DNA polymerase IIIC inhibitor ibezapolstat, first of a new class of antibiotics with a novel mechanism of action: Clinical Trial Update

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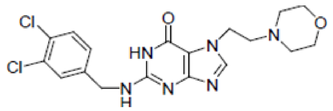
BACKGROUND

Pre-clinical development

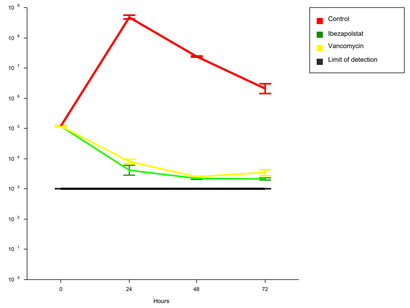
Ibezapolstat (ACX-362E)



- DNA Pol IIIC essential for replication of low G+C content Gram-positive bacteria
- DNA Pol IIIC strongly conserved across broad spectrum of low G+C Gram-positive pathogens
- DNA Pol IIIC possesses a unique active site which renders it specifically susceptible to inhibition

- Ibezapolstat designed as a small-molecule DNA Pol IIIC inhibitor based upon competitive inhibition of dGTP

Time kill curves demonstrate good activity against ribotype 027



Preclinical development strongly supported continued development into phase I/II clinical trials

OBJECTIVES

To summarize data from the ongoing ibezapolstat clinical development program

Phase I Healthy Volunteer Study

OBJECTIVES
Primary: To determine safety of ACX-362E in both single- and multiple-dose administration to healthy subjects
Secondary: To determine, in both single- and multiple-dose administration:
Systemic pharmacokinetics (PK) of ACX-362E;
Fecal PK of ACX-362E;
Fecal microbiome effects of ACX-362E compared to those of oral vancomycin (*multiple-dose only*)

METHODS

	Part 1	Part 2	Part 3
Design	Single-ascending dose	Food effect crossover	Multiple, ascending dose (MAD)
Treatment days	1 dose	1 dose	10 days (20 doses)
Dose cohort	150, 300, 600, 900 mg	300	300, 450 mg
N	6/cohort	8	6/cohort
Comparator (n=)	Placebo (n=2/cohort)	None	Vancomycin (n=3/cohort) Placebo (n=2/cohort)

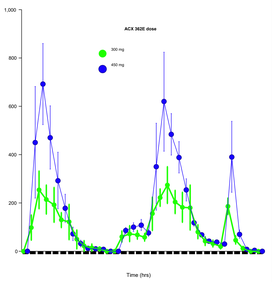
RESULTS

Safety date: Adverse events similar to placebo

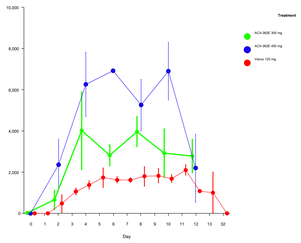
	Single ascending dose		Food effect	Multiple ascending dose	
Dose	*Ibezapolstat (n=6)*	*Placebo (n=2)*	*Ibezapolstat (n=8)*	*Ibezapolstat (n=6)*	*Placebo (n=2)*
300	0%	50%	37.50% ##	33%	50%
450			X	0%	0%
600	33%	50%	X	X	X
900	33%	50%	X	X	X
Summary	5 AE in 5 subjects	5 AE in 4 subjects	3 AE in 2 subjects	5 AE in 2 subjects	1 AE in 1 subject

Pharmacokinetics: Minimal systemic absorption.
Stool concentrations several log higher than the MIC

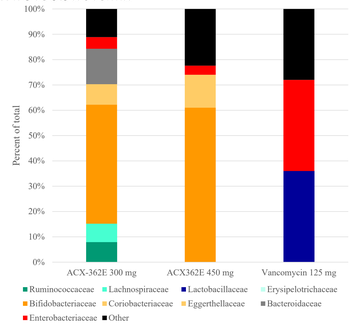
Plasma PK Multiday ascending dose



Stool PK Multiday ascending dose



Microbiome: Ibezapolstat increased proportion of Bifidobacterium vs. vancomycin which increased Proteobacteria



Phase IIa C. *difficile* clinical trial

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

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

METHODS

Proof-of-principle trial for novel MOA
- Enabling to Phase 2B segment
- Open-label treatment with Ibezapolstat
- 10 patients with mild-moderate CDI
- Dosing @ 450 mg BID x 10 days

RESULTS

Clinical Evaluation

- Primary:
  - Clinical Cure (Day 12) = **10 out of 10**
- Secondary:
  - Sustained Clinical Cure (Day 38) = **10 out of 10**

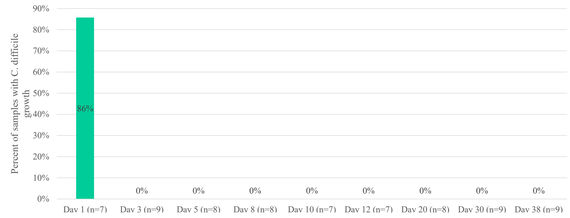
- **FIRST human validation of DNA polymerase IIIC target**

Safety evaluation

AE DESCRIPTION	INTENSITY	RELATIONSHIP
HEADACHE	MILD	UNRELATED
TEMPORAL HEADACHE	MILD	UNRELATED
MIGRAINE HEADACHE EXACERBATION*	SEVERE	UNRELATED
INTERTRIGINOUS CANDIDIASIS*	MODERATE	UNRELATED
VOMITING*	MODERATE	UNRELATED
NAUSEA*	MODERATE	UNRELATED
NAUSEA	MODERATE	PROBABLY RELATED

*4 AEs reported in the same subject

Microbiologic evaluation



CONCLUSIONS

Phase I healthy volunteer study
Safety: Ibezapolstat was found to be safe with similar adverse events to placebo

PK: Low systemic absorption, high colonic concentrations

Microbiome: Favorable microbiome signature consistent with the mechanism of action of Ibezapolstat. Ibezapolstat increased proportion of Bifidobacterium vs. vancomycin which increased Proteobacteria

Phase IIa Clinical trial
Safety: Ibezapolstat was found to be safe with minimal adverse events

PK: Confirmed low systemic absorption in CDI patient population

Clinical: Clinical cure and sustained clinical cure in all ten patients

Microbiologic: No growth of *C. difficile* after baseline cultures.

These results support the continued clinical development of ibezapolstat

FUNDING

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Acurx Pharmaceuticals

REFERENCES

Garey KW, Begum K, Lancaster C, et al. A randomized, double-blind, placebo-controlled, single and multiple ascending dose Phase 1 study to determine the safety, pharmacokinetics and food and faecal microbiome effects of ibezapolstat administered orally to healthy subjects. *J Antimicrob Chemother* 2020.

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