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

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ABSTRACT

Background. Ibezapolstat (IBZ) is Gram-positive selective spectrum antibiotic that inhibits the bacterial DNA polymerase IIIC currently in clinical trial development for the treatment of *C. difficile* infection (CDI) in adults. In the open-label, non-comparative, phase 2a study, 10 of 10 IBZ-treated CDI patients experienced clinical cure. The purpose of the phase 2b study was to assess the safety and efficacy of IBZ versus vancomycin (VAN) for treatment of CDI.

Methods. Phase 2b was a randomized, double-blind, active-comparator study. Participants with signs and symptoms of CDI and a positive enzyme immunoassay toxin test result were recruited from 12 centers in the USA and randomly assigned (1:1) to receive oral IBZ 450 mg every 12 h or oral VAN 125 mg every 6 h for 10 days. The primary endpoints were clinical cure at the end of therapy visit and safety. The trial is registered with ClinicalTrials.gov, number NCT04247542.

Results. Thirty-two patients were recruited; the primary efficacy analysis included 16 IBZ-treated patients and 14 VAN-treated patients. 15 of 16 (93.8%) patients given IBZ had a clinical cure versus 14 of 14 (100%) patients given VAN (treatment difference: -6.3%; 95% CI: -30.7-19.4%). IBZ was well tolerated; three IBZ-treated patients experienced mild and self-limited adverse events possibly related to drug and one VAN-treated patient experienced a moderate adverse event possibly drug-related. No changes in therapy were required for any adverse event.

Conclusions. In the phase 2b study, IBZ had a clinically comparable cure rate and safety profile to oral vancomycin. 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.

OBJECTIVES

The purpose of the phase 2b study was to assess the safety and efficacy of IBZ versus vancomycin (VAN) for treatment of CDI.

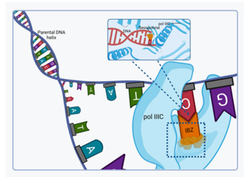
1. To assess clinical cure and sustained clinical cure
2. To assess microbiologic eradication rates
3. To assess changes in key Firmicute taxa

BACKGROUND

Ibezapolstat (IBZ; ACX362E)

Ibezapolstat (IBZ): 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)



IBZ Clinical trial history

Phase 1, Healthy Volunteer: Completed

- IBZ 450 mg twice daily chosen for phase 2 studies
  Garey et al. *J Antimicrob Chemother* 2020.
- Microbiome evaluations predicted an anti-recurrence effects
  McPherson et al. *Antimicrob Agents Chemother* 2022

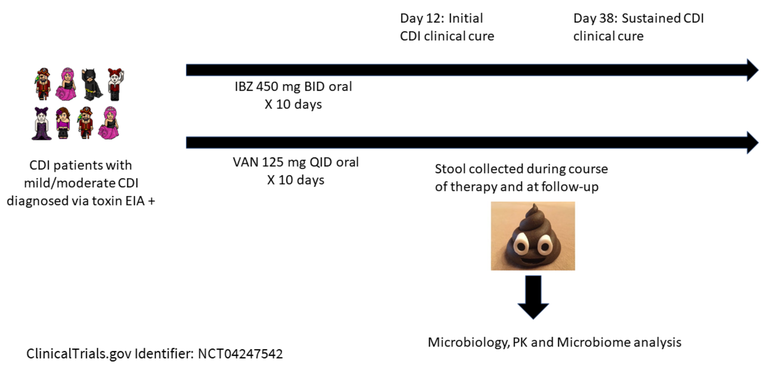
Phase 2a (n=10): Completed

- IBZ 450 mg demonstrated 100 clinical cure without recurrence
- Anti-recurrence microbiome effects validated
  Garey et al. *Clin Infect Dis* 2022

METHODS

Phase 2b randomized controlled study

Phase 2b randomized, double-blind, clinical trial study design



ClinicalTrials.gov Identifier: NCT04247542

Patients

Adults aged 18-90 years with CDI defined as >3 watery bowel movements in the 24 hours prior to enrollment and classified as non-severe CDI as defined by Infectious Diseases Society of America/Society for Healthcare Epidemiology of America guidelines Enrolled patients must have been diagnosed via positive free toxin-based fecal test

Toxigenic *C. difficile* culture

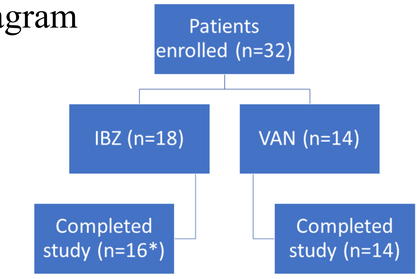
Stool samples cultured for *C. difficile* growth on a selective cycloserine-cefoxitin fructose agar (CCFA) at 37°C under anaerobic conditions for 48 hours. Toxigenic *C. difficile* confirmed by PCR for *C. difficile* toxin and tpi genes

Quantitative PCR (qPCR) Microbiome analysis

Using the 7300 Real Time PCR System (Applied Biosystems), qPCR was performed on extracted DNA from stool samples for Clostridium coccioides and Clostridium leptum.

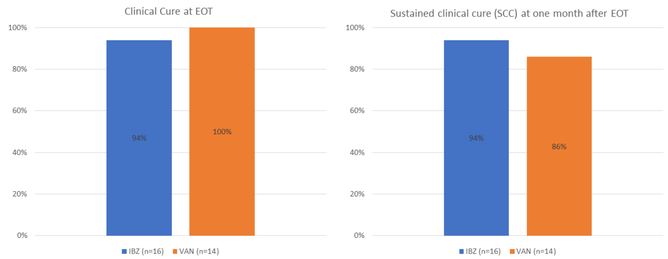
RESULTS

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.

Clinical outcomes from the IBZ phase 2b study

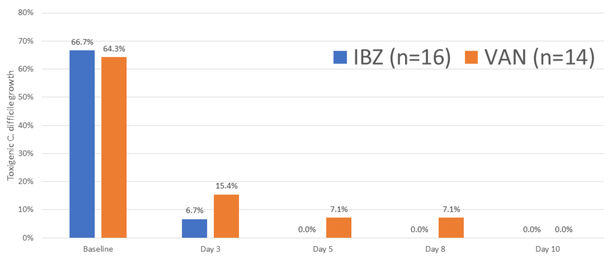


1 patient given IBZ experienced a clinical failure

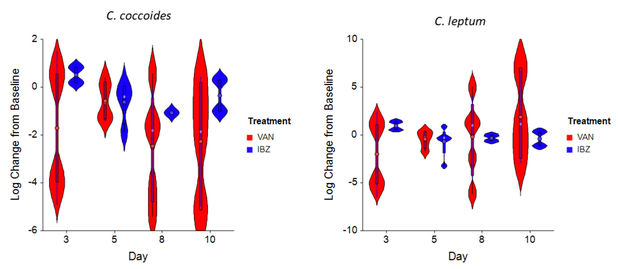
2 patients given vancomycin experienced CDI recurrence

C. difficile microbiologic eradication

One of 16 patients given IBZ had persistently positive cultures after starting treatment compared to 4 of 14 given VAN



IBZ demonstrated consistent preservation of key beneficial Firmicutes



Values above 0 indicate increased concentration from baseline; values below 0 indicate decreased concentration

CONCLUSIONS

- IBZ had a clinically comparable cure rate and safety profile to oral vancomycin.
- More patients given vancomycin had persistently positive *C. difficile* cultured
- IBZ preserved key beneficial Firmicutes vs VAN
- 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.

FUNDING

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