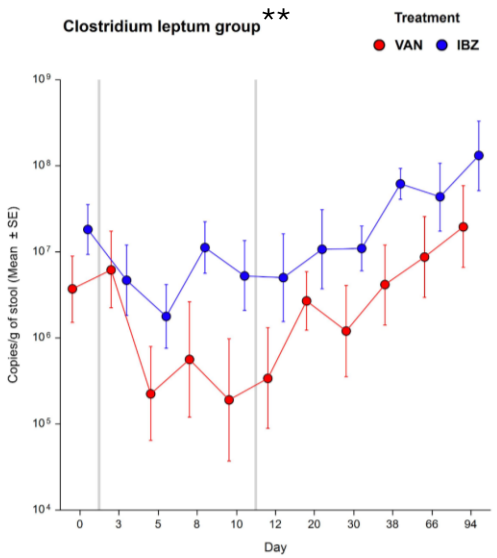


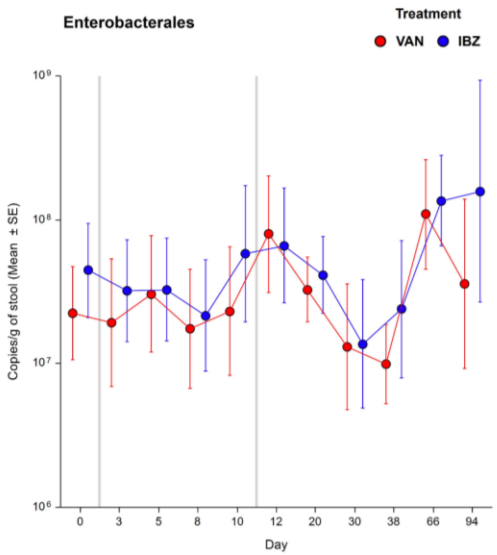


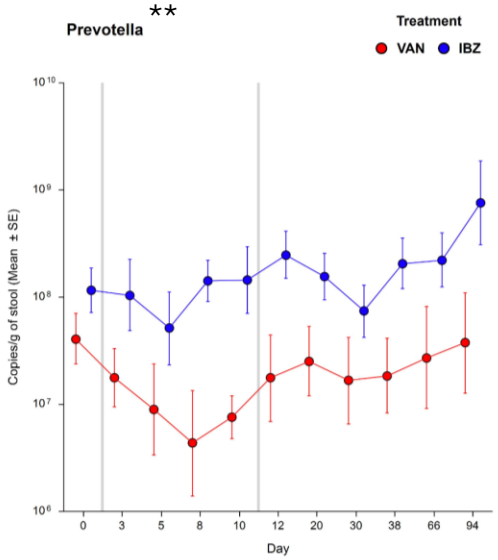
Mallick H et al, Huttenhower C (2021). Multivariable Association Discovery in Population-scale Meta-omics Studies PLoS Computational Biology, 17(11):e1009442. Maaslin2

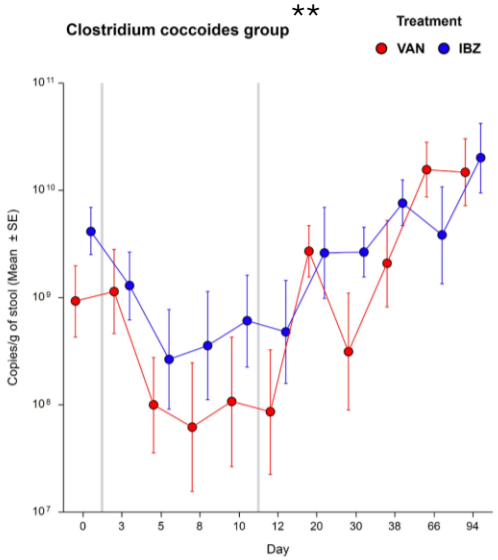
IBZ qPCR microbiome analysis

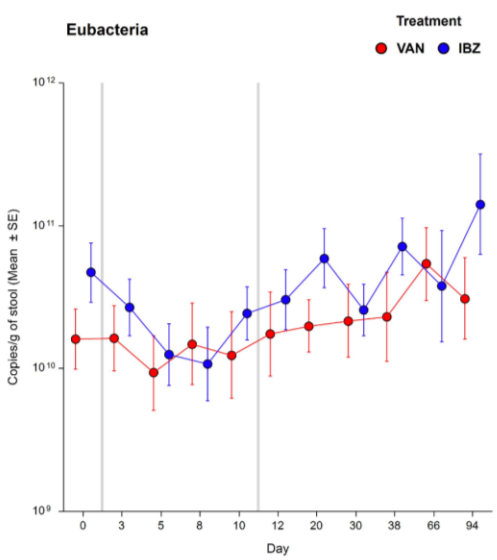












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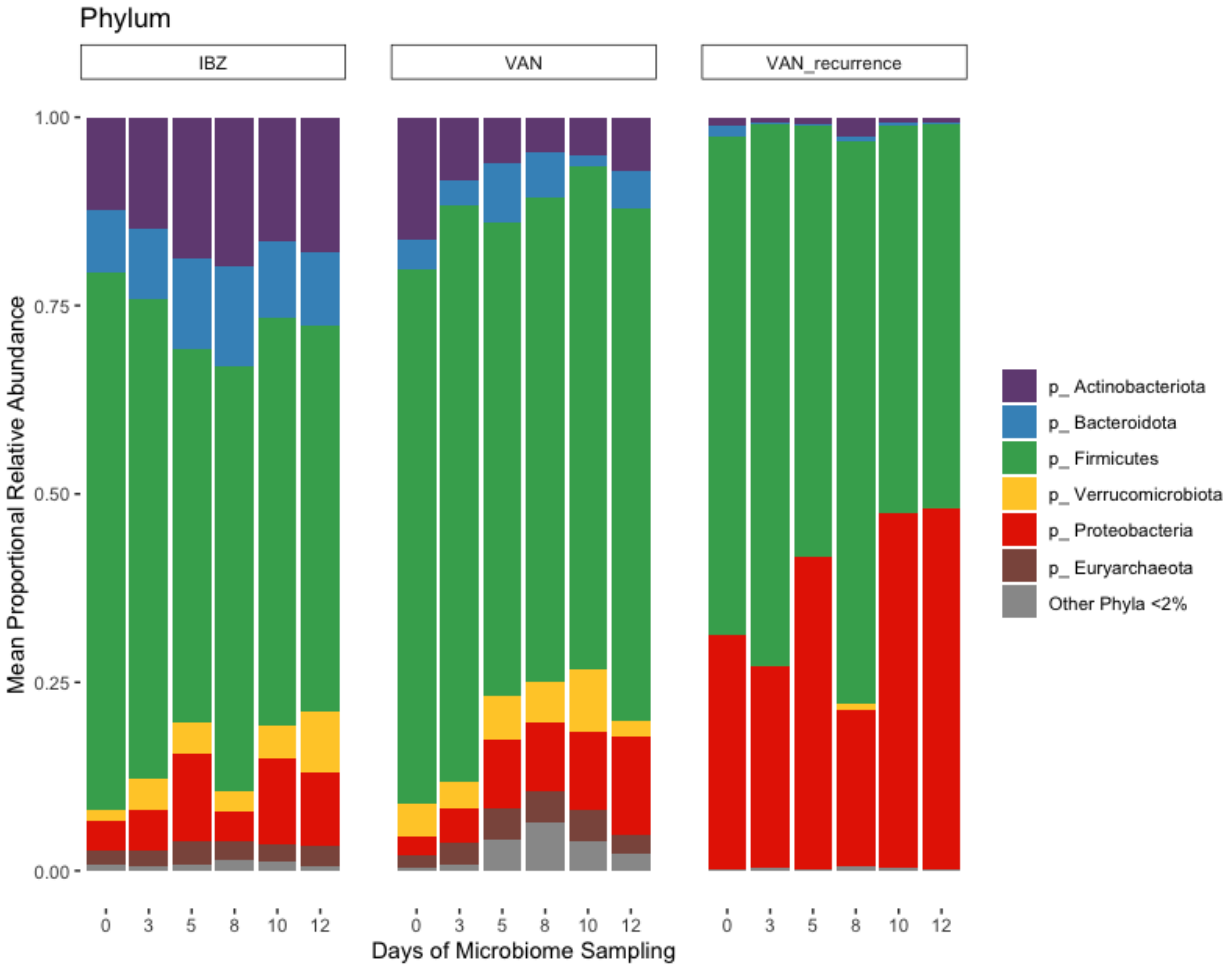
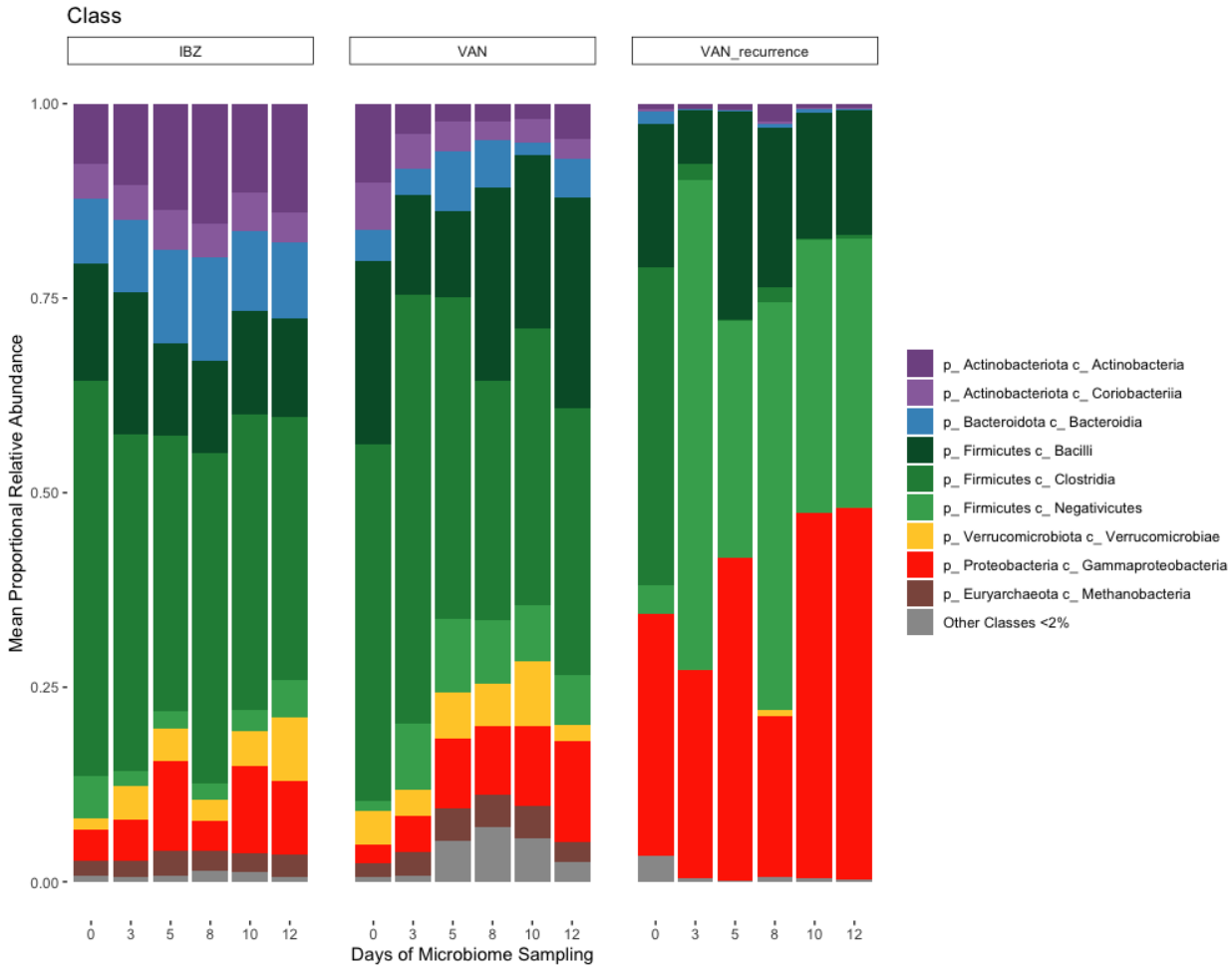
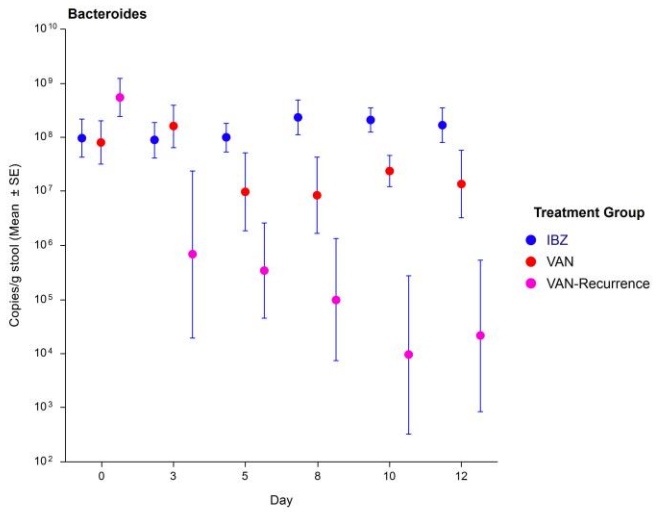
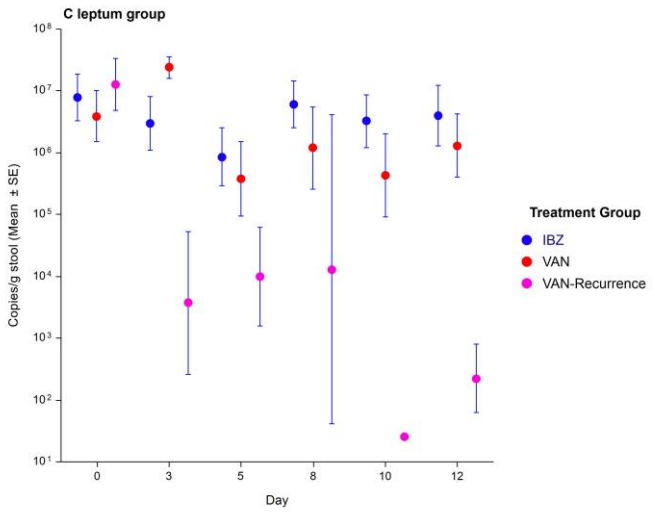
CDI recurrence associated with marked microbiome disruption

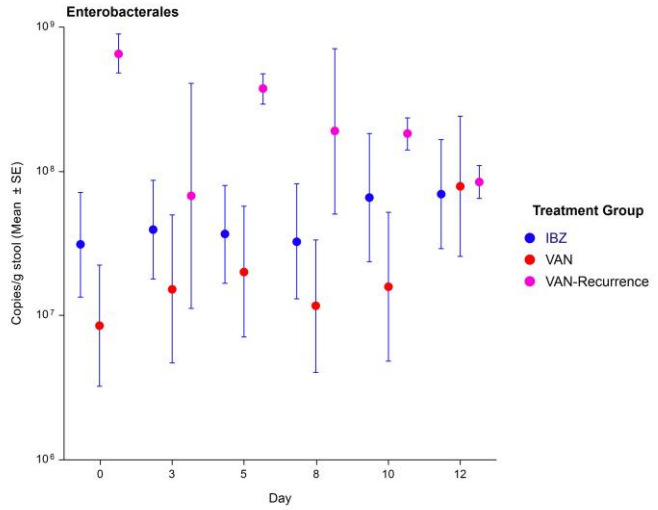


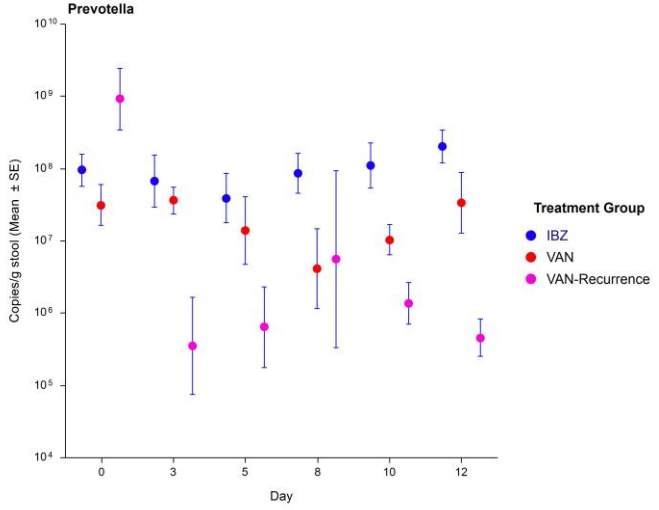


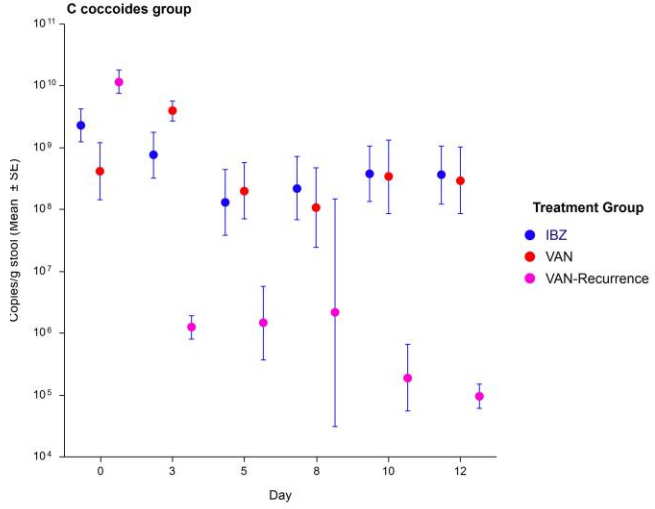
CDI recurrence associated with marked microbiome disruption

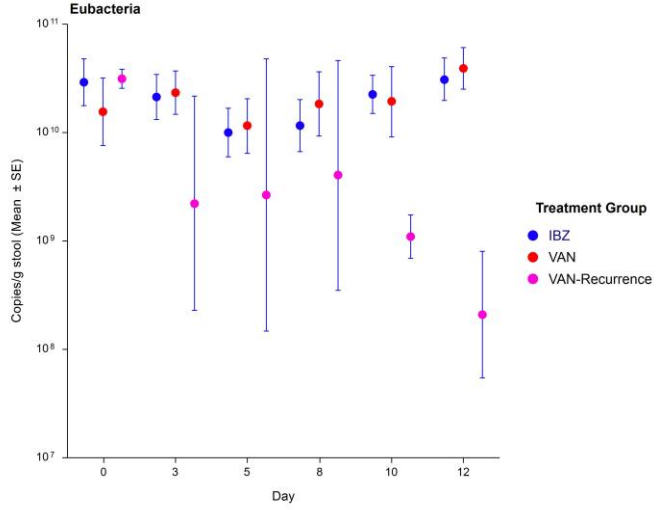












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Conclusions

- IBZ had a clinically comparable cure rates and safety profile to VAN
- Favorable microbiome results were observed in IBZ-treated patients
  - More patients given VAN had persistently positive *C. difficile* cultured
  - IBZ treated patients had increased proportion of Actinobacteriota
  - IBZ treated patients had increased quantity of beneficial Bacillota (Firmicutes)
- Bile acid and short chain fatty analysis: Pending

These results warrant further development in phase 3 trials.

Acknowledgements

The Garey Lab

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