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

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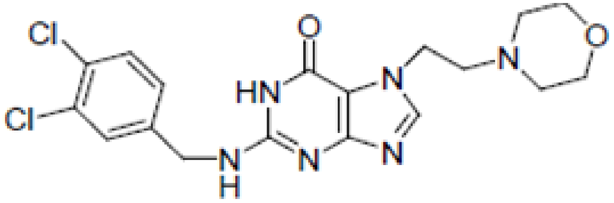
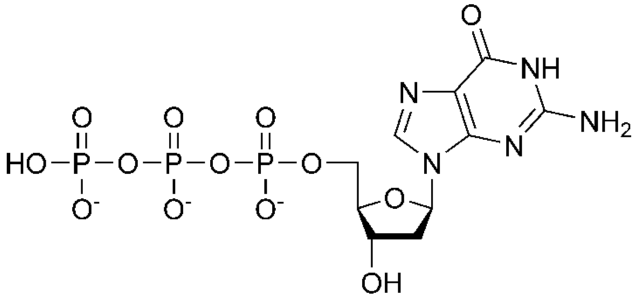
UNIVERSITY of HOUSTON | COLLEGE OF PHARMACY

Ibezapolstat (IBZ; ACX362E)

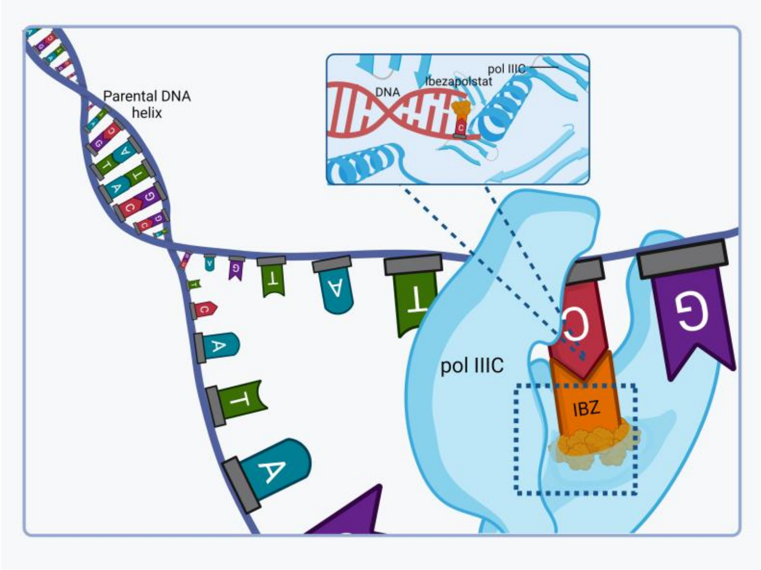


ACX-362



dGTP

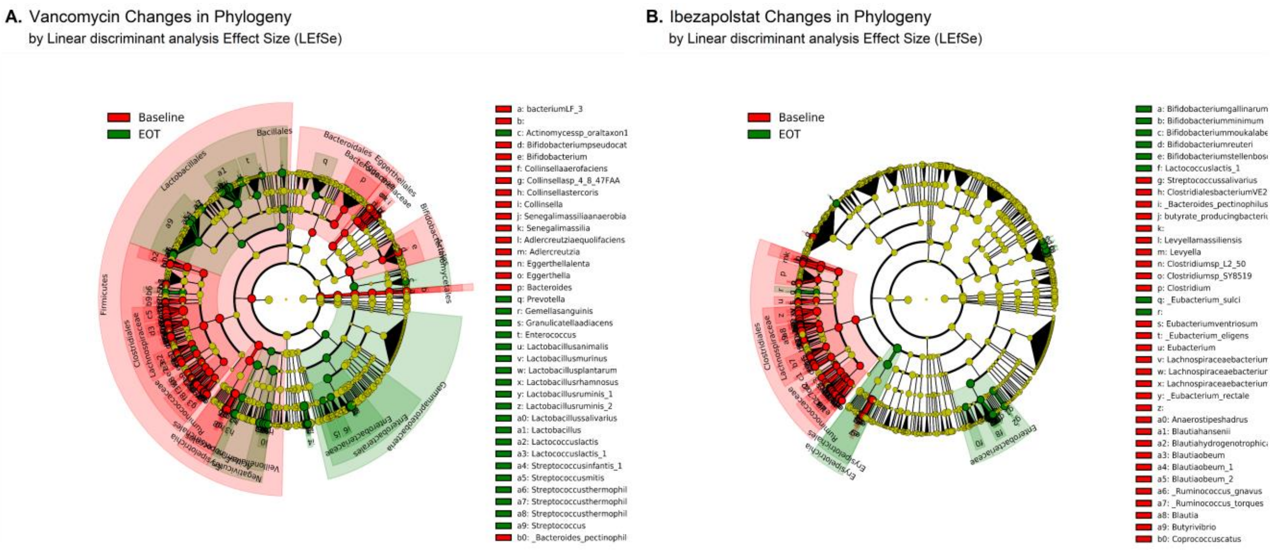
- Ibezapolstat: small-molecule inhibitor of DNA pol IIIC enzyme based upon competitive inhibition of dGTP (guanosine analog)
- DNA pol IIIC: essential for replication of low G+C content Gram-positive bacteria (Bacillota / Firmicutes)
- Novel mechanism of action GPSS™ (**G**ram **P**ositive **S**elective **S**pectrum) including selective killing of certain Firmicutes but not others
  - Other DNA pol IIIC inhibitor compounds, in preclinical development for systemic treatment of resistant infections, show in vitro activity vs. the bioterrorism Category A pathogen *B. anthracis (Anthrax)*, including a ciprofloxacin-resistant strain, with MICs of 0.5-2 ug/mL. Selective microbiome effects will be tested in these compounds as well



Xu et al. Bioorg Med Chem. 2019
https://www.nature.com/articles/d43747-021-00149-0

IBZ has been shown to have favorable effects on the microbiome

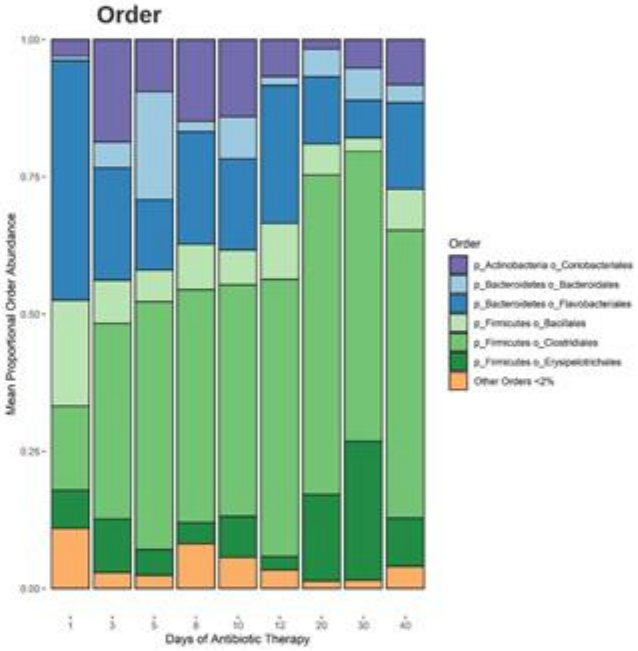
IBZ Phase 1 Healthy volunteer study in comparison with VAN



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 Clostriales

Garey et al CID 2022

Phase 2b Study design

Patients followed daily for 12 days + follow-up

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

Outcome Measures

Initial clinical cure (day 12 evaluation)

Sustained clinical cure (day 38)

Extended clinical cure (3 months)

Time to resolution of diarrhea (days 0-12)

Safety (day 38)

Pharmacokinetics (days 0-12)

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

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

ClinicalTrials.gov ID NCT04247542

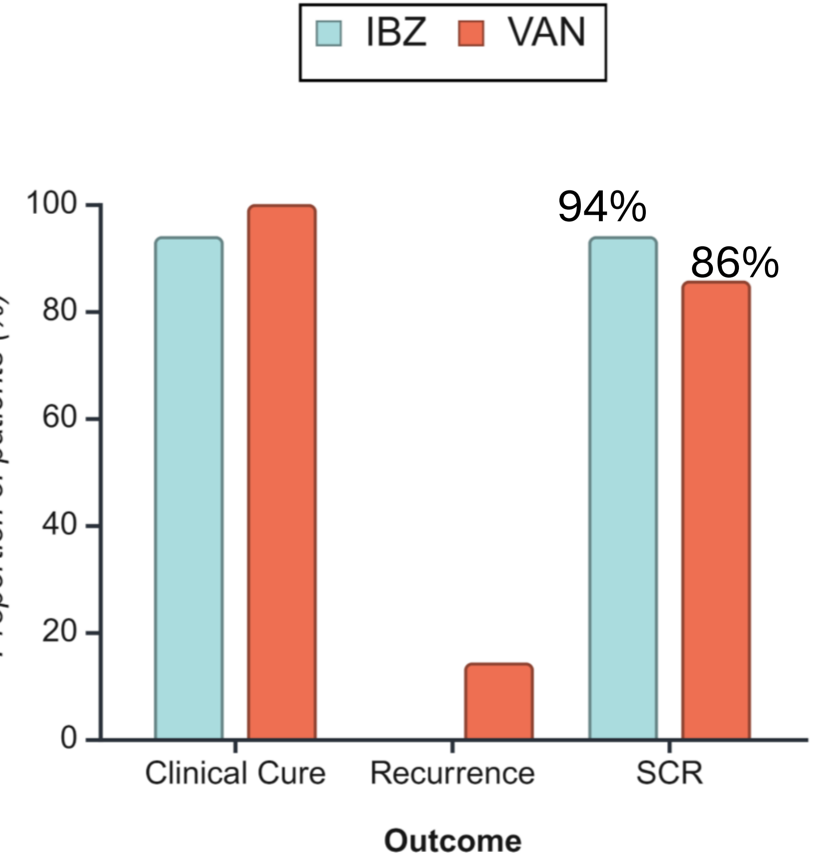
IBZ PH2b Microbiome Objectives

- Evaluate IBZ vs. vancomycin (VAN) in patients with CDI
  - Fecal microbiome effects
    - Pharmacokinetics
    - Microbiologic eradication
    - Metagenomic proportional change (16s rRNA)
    - Quantitative changes in relative taxa (qPCR)

RESULTS: Demographics and Baseline Information

	IBZ (n=16)	**VAN (n=14)**	**P value**
N	16	14	
Age, years	64±13	62±10	0.57
≥75 yo	5 (31.2%)	2 (14.3%)	
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	

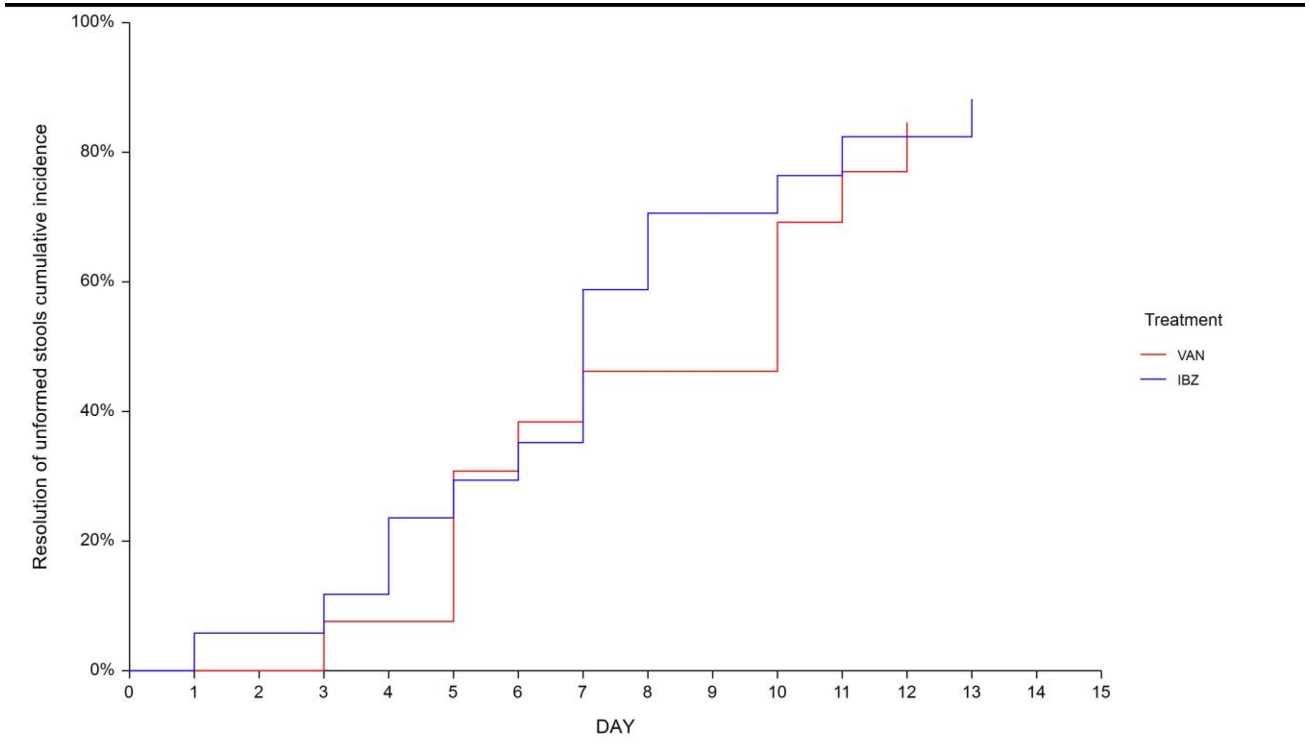
Figure 2a. Efficacy analysis



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

Figure 2b. Time to resolution of diarrhea

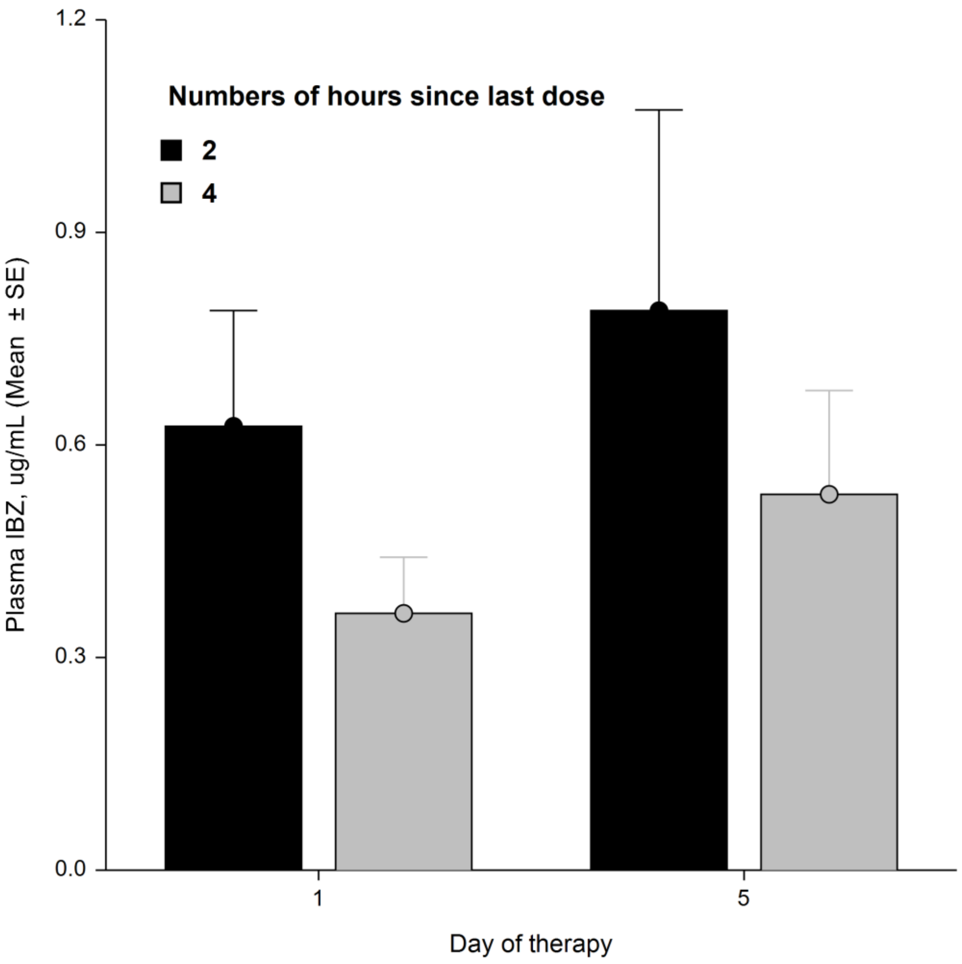
Cumulative incidence of UBM resolution



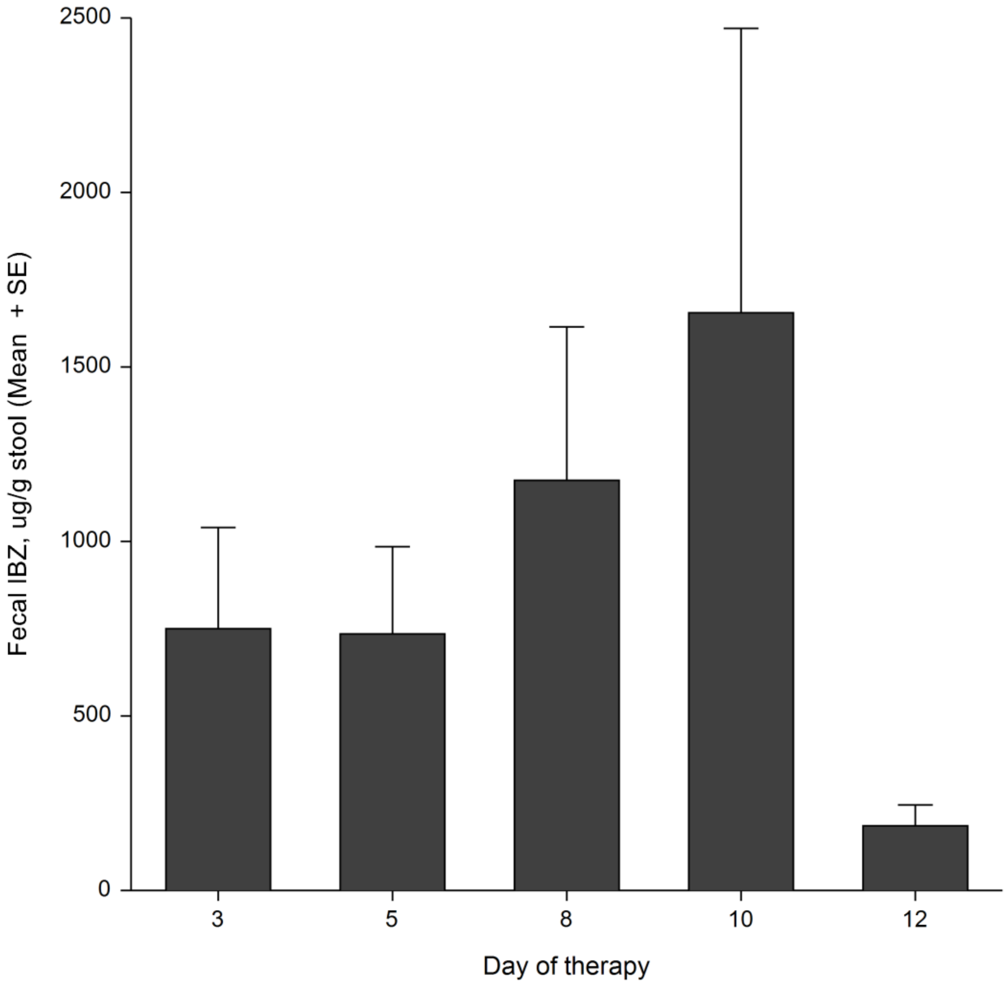
SCR: sustained clinical response; UBM: unformed bowel movement

IBZ Plasma and Fecal Concentrations

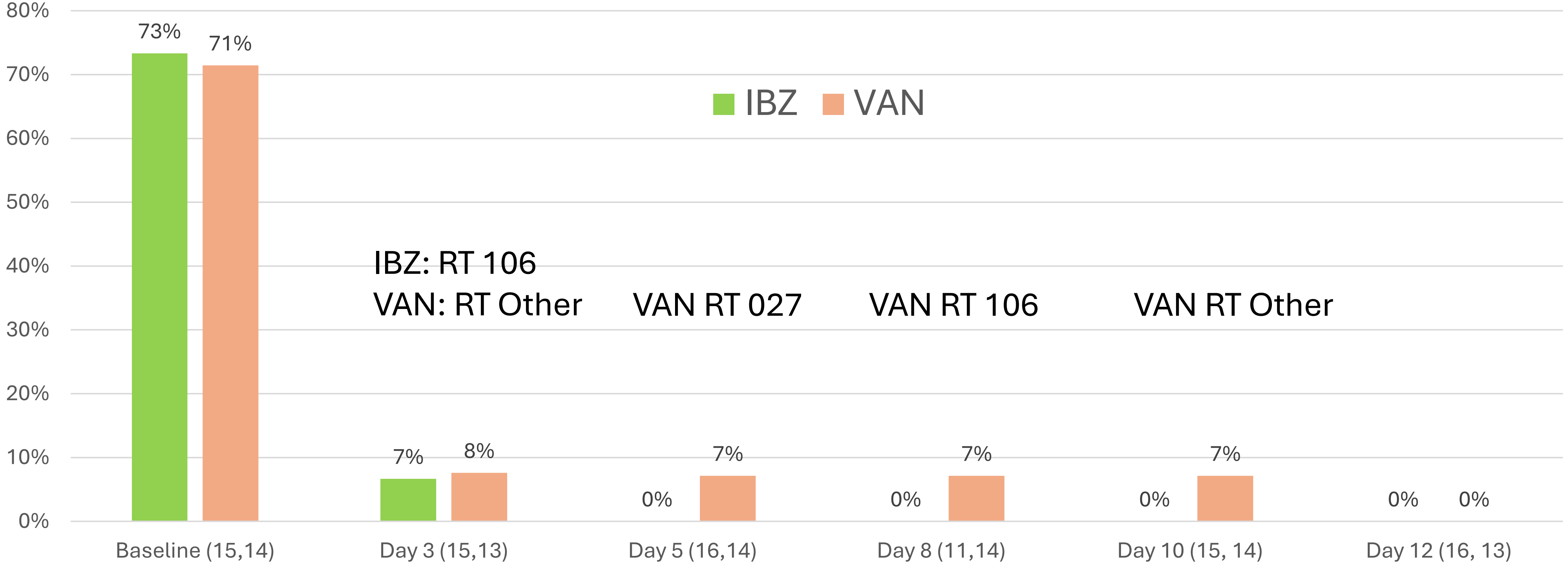
a. Plasma concentrations



b. Fecal concentrations



Microbiologic Eradication



IBZ: RT 106
VAN: RT Other

VAN RT 027

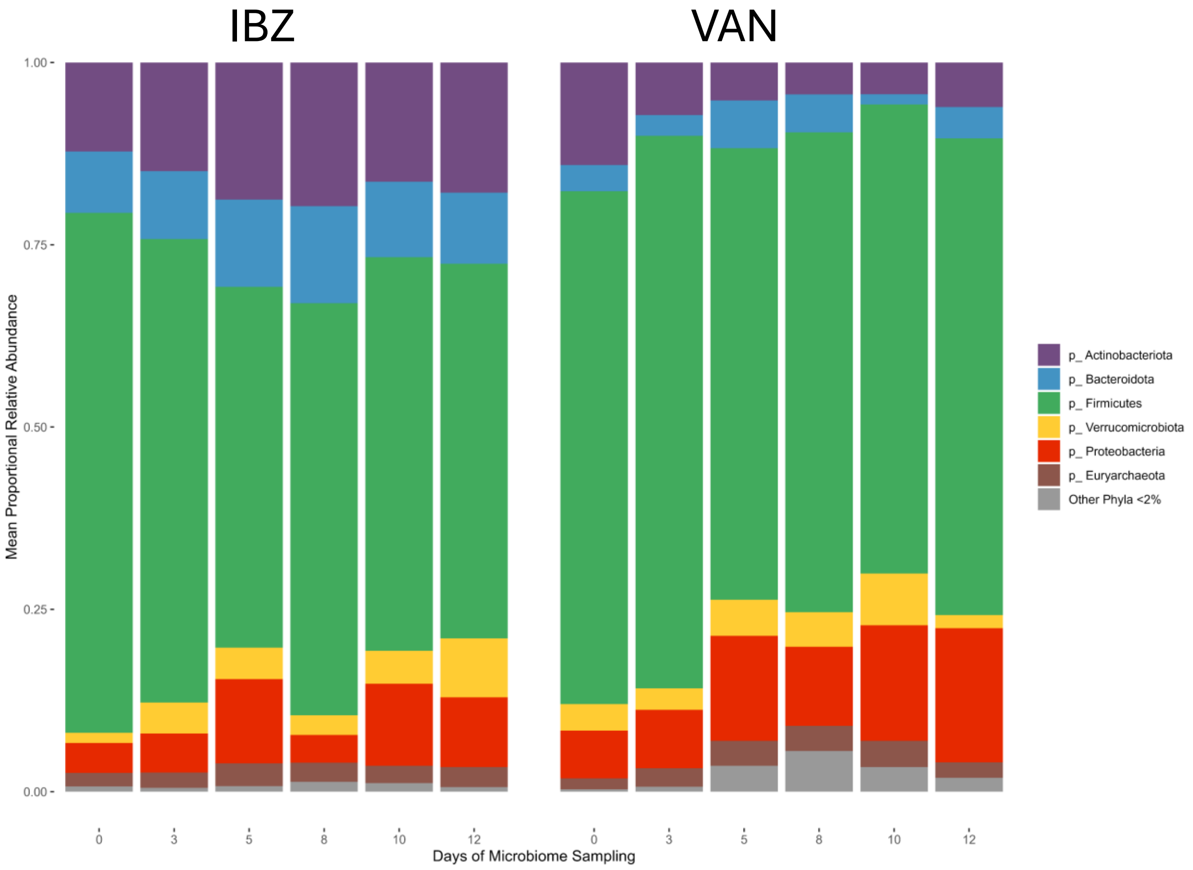
VAN RT 106

VAN RT Other

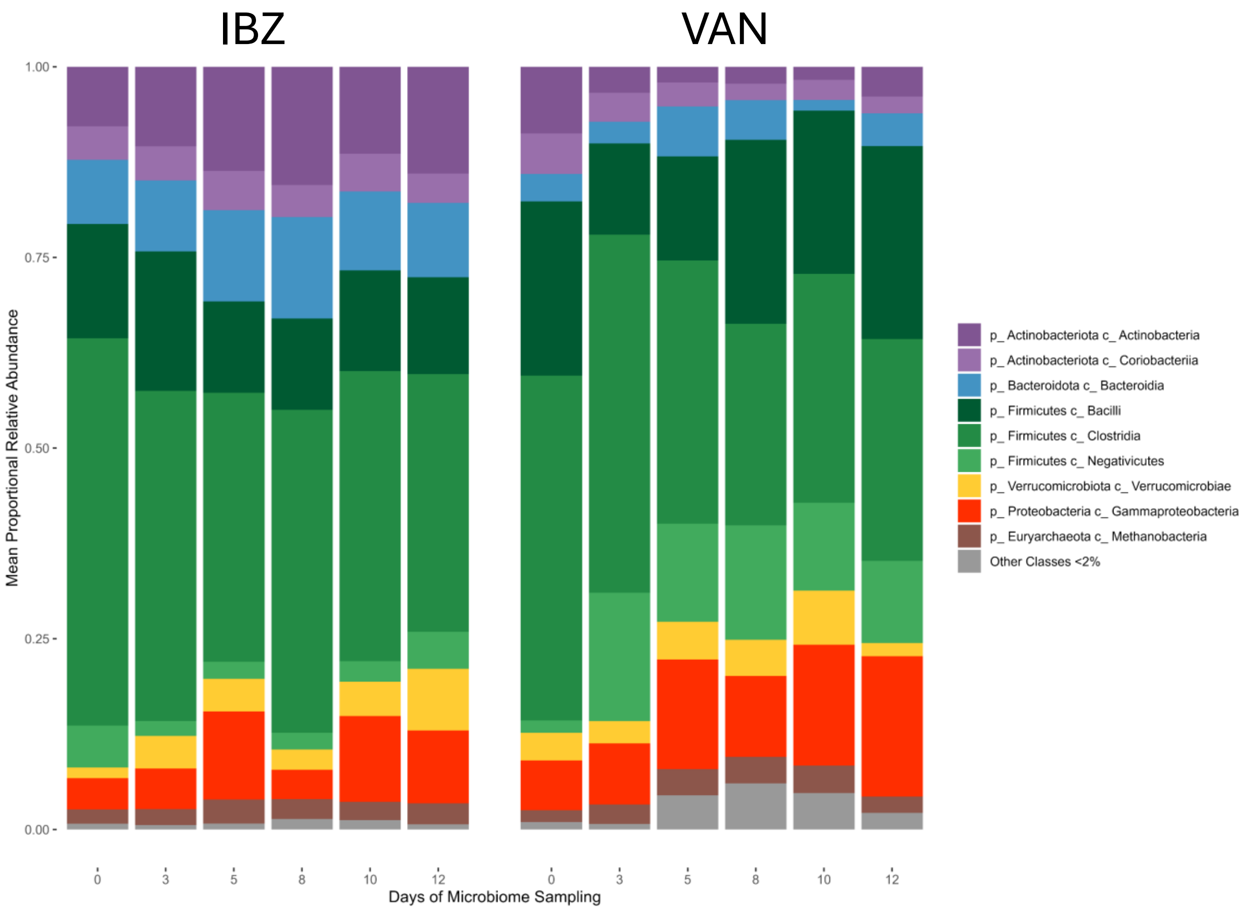
IBZ: One patient with positive *C. difficile* growth past baseline
VAN: Four patients with positive *C. difficile* growth past baseline

Microbiome. Favorable microbiome results were observed with IBZ

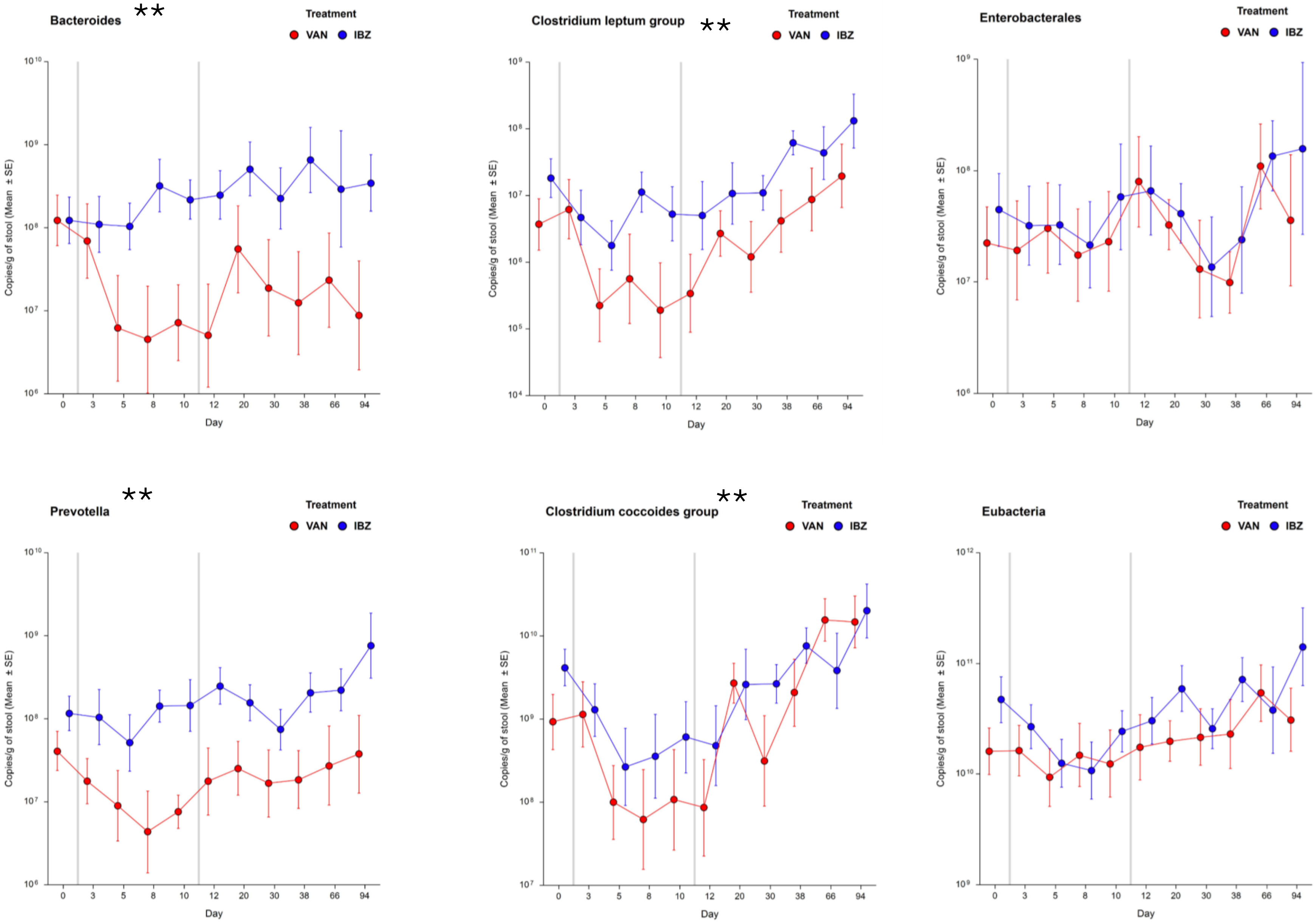
Phylum



Class



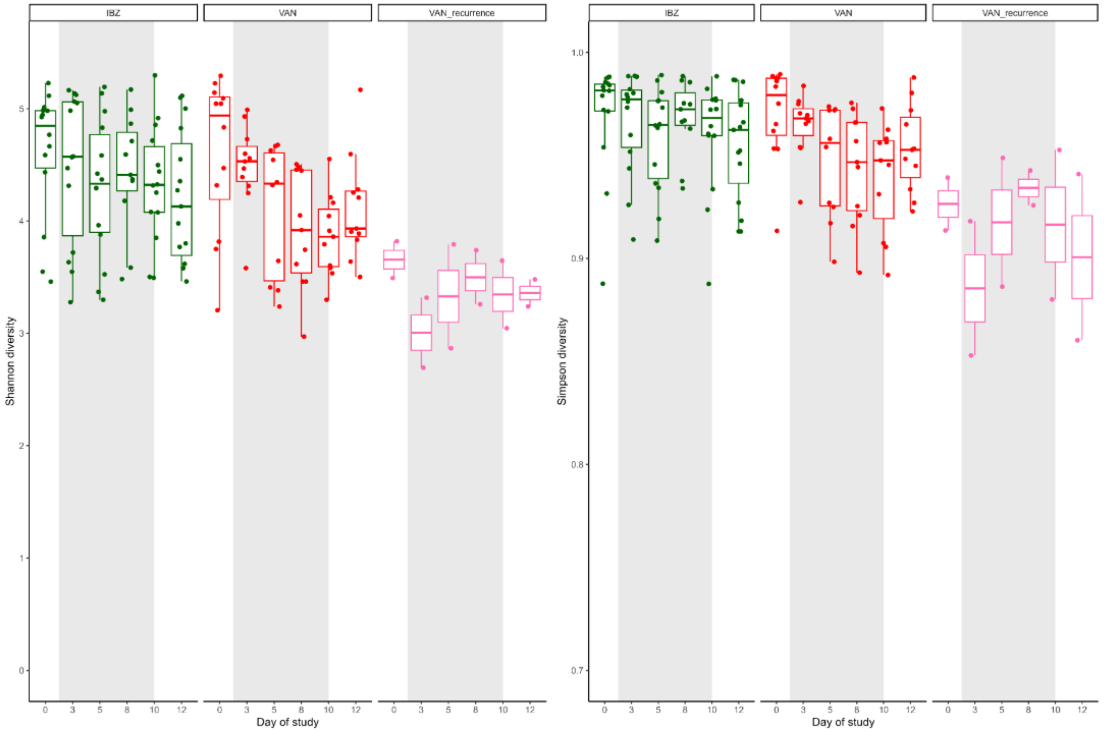
IBZ qPCR microbiome analysis



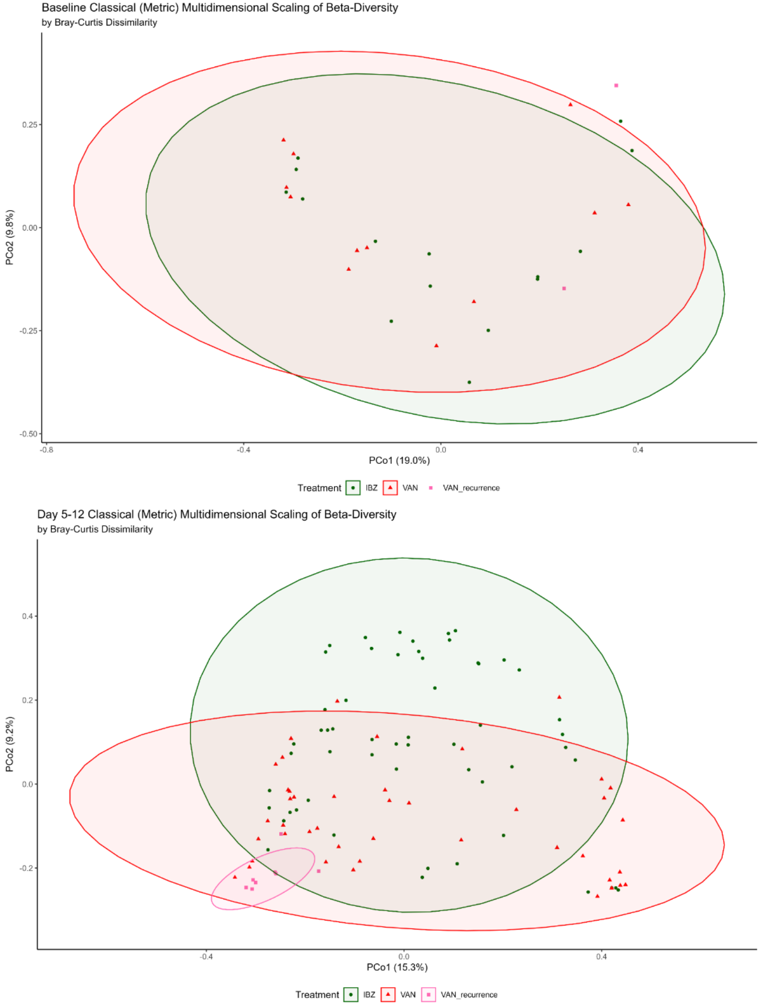
**$p<0.01$

Focus on CDI Recurrence. Alpha and Beta Diversity

a. Alpha diversity plots

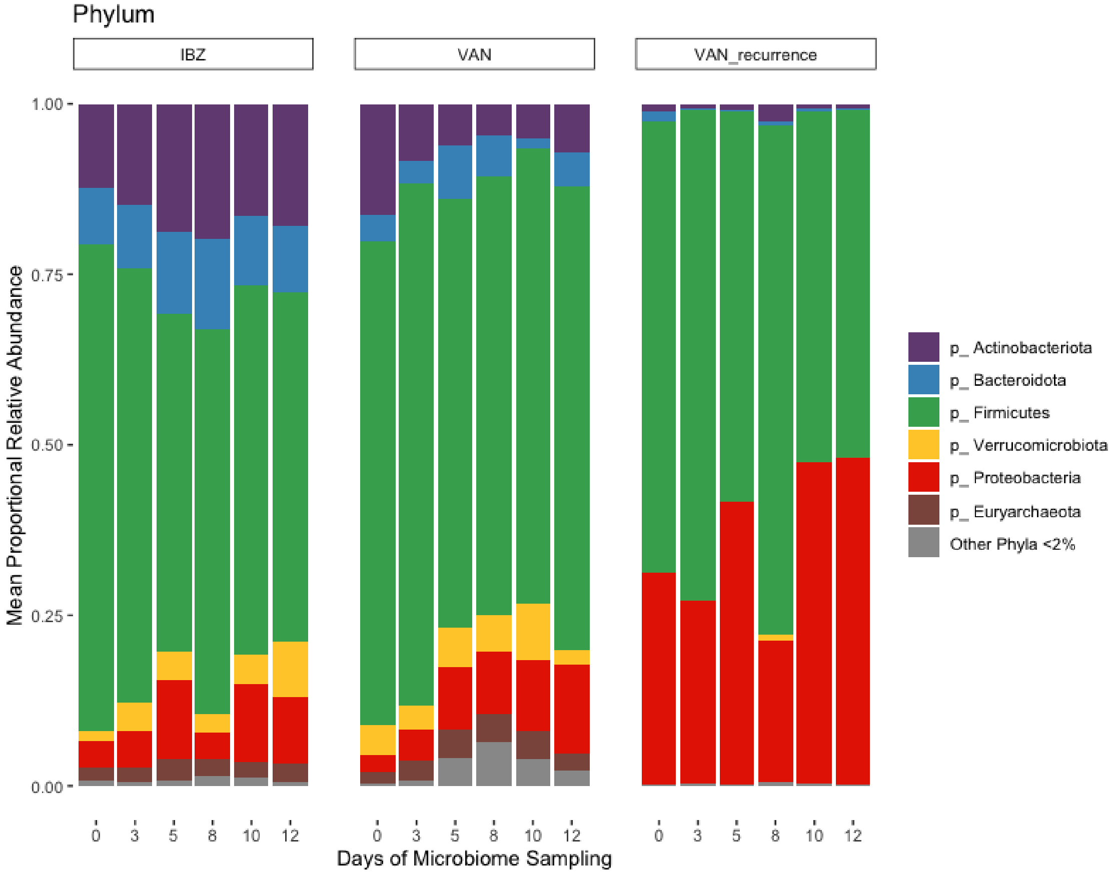


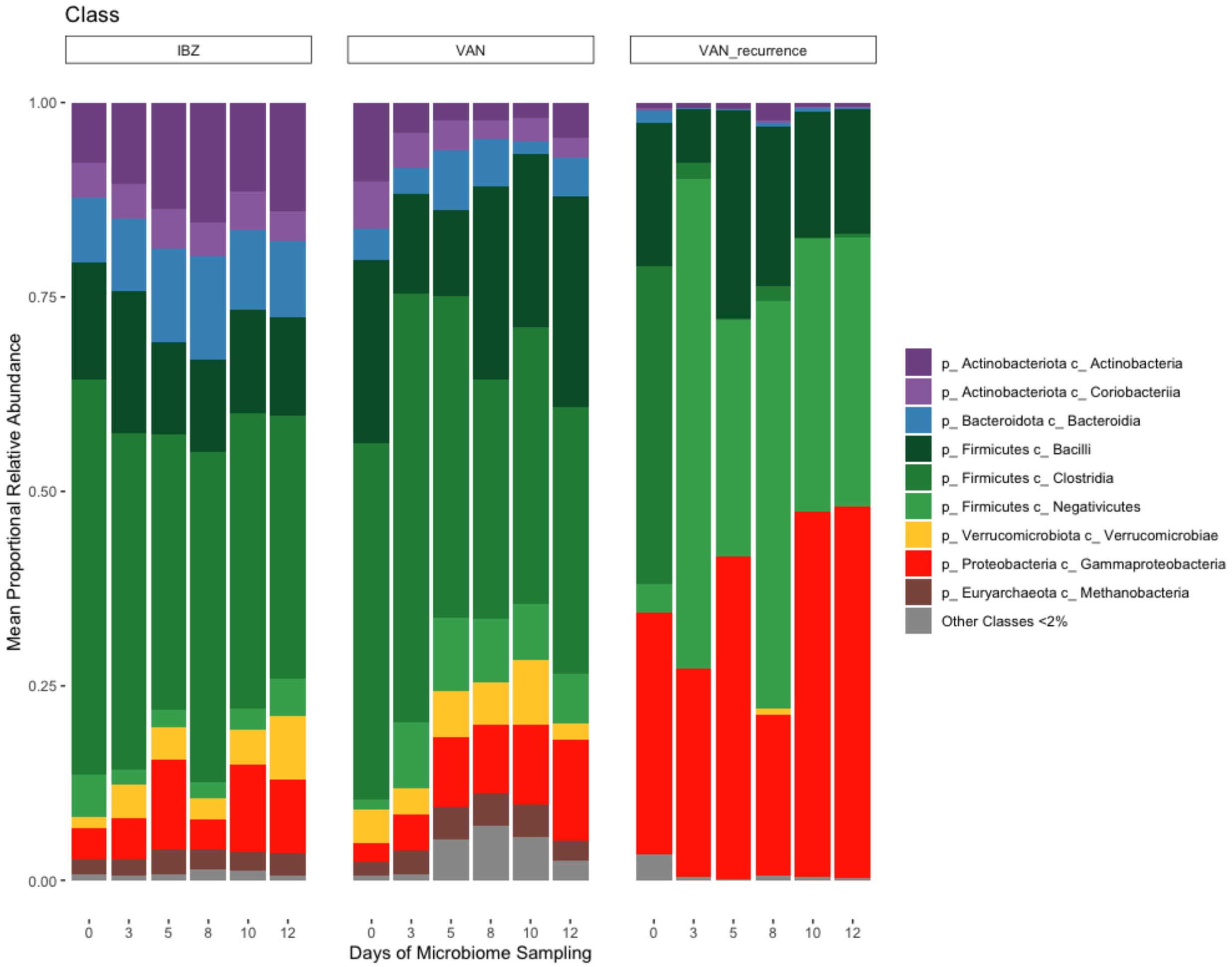
b. Beta diversity plots



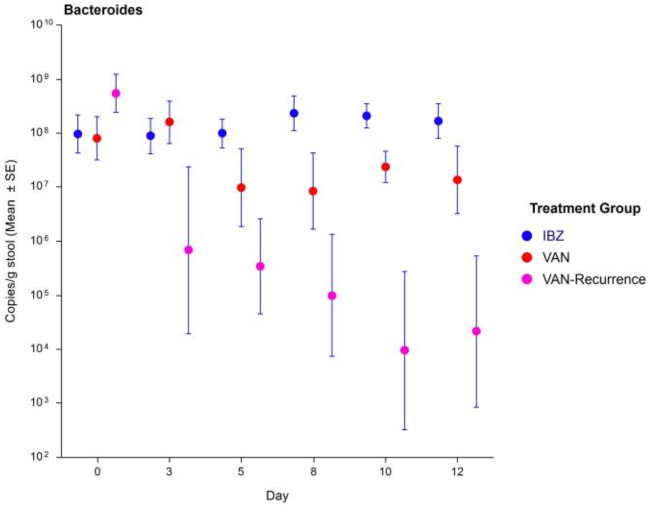
IBZ: n=16; VAN (no recurrence): n=12; VAN (recurrence: n=2)

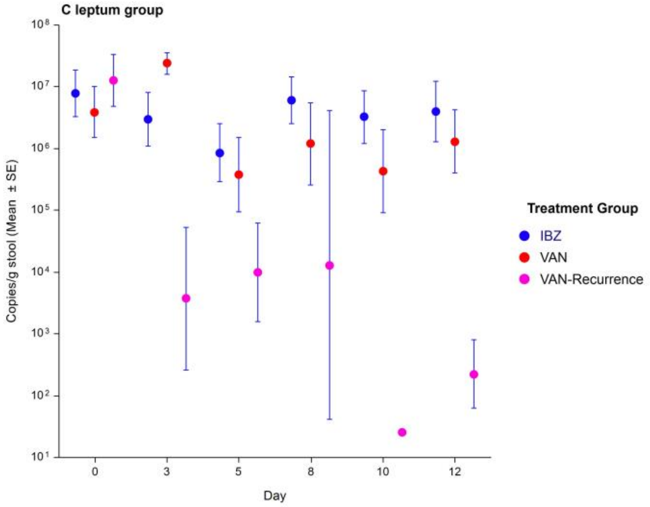
CDI recurrence associated with marked microbiome disruption

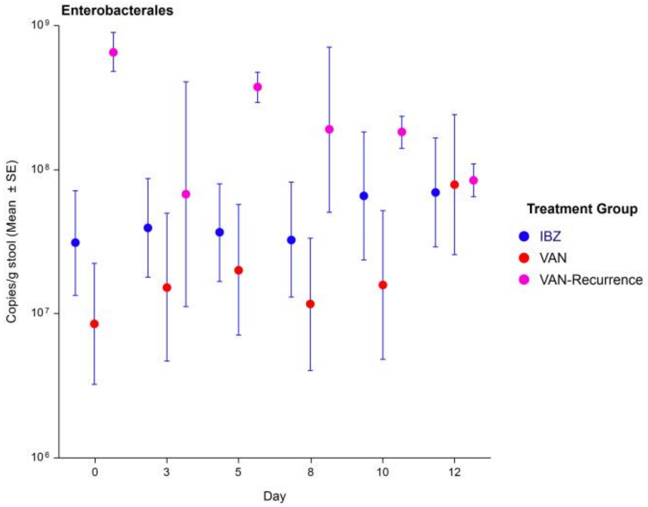


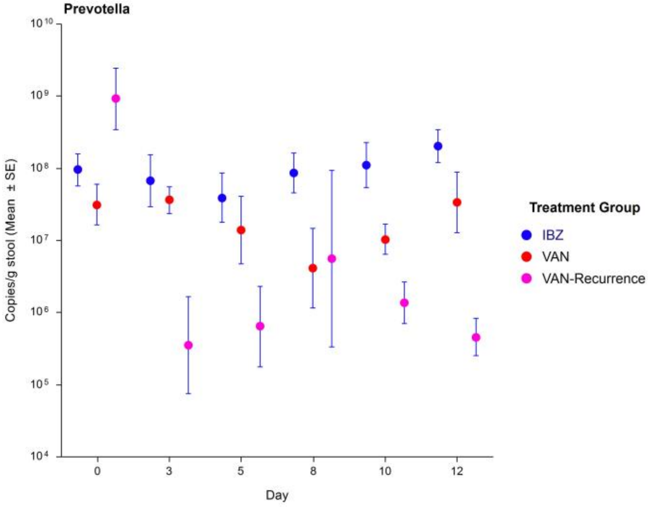


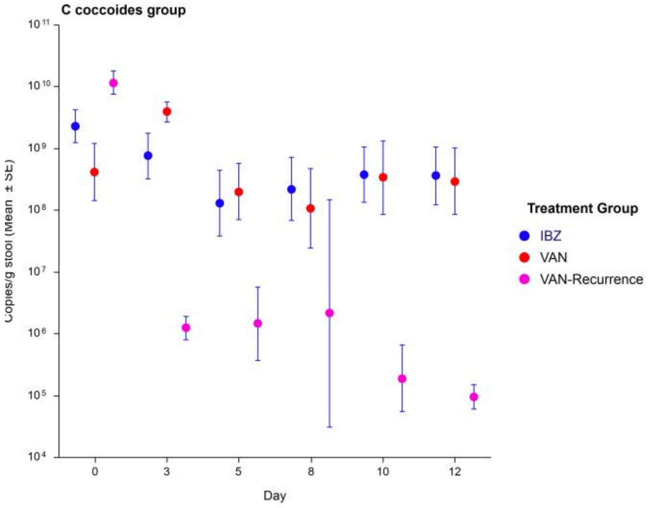
CDI recurrence associated with marked microbiome disruption

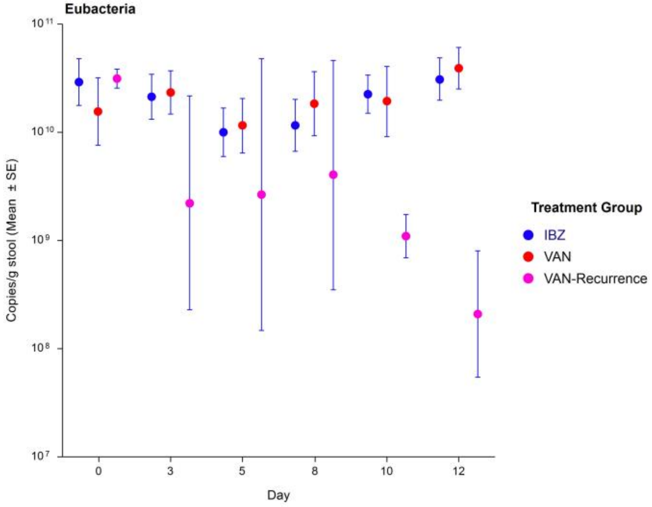

Bacteroides


C leptum group


Enterobacterales


Prevotella


C coccoides group


Eubacteria

Conclusions

- IBZ had a clinically comparable cure rates and safety profile to VAN
    - No CDI recurrence vs. 2 VAN-treated patients
- IBZ had favorable PK and microbiome results to VAN
    - Higher colonic / low systemic concentrations
    - Fewer cases of persistently positive *C. difficile*
    - Increased proportion of Actinobacteriota
    - Increased quantity of beneficial Bacillota (Firmicutes)

- These results warrant further development in phase 3 trials.

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