An Open-label Phase 2a study of Ibezapolstat, a Unique Gram-positive Selective Spectrum (GPSS) Antibiotic, for Patients with *Clostridioides difficile* Infection

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ABSTRACT

Background: Ibezapolstat, a DNA polymerase IIIC inhibitor, is currently in Phase 2 clinical development for treatment of *C. difficile* infection (CDI). Its unique mechanism of action targets low G+C content Gram-positive bacteria, primarily Firmicutes including *C. difficile*. Phase I healthy volunteer results demonstrated a favorable microbiome profile suggestive of an anti-recurrence effect. The purpose of this study was to report clinical outcomes, pharmacokinetics (PK), and microbiome changes from the Phase 2a clinical study and to continue to test for anti-recurrence microbiome properties.

Methods: Ibezapolstat 450 mg was given twice daily for 10 days to patients with mild-moderate CDI defined as diarrhea plus a positive *C. difficile* toxin test. Test of cure was evaluated at day 12 and sustained clinical cure at day 38. Stool samples were evaluated for *C. difficile* cultures and microbiome changes.

Results: Ten subjects (female: 50%) aged 50 ±15 years were enrolled. All 10 subjects experienced a clinical cure by the test of cure visit at day 12 and all 10 subjects experienced a sustained clinical cure at the day 38 visit. Ibezapolstat was well tolerated with 1 adverse event (nausea) probably related to drug. Ibezapolstat systemic exposure was minimal with no plasma level reaching 1 ug/mL any time during therapy. Ibezapolstat colonic concentrations averaged 400 ug/g stool at day 3 and greater than 1,000 ug/g by day 10 of dosing. Six of the seven available baseline stool samples grew toxigenic *C. difficile* of various ribotypes including RT078-226 and RT014-020 (Ibezapolstat MIC range: 0.25-1 ug/mL). Follow-up cultures were no growth starting from day 3 stool cultures. Microbiome changes included overgrowth of Actinobacteria and/or Firmicute phylum species while on therapy.

Conclusions: Favorable clinical efficacy and safety results were observed in ibezapolstat patients with CDI including 100% clinical cure and sustained clinical cure. These results begin to validate our approach to ibezapolstat development in that the favorable microbiome effects seen in healthy Phase 1 volunteers may be predictive of beneficial patient outcomes, including low rates of recurrence. These results support the continued clinical development of ibezapolstat.

OBJECTIVES

The purpose of this study was to report clinical outcomes and microbiome changes from the Phase 2a ibezapolstat clinical study and to continue to test for anti-recurrence microbiome properties.

METHODS

Phase IIa C. *difficile* infection clinical trial

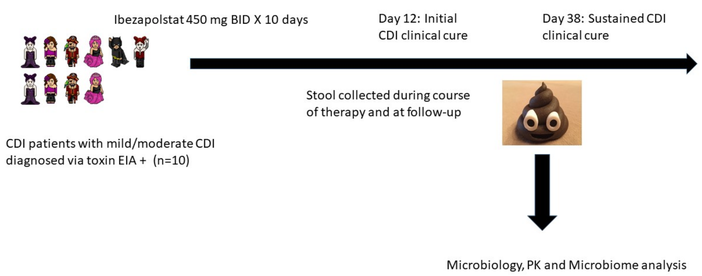
CLINICAL TRIAL OUTCOMES

Primary:
- Initial CDI cure rates 2 days after the end of treatment (EOT) and safety/tolerability

Secondary:
- Sustained clinical cure at Day 38
- Systemic and fecal concentrations of Ibezapolstat
- Microbiologic and microbiome evaluations

METHODS

Phase IIa Open-label Clinical Trial

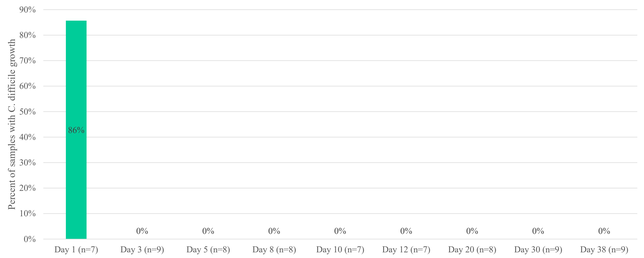


CLINICAL TRIAL RESULTS

Clinical Evaluation

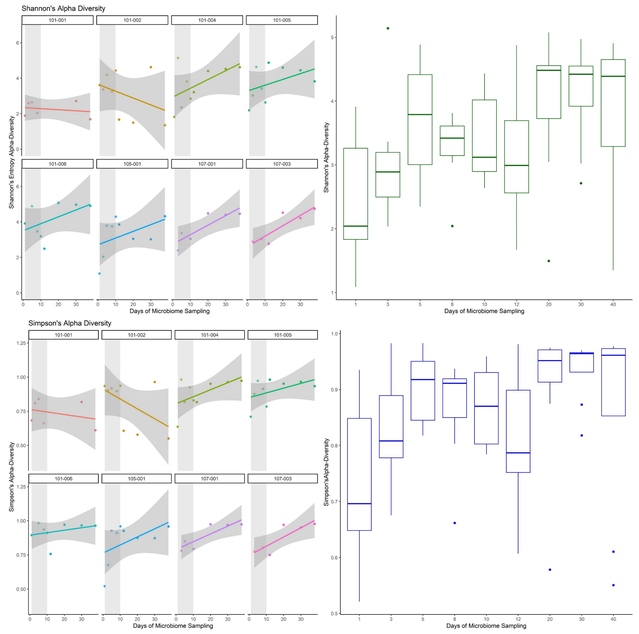
- Primary:
  - Clinical Cure (Day 12) = **10 out of 10**
- Secondary:
  - Sustained Clinical Cure (Day 38) = **10 out of 10**
  - Ibezapolstat systemic exposure was minimal: **<1 ug/mL in plasma**
  - Fecal concentrations averaged 400 ug/g stool at Day 3 and were **>1,000 ug/g by Day 10**
- Safety signals: Ibezapolstat was **well tolerated** with only 1 adverse event, nausea, classified as drug-related
- **FIRST human validation of DNA polymerase IIIC target**

Microbiologic evaluation: MIC range = 0.25-1ug/mL



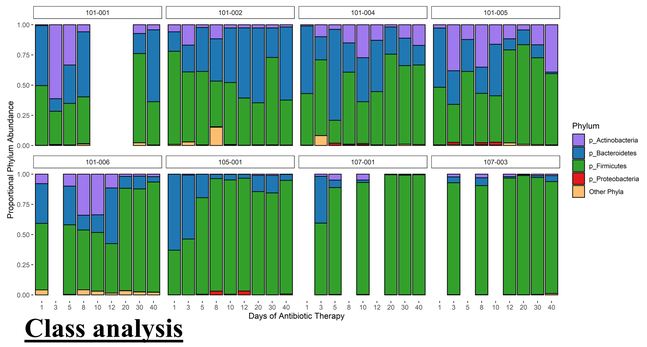
MICROBIOME RESULTS

Alpha Diversity Increased While on Ibezapolstat

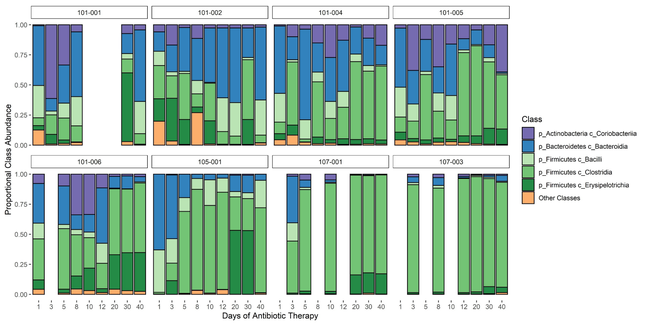


Bacterial Abundance: Increased alpha diversity marked by regrowth of healthy gut microbiota

Phylum analysis



Class analysis



CONCLUSIONS

Phase 2a Clinical trial

Safety: Ibezapolstat was well-tolerated

Efficacy: Clinical cure and sustained clinical cure in all 10 patients

PK: Colonic levels exceed MIC by up to 3 logs; but low systemic exposure

Microbiologic: No growth of *C. difficile* after baseline cultures; MIC ≤1 ug/mL

Microbiome Results

Increased alpha diversity observed during and after ibezapolstat therapy

Increased bacterial abundance, especially overgrowth of healthy gut microbiota Actinobacteria and Firmicute phylum species during and after therapy

The good tolerability, promising efficacy outcomes, favorable PK behavior, and differential microbiome effects all support the continued clinical development of ibezapolstat. Its unique spectrum of activity, which includes *C. difficile* but spares other Firmicutes and the important Actinobacteria phylum, appears to contribute to the maintenance of a healthy gut microbiome.

FUNDING

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REFERENCES

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