Development Update on Ibezapolstat for the Treatment of *Clostridioides difficile* infection: Focus on the Microbiome

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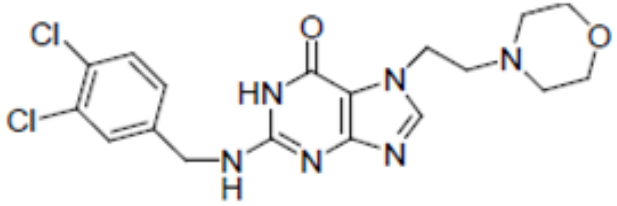
Ibezapolstat (IBZ; ACX362E)



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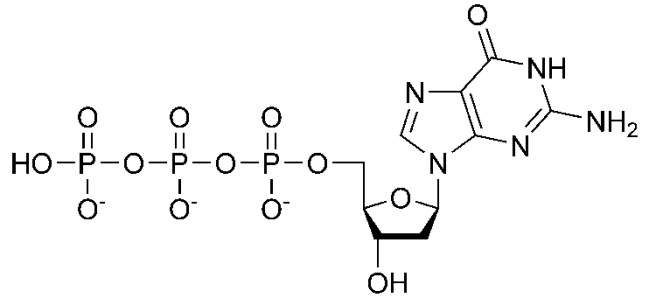
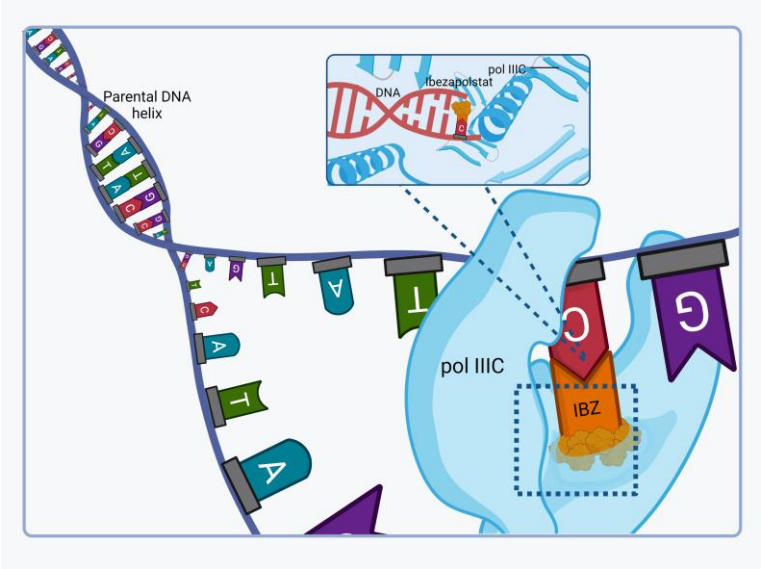


dGTP

- 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)



Xu et al. Bioorg Med Chem. 2019 Aug 1;27(15):3209-3217;
https://www.nature.com/articles/d43747-021-00149-0
Figure by BioRender created by Avalon Starr

Spectrum of activity: Ibezapolstat vs. vancomycin

Phylum	Antibiotic activity	
	Ibezapolstat	Vancomycin (oral)
Actinobacteria	No	Yes
Bacteroidetes	No	Yes
Firmicutes	Selective	Yes
Fusobacteria	No	No
Proteobacteria	No	No

Phase 1 Study design

Stool collected daily for 13 days

Healthy volunteers
>18 years old (n=22)

Ibezapolstat 450 mg BID X 10 days

Ibezapolstat 300 mg BID X 10 days

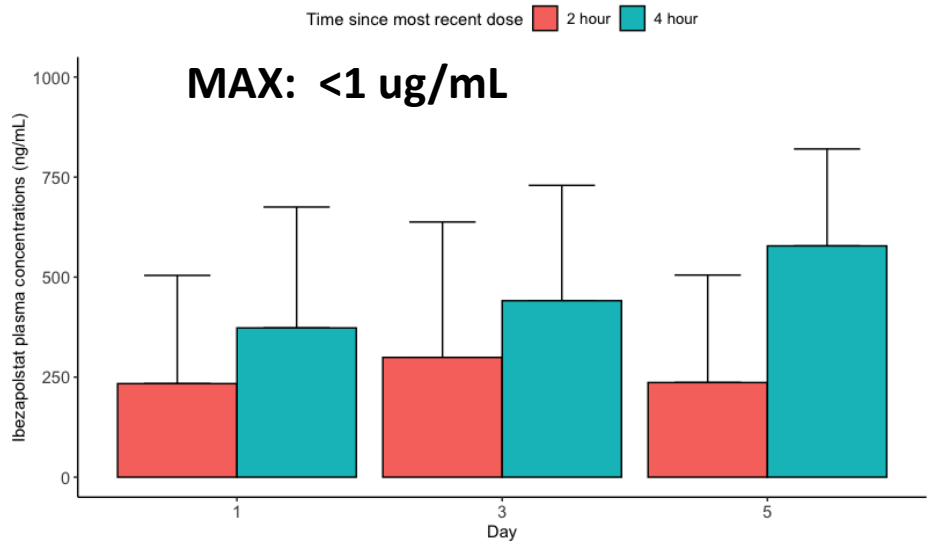
Vancomycin 125 mg QID X 10 days

Placebo X 10 days

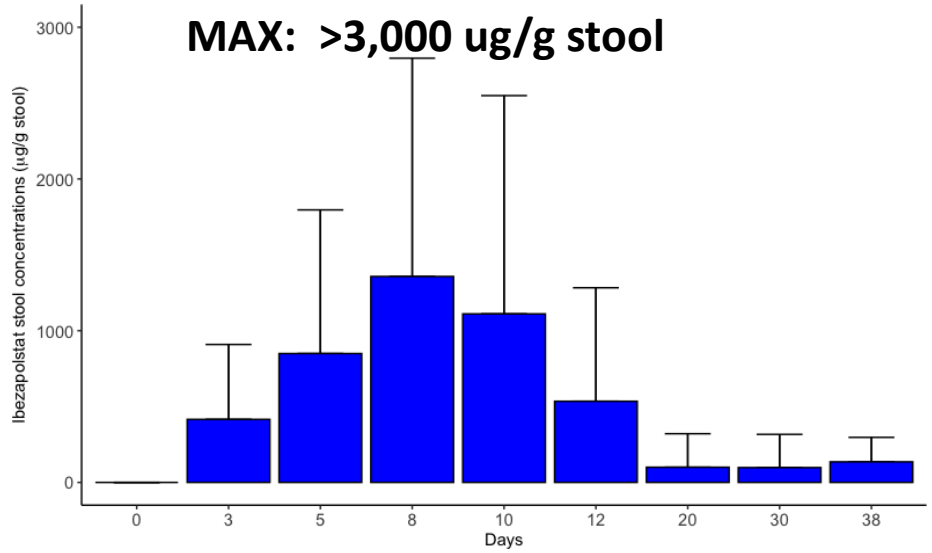
Shotgun metagenomics (Illumina NextSeq 500)

IBZ PH1 results: Ideal PK Properties for GI infections (also safe)

Plasma:
ng/mL



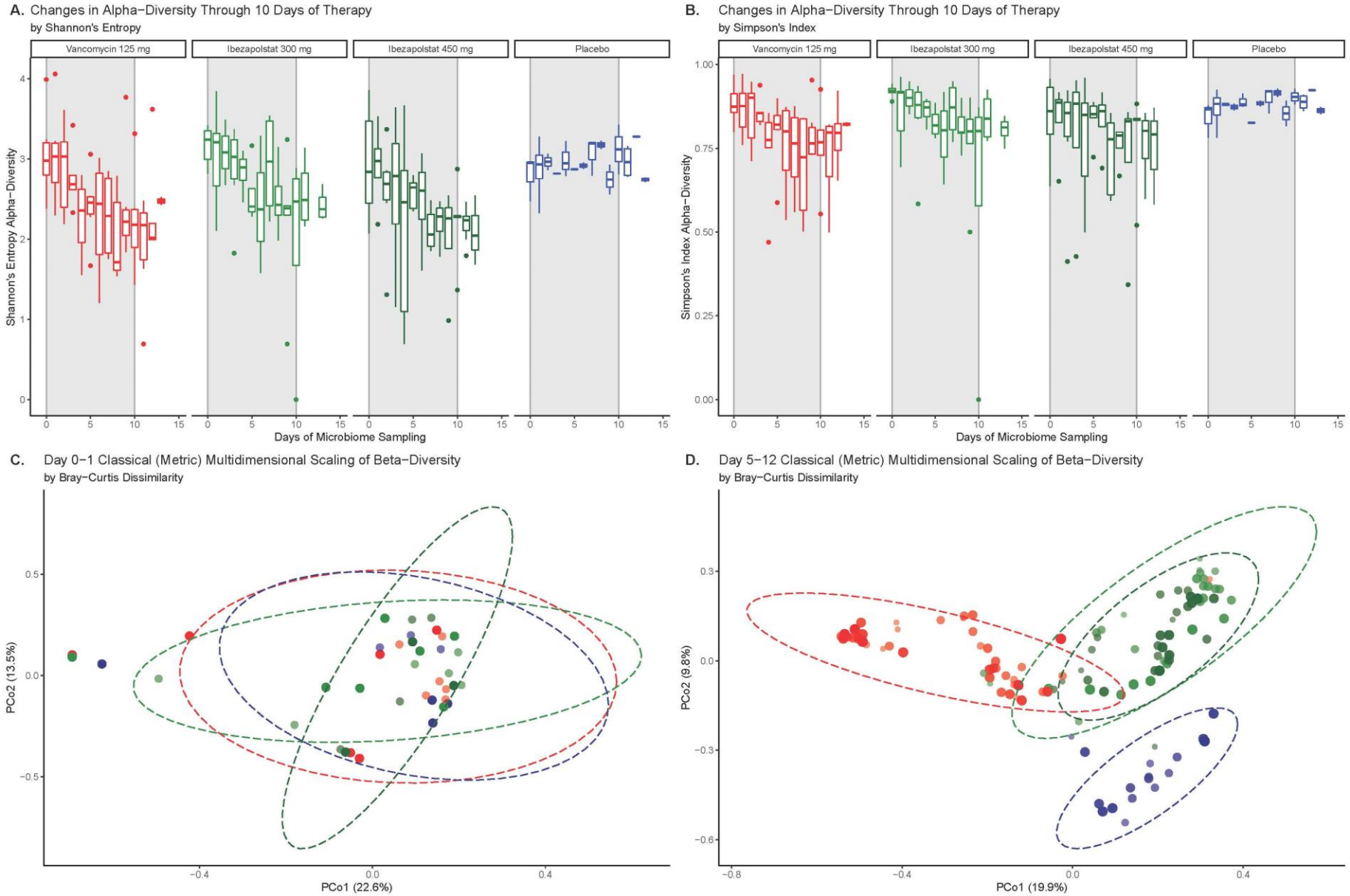
Stool:
ug/g stool



Ibezapolstat: Well-tolerated in Phase 2a:
7 AEs, 0 serious AEs

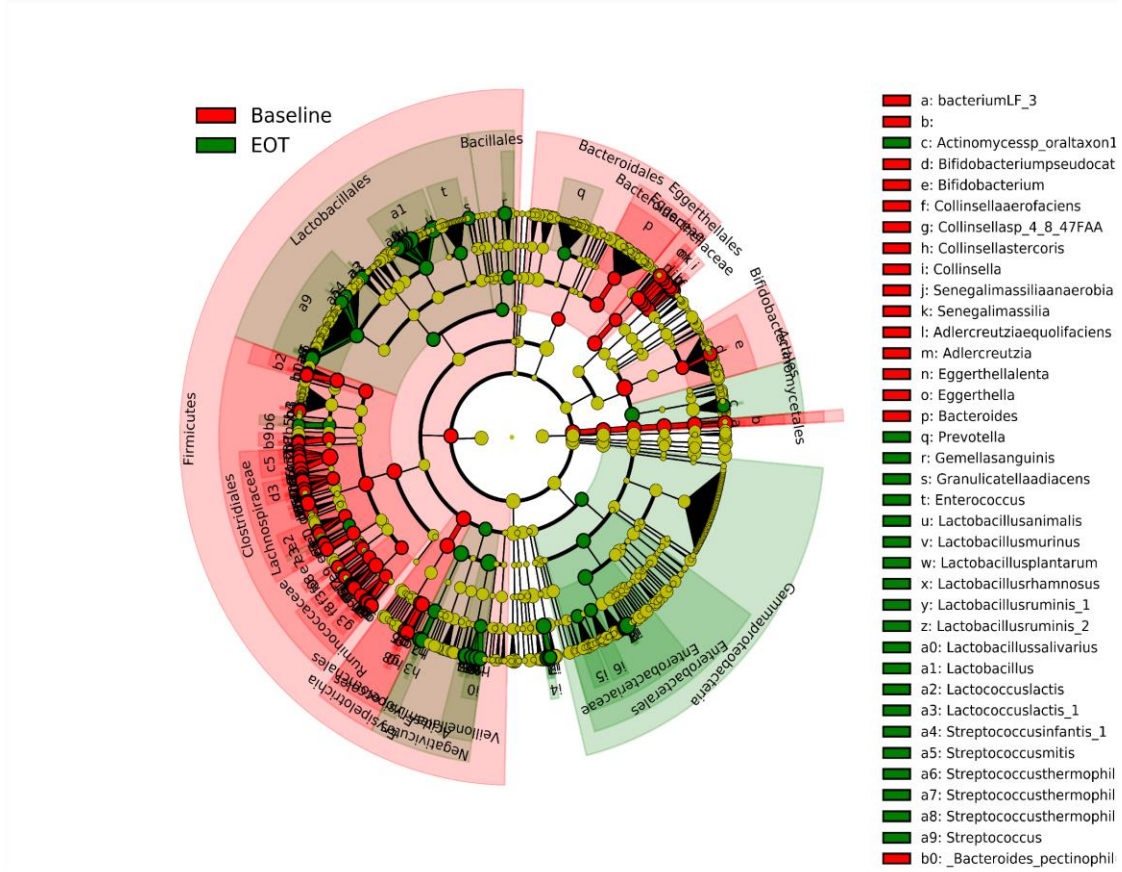
Adverse event	Intensity	Relationship to study drug	Serious AE	Outcome	Treatment required
Headache	Mild	Unrelated	No	Resolved	No
Headache	Mild	Unrelated	No	Resolved	No
Intertriginous Candidiasis	Moderate	Unrelated	No	Resolved	Yes
Migraine headache	Severe	Unrelated	No	Resolved	Yes
Nausea	Moderate	Probably	No	Resolved	No
Nausea	Moderate	Probably	No	Resolved	No
Vomiting	Moderate	Probably	No	Resolved	Yes

Both IBZ and vanco decreased alpha diversity but resulted in very distinct microbe populations

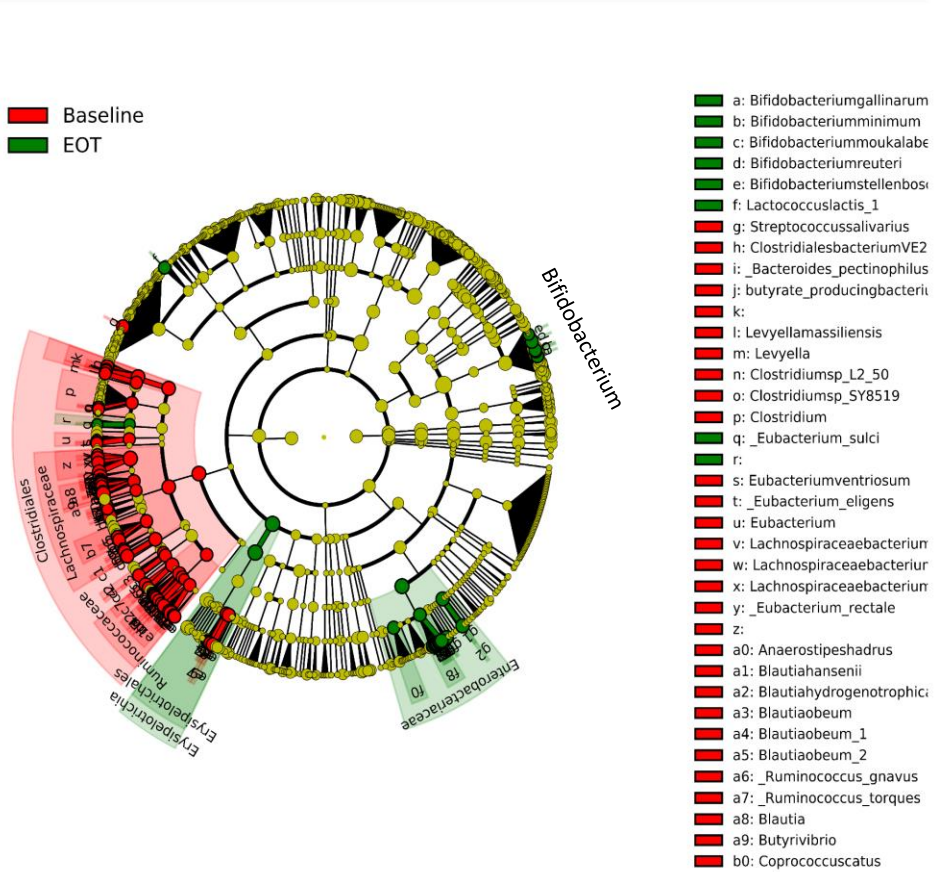


IBZ had a more selective change in Firmicutes vs. vanco

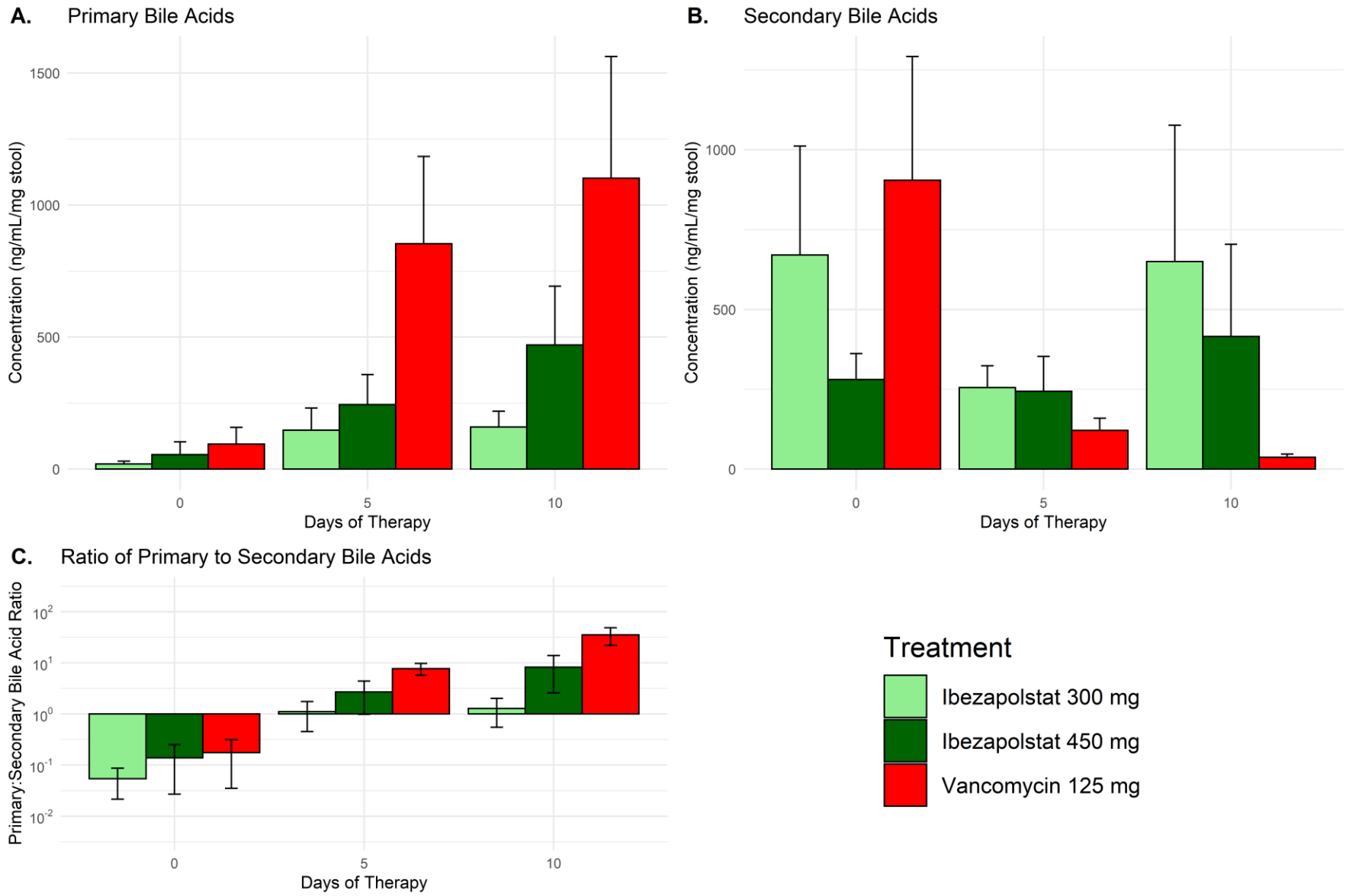
A. Vancomycin Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)



B. Ibezapolstat Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)



Ibezapolstat Phase 1 study showed beneficial effects on bile acids



Phase 2a Open-label Clinical Trial

Ibezapolstat 450 mg BID X 10 days

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

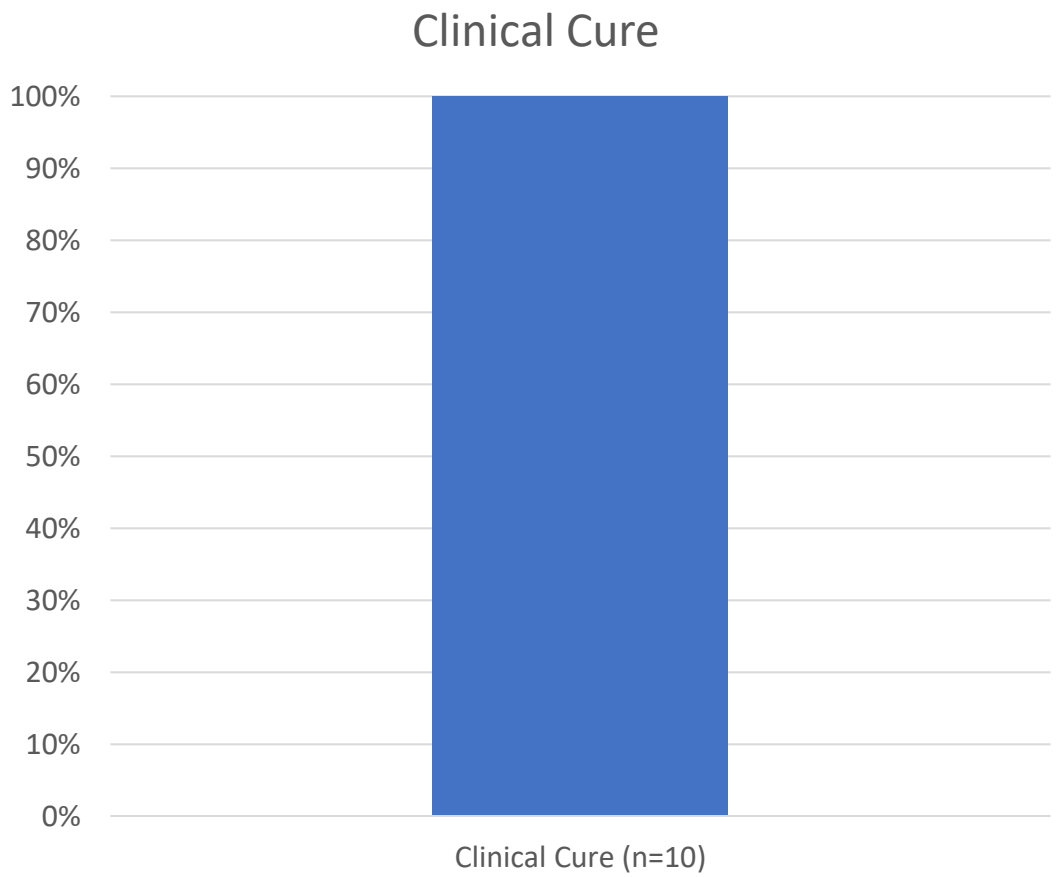
Day 12: Initial CDI clinical cure

Day 38: Sustained CDI clinical cure

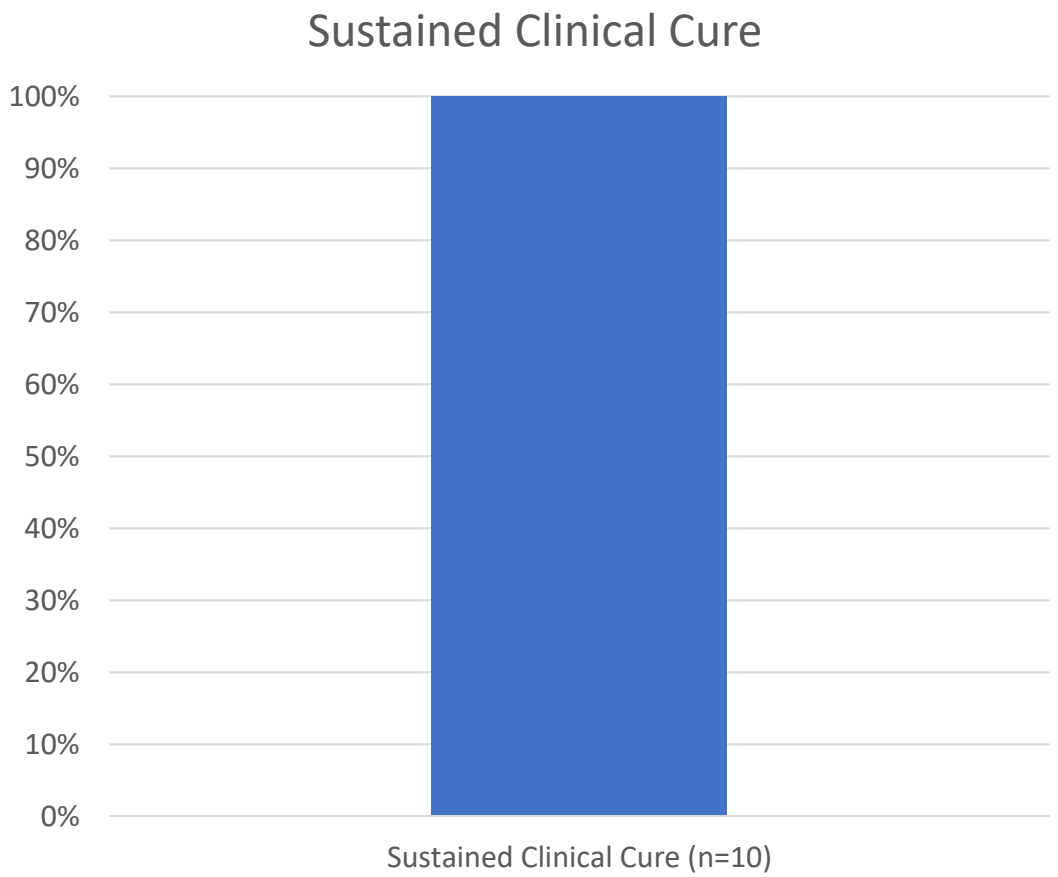
Stool collected during course of therapy and at follow-up

Microbiology, PK and Microbiome analysis

Ibezapolstat Phase 2a Clinical Trial Results



Clinical cure: resolution of diarrhea in the 24-hour period immediately before EOT that is maintained for 48 hours post EOT

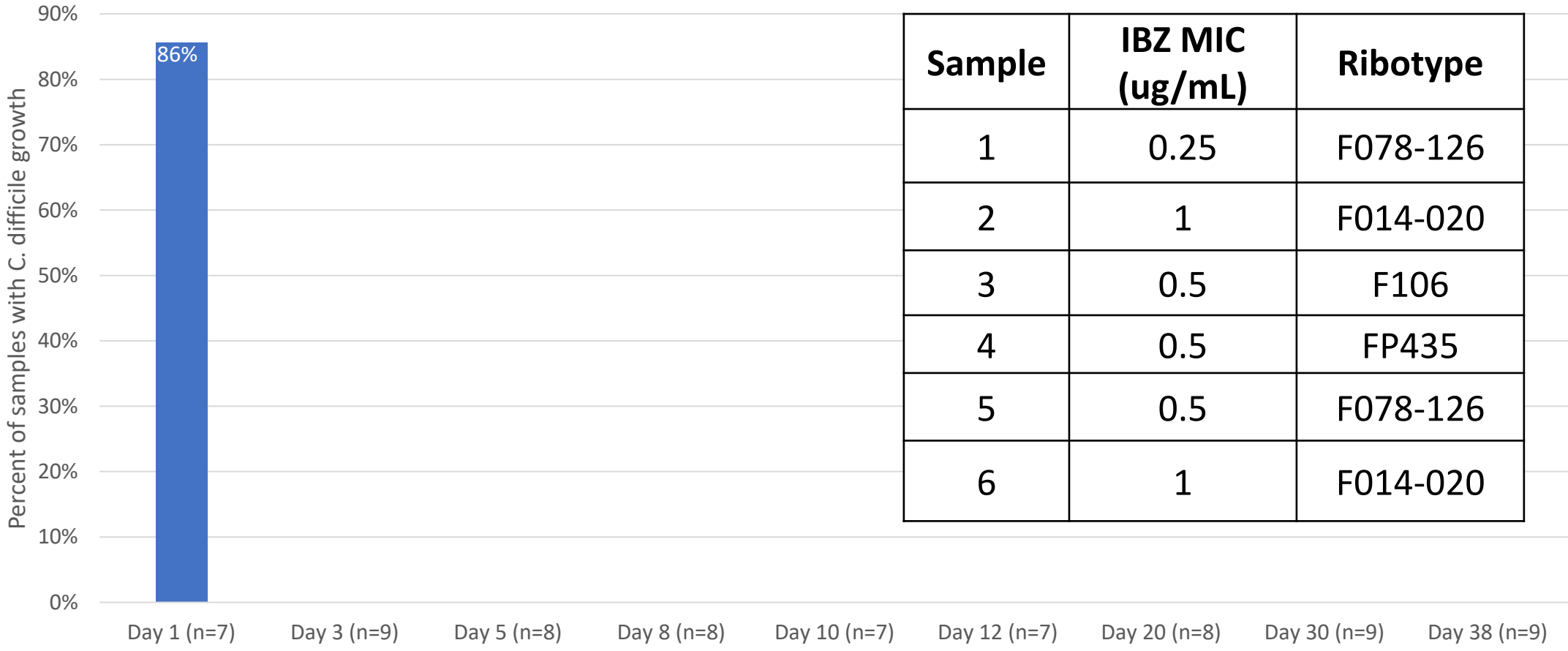


Sustained clinical cure: clinical cure at the test of cure visit and no recurrence of CDI within 28±2 days post EOT

EOT: End of therapy

Ibezapolstat had potent *C. difficile* activity (Phase 2a study)

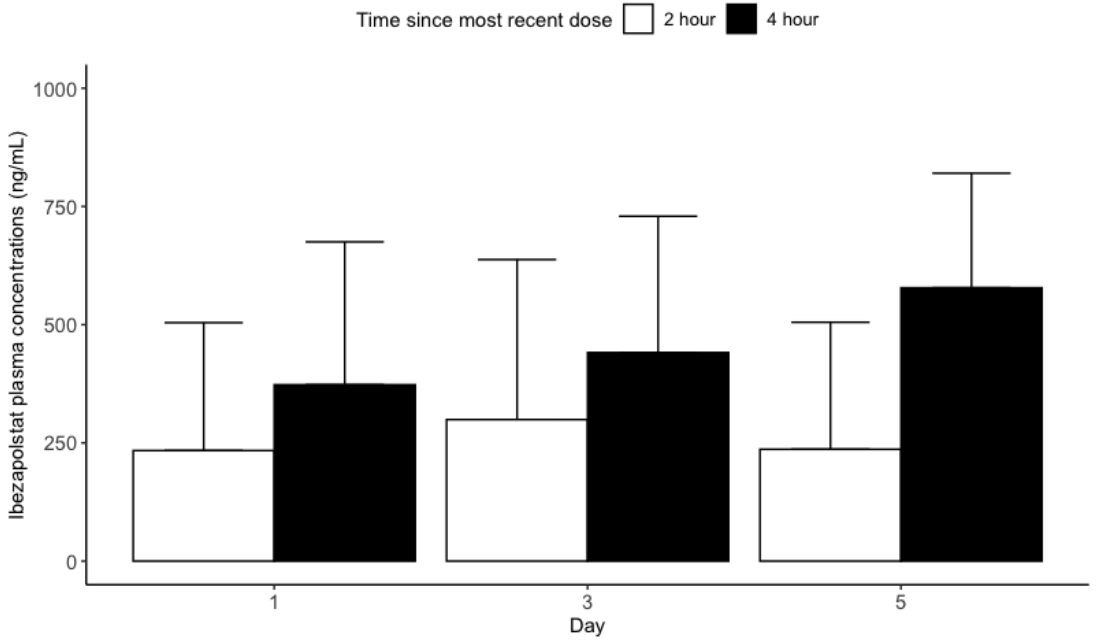
All samples underwent a 48-hour enrichment step with taurocholate prior to plating on CCFA plates.



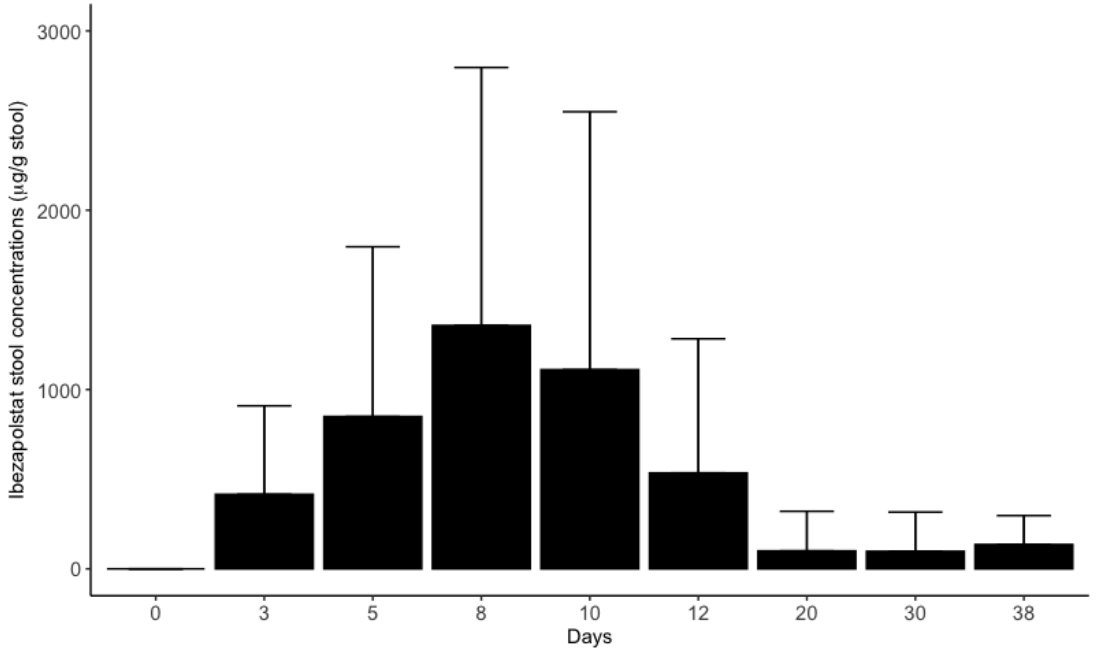
Sample	IBZ MIC (ug/mL)	Ribotype
1	0.25	F078-126
2	1	F014-020
3	0.5	F106
4	0.5	FP435
5	0.5	F078-126
6	1	F014-020

Plasma and stool PK were consistent from the PH1 study, as was the favorable safety profile

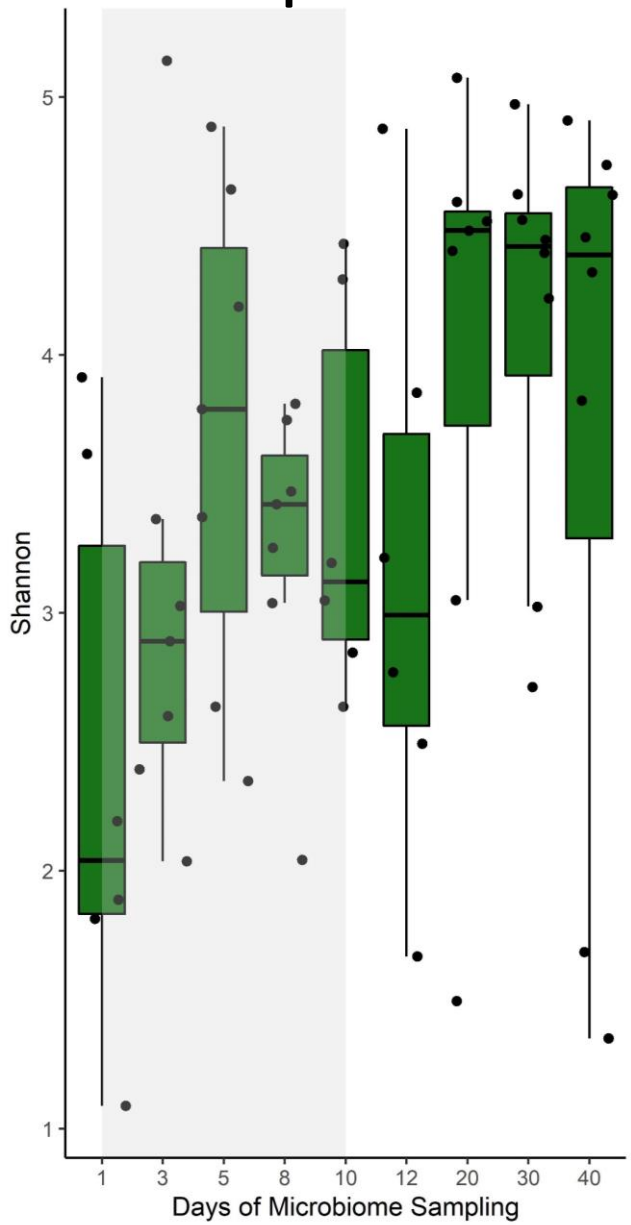
A) Plasma PK

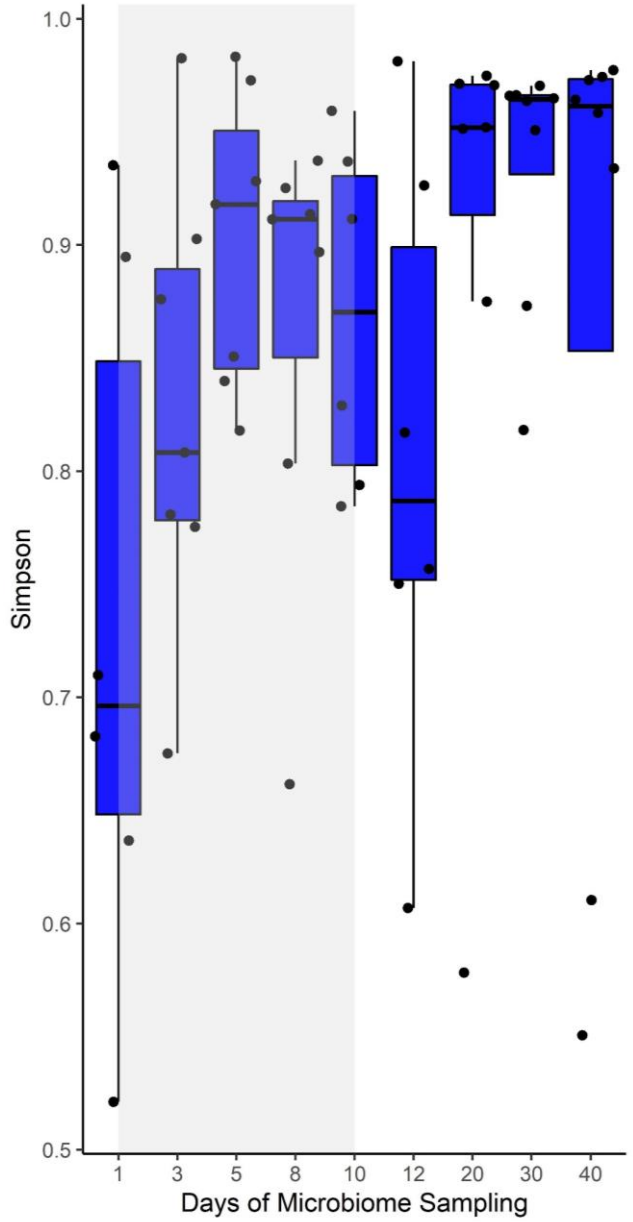


B) Stool PK

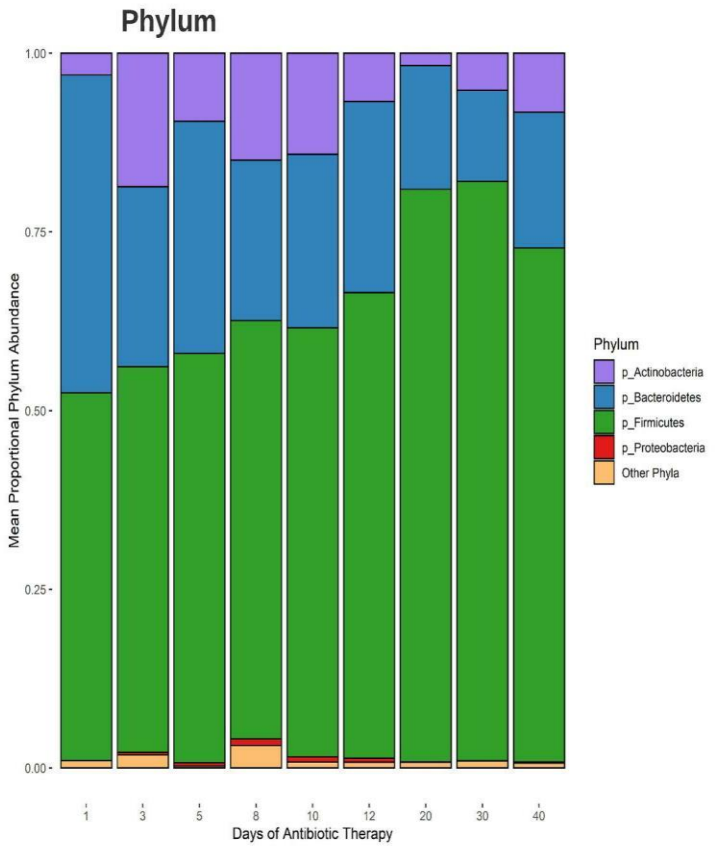


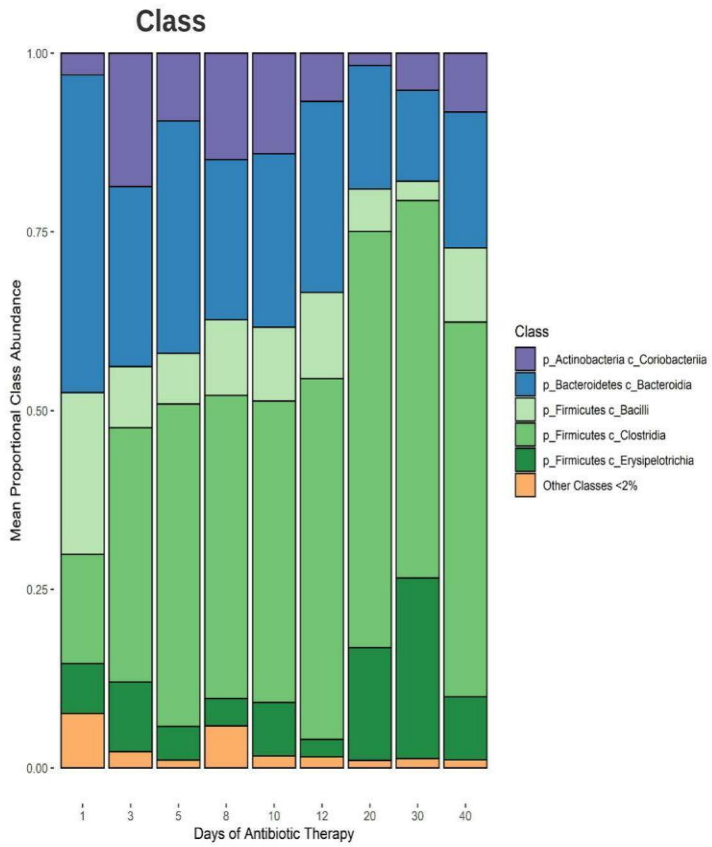
Increased alpha diversity *while on therapy*

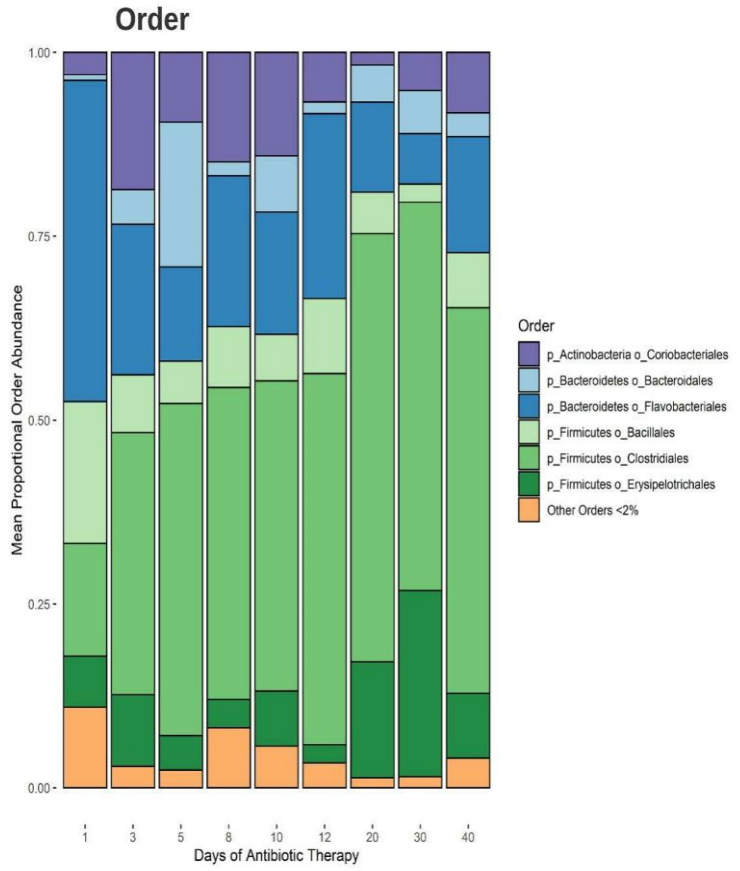




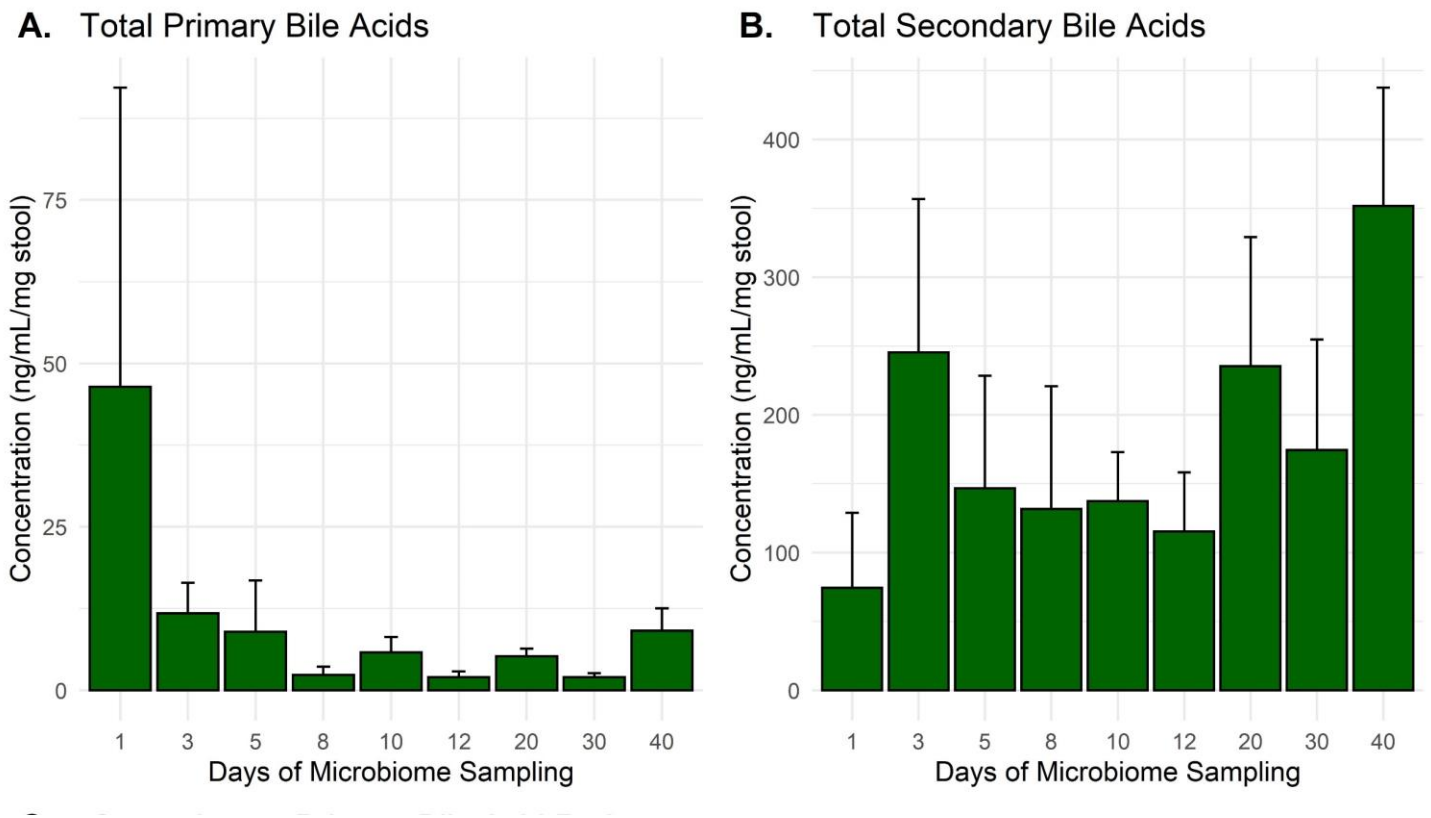
Increased proportion of Firmicutes was observed on ibezapolstat therapy, Clostridiales most common taxa







IBZ Phase 2a continued to show beneficial effects on bile acids.

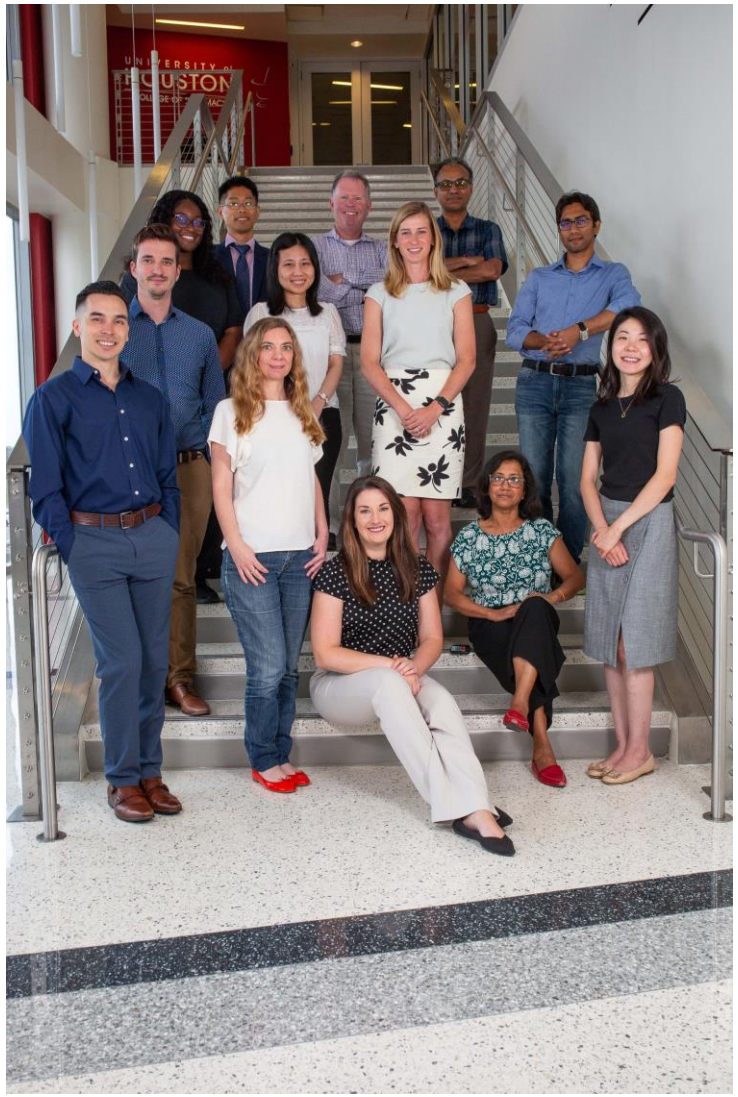


Conclusions: IBZ for the treatment of CDI

- Clinical Trial
  - IBZ: Ideal PK characteristics (high fecal concentrations / minimal systemic exposure)
  - Well tolerated in healthy volunteers and CDI patients
- Microbiome Results
  - Added value of an active comparator (vancomycin) control group in PH1 – this pioneering approach may become the new paradigm for early-phase CDI drug development
  - Metagenomics with bile acid data allowed PH1 trial prediction of CDI anti-recurrence properties
  - Beneficial effects on the fecal microbiome in CDI patients consistent and expanded from PH1 results
- Results support further development of ibezapolstat
  - Using PH1 and PH2a data, a strong hypothesis for an anti-CDI recurrence effect has been developed and is being tested in the ongoing PH2b trial

Acknowledgements

The Garey Lab



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