Efficacy and safety of ibezapolstat compared with vancomycin for the treatment of *Clostridioides difficile* infection: a phase 2, randomized, double-blind study

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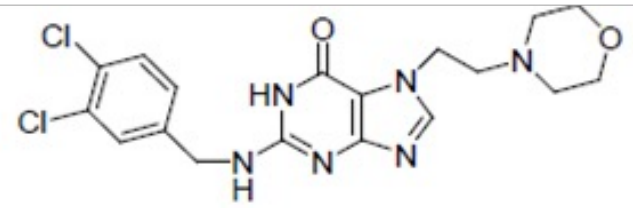
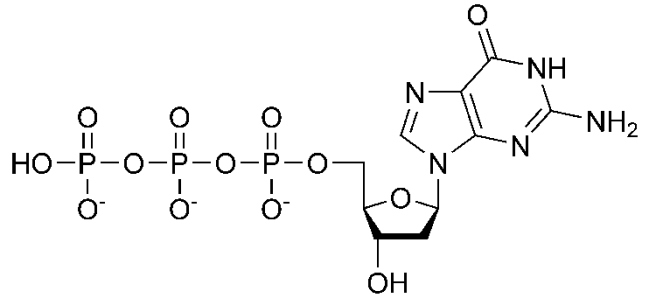
UNIVERSITY of HOUSTON | COLLEGE OF PHARMACY

Ibezapolstat (IBZ; ACX362E)

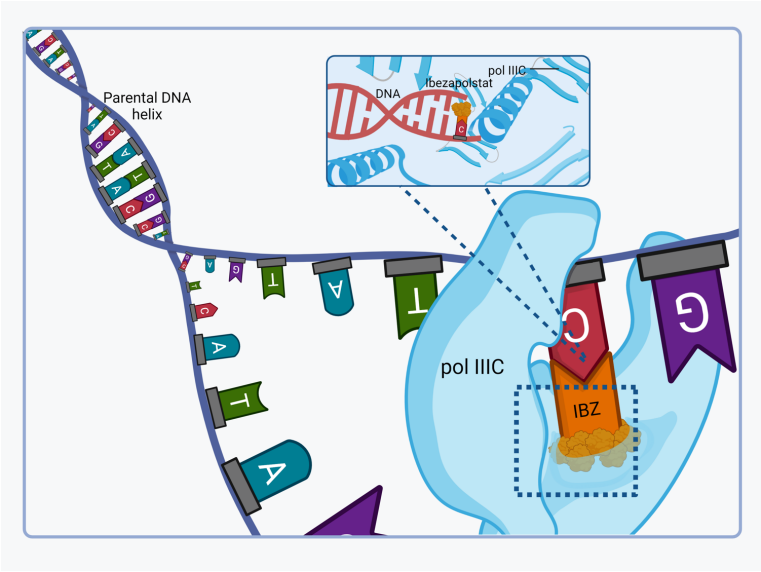


ACX-362



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 (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

IBZ Clinical Trial Update

Phase 1 Study design

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

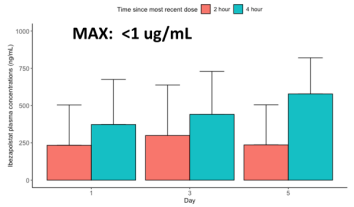

Placebo X 10 days

Stool collected daily for 13 days

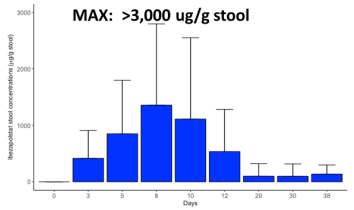
Shotgun metagenomics (Illumina NextSeq 500)

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

Phase IIa Open-label Clinical Trial


Ibezapolstat 450 mg BID X 10 days

Day 12: Initial CDI clinical cure

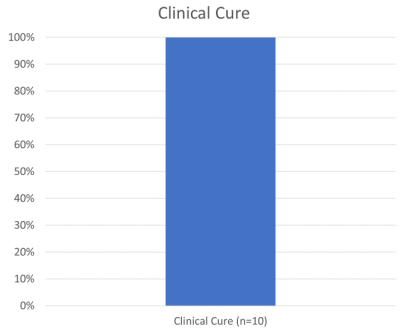
Day 38: Sustained CDI clinical cure

Stool collected during course of therapy and at follow-up

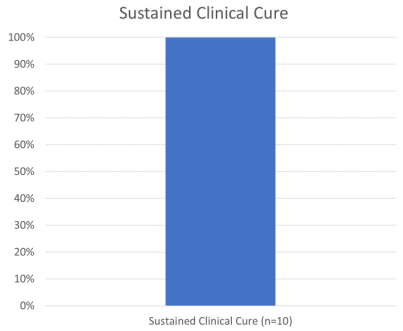
CDI patients with mild/moderate CDI diagnosed via toxin EIA + (n=10)

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

Garey et al. *J Antimicrob Chemother* 2020; Garey et al. Clin Infect Dis 2022

IBZ PH2b Objectives

- Evaluate IBZ vs. Vanco in patients with CDI for
  - Efficacy*
    - Initial cure, sustained clinical cure, microbiologic eradication, time to resolution of diarrhea
  - Safety*
  - Pharmacokinetics and fecal concentrations
  - Fecal microbiome effects

*Focus of this presentation

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

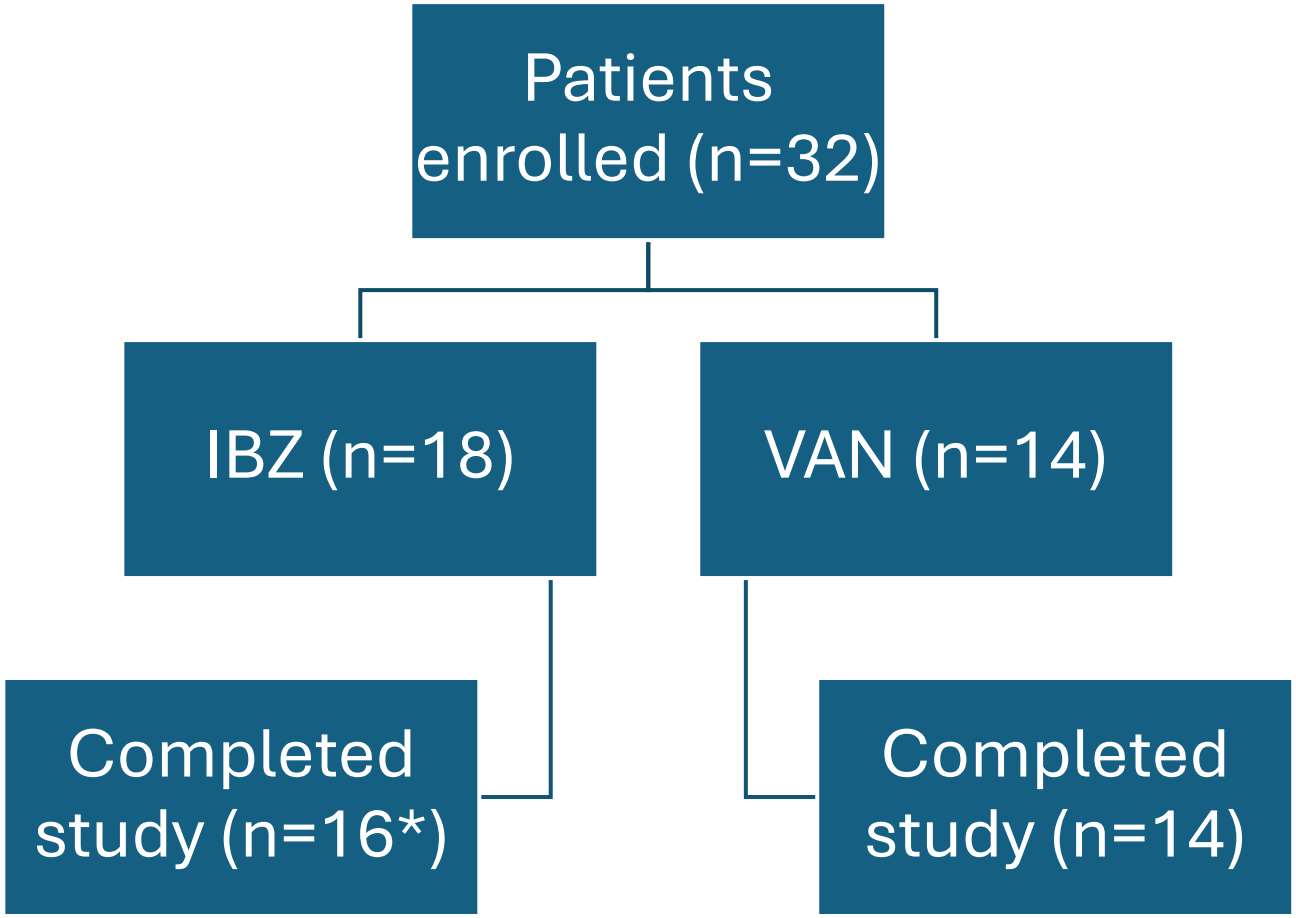
Vancomycin 125 mg QID X 10 days

Outcome Measures

- Initial clinical cure (day 12 evaluation)
- Sustained clinical cure (day 38)
- Extended clinical cure (3 months)
- Microbiologic eradication (days 0-12)
- Time to resolution of diarrhea (days 0-12)
- Safety (day 38)

ClinicalTrials.gov ID NCT04247542

Consort Diagram



*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.

The trial was originally designed to be a non-inferiority (NI) trial and was discontinued early due to success.

Decision made in consultation with medical and scientific advisors and statisticians based on observed aggregate blinded data and other factors, including the cost to maintain clinical trial sites and slow enrollment due to COVID-19 and its aftermath.

The trial performed as anticipated for both treatments, with high rates of clinical cure observed across the trial without any emerging safety concerns.

Results: Demographics and Baseline Information

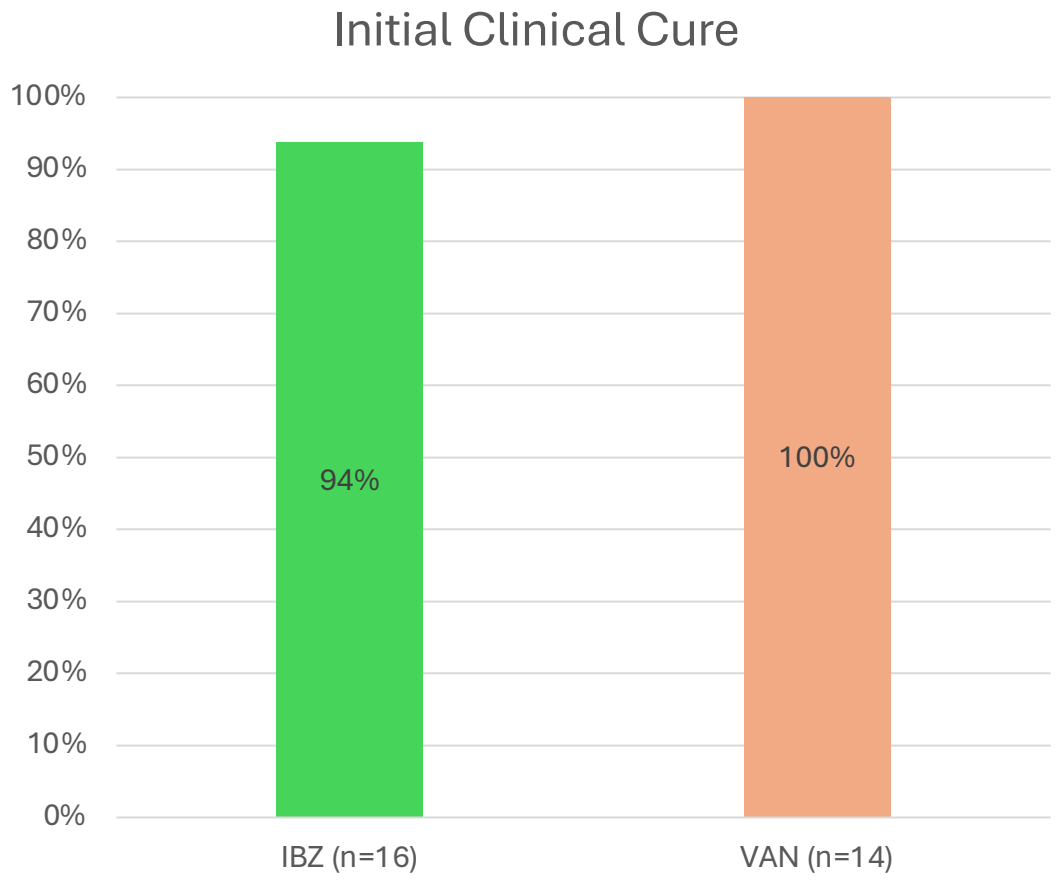
Demographics

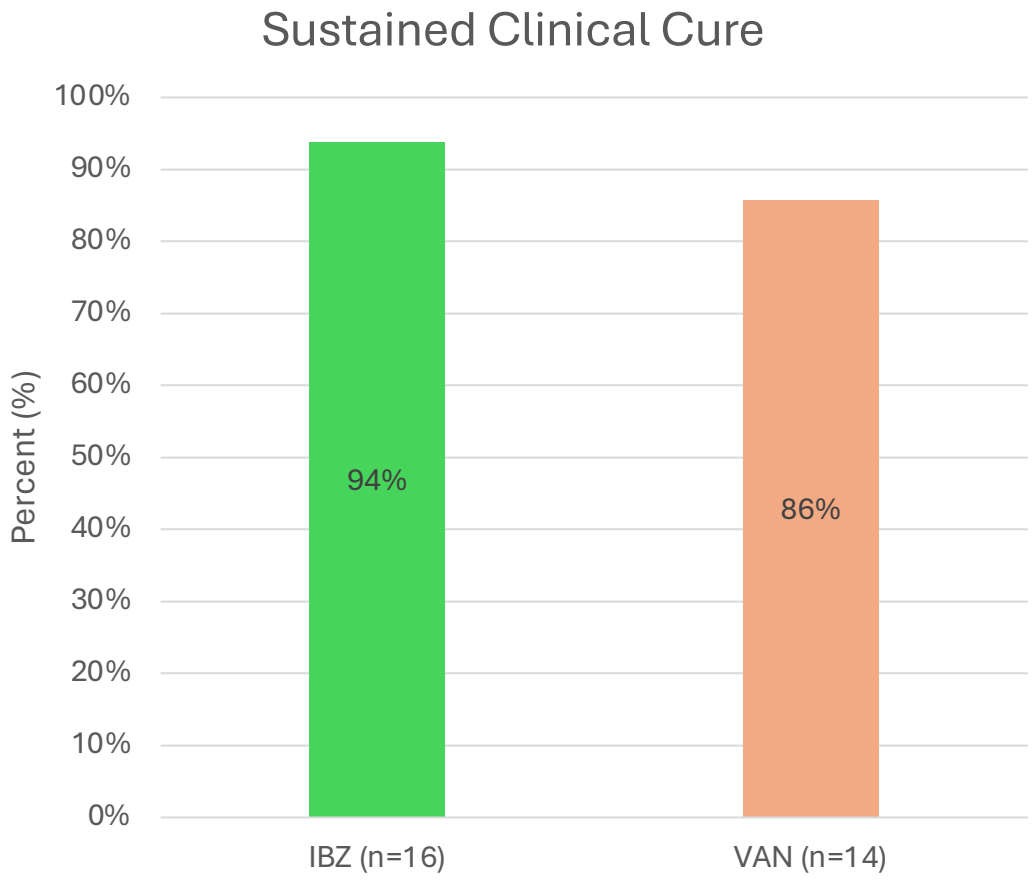
	IBZ	VAN	P value
N	16	14	
Age, years	64±13	62±10	0.57
Female	13 (81%)	11 (79%)	0.85
White	16 (100%)	13 (93%)	0.27
Hispanic or Latino	11 (69%)	11 (79%)	0.54
Charlson Comorbidity index	2.6±1.5	2.2±1.5	0.47

Baseline Ribotypes

Ribotype	N
F027	5
F106	4
F002	3
F014-020	3
F116	1
Other	6

Initial, Sustained, and Extended Clinical Cure





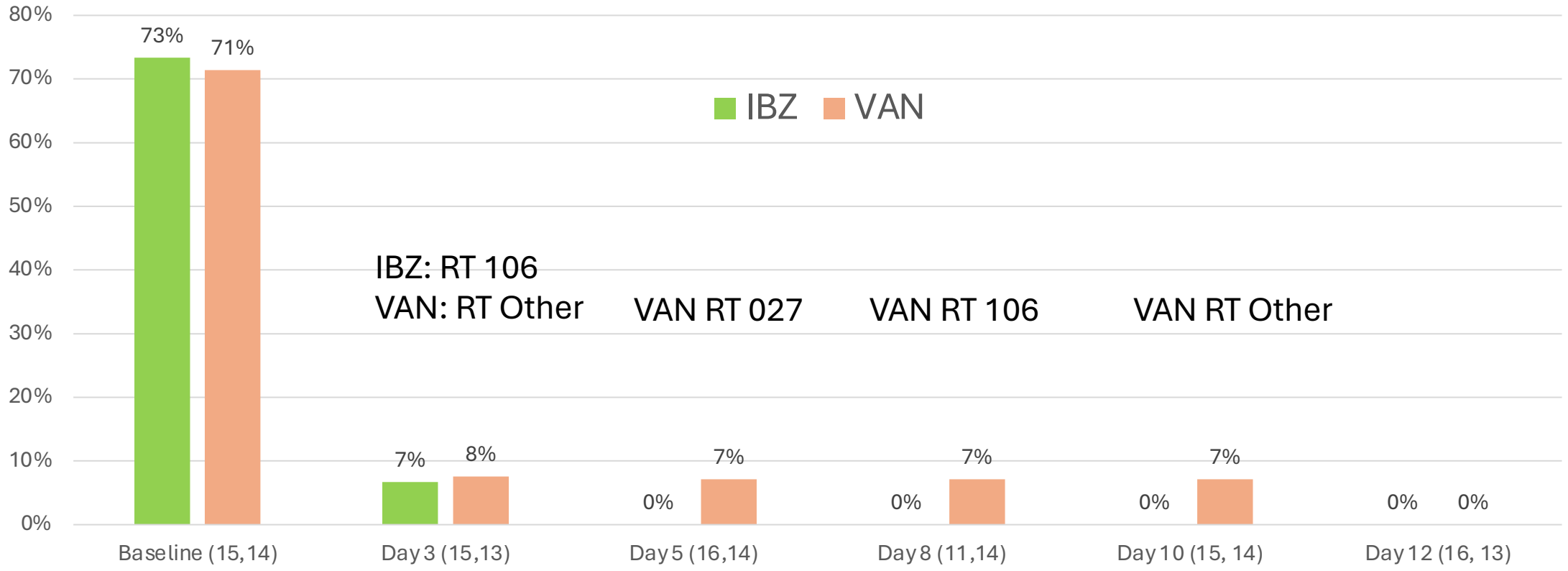
IBZ Initial Clinical Failure (n=1): RT 027 isolated

VAN Sustained Clinical Failure (n=2): RT 116 and FP409 isolated

VAN CDI recurrence: 2 of 14 (14%) on days 22 and 25

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

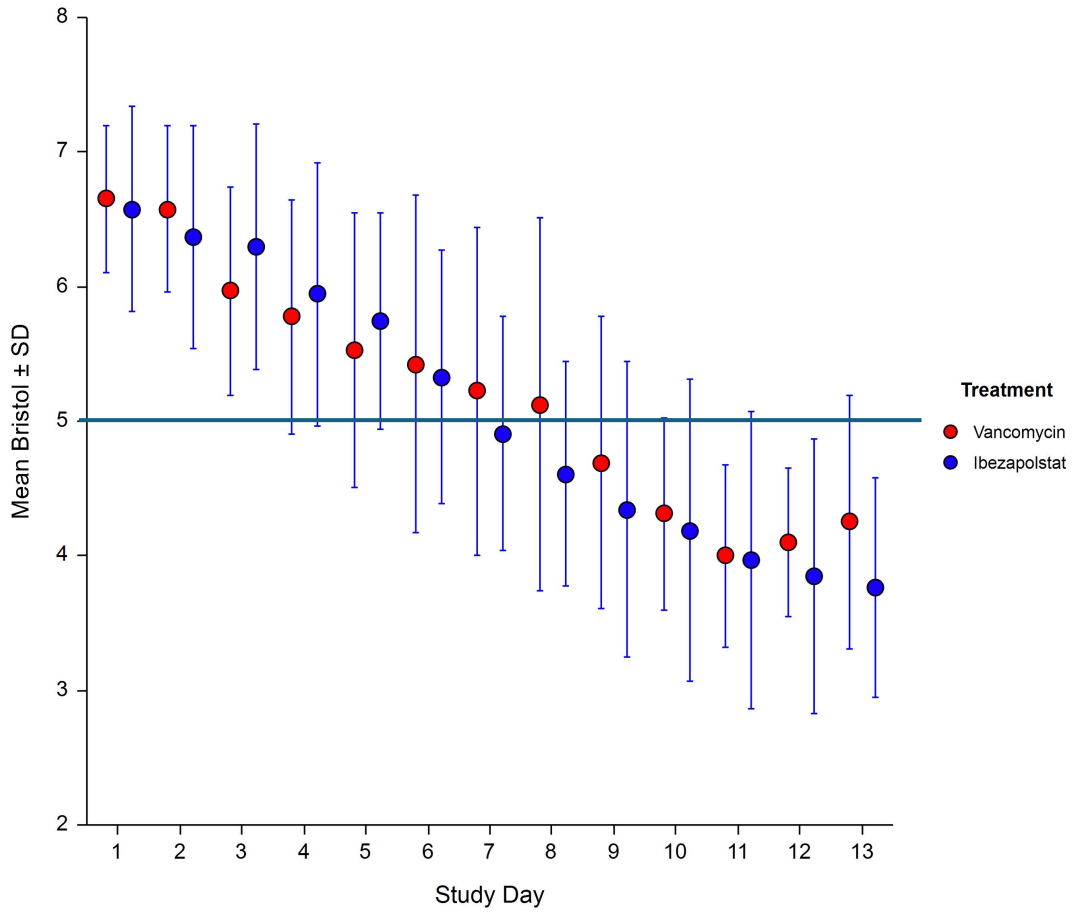
Microbiologic Eradication



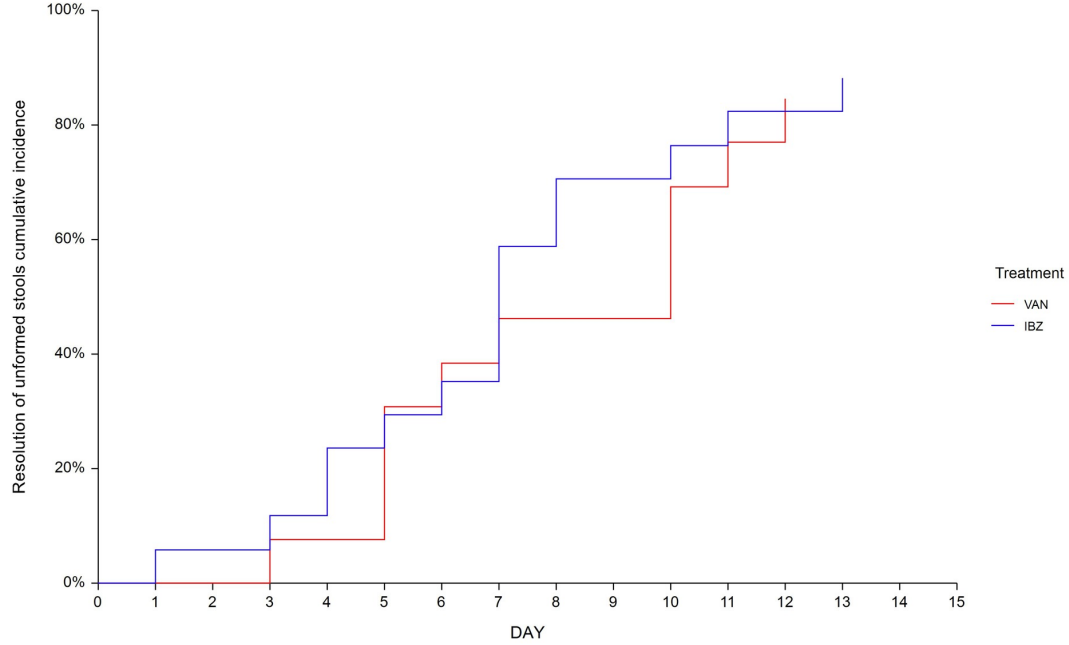
IBZ: One patient with positive *C. difficile* growth past baseline
VAN: Four patients with positive *C. difficile* growth past baseline

IBZ as effective as VAN for Time to Resolution of Diarrhea

Average Bristol score per day



Cumulative incidence of UBM resolution



UBM: unformed bowel movement

Time to resolution of diarrhea defined as the time from onset of treatment to the first formed bowel movement not followed within the next 24 hours by a UBM. A UBM is defined as a Type 5, 6, or 7 bowel movement on the Bristol Stool Chart

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

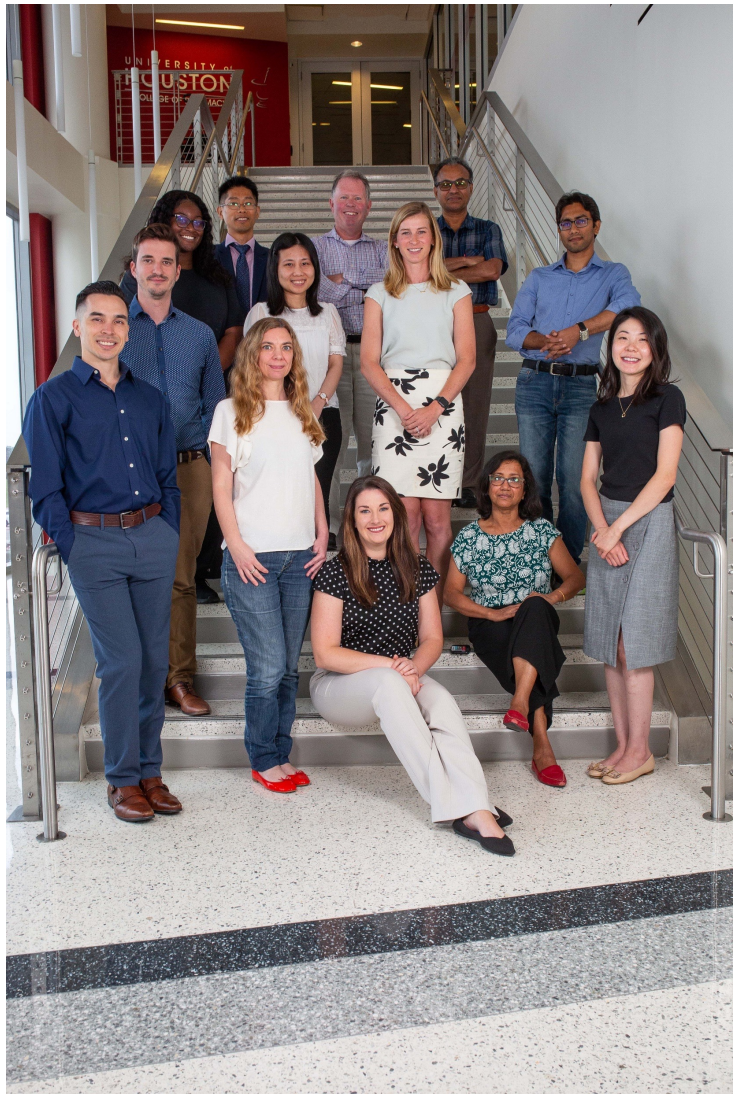
All adverse events resolved without treatment

Discussion and Conclusions

- IBZ had a clinically comparable cure rates, TTRD, and safety profile to oral vancomycin.
  - More patients given vancomycin had persistently positive *C. difficile* cultured
- Phase 2 experience (Ph2a+Ph2b): Of 26 CDI patients enrolled during IBZ phase 2 trials, 25 of 26 experienced clinical cure after 10 days of treatment, for an overall success rate of 96%.
- These results warrant further development in phase 3 trials.

Acknowledgements

The Garey Lab



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