A Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Phase 1 Study to Determine the Safety, Pharmacokinetics, Food, and Fecal Microbiome Effects of ACX-362E Administered Orally to Healthy Subjects

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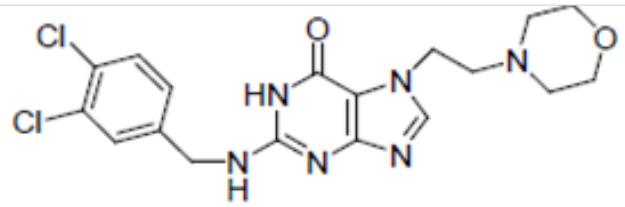
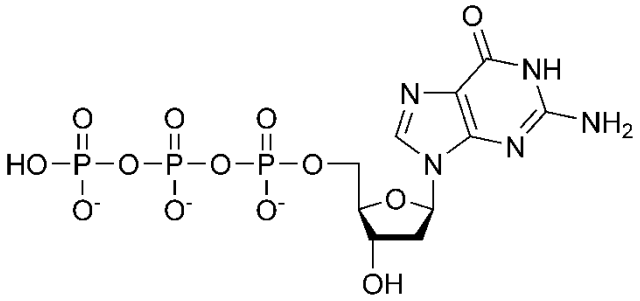
ACX-362E

Acurx Pharmaceuticals



ACX-362



dGTP

- Small-molecule inhibitor of DNA Pol IIIC enzyme based upon competitive inhibition of dGTP
  - DNA Pol IIIC
    - essential for replication of low G+C content Gram-positive bacteria
    - Pol IIIC active-site domain incorporates a unique pocket which renders it specifically susceptible to ACX-362E
- Minimally absorbed, low systemic concentrations expected

Xu et al. Bioorg Med Chem. 2019 Aug 1;27(15):3209-3217

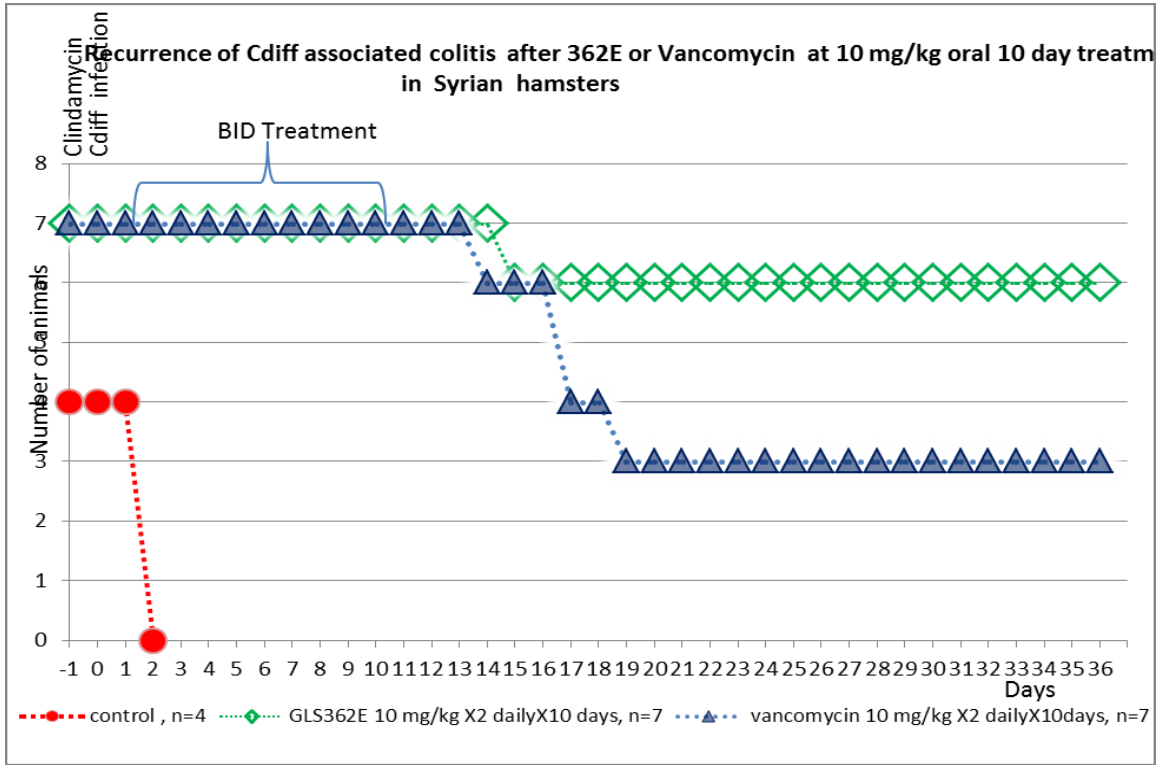
ACX-362E has in vitro/ in vivo activity against *Clostridioides difficile*

In vitro susceptibility against 96 clinical isolates

	362E	MTX	VAN	FDX
MIC range	0.5-8	0.25 - >32	0.5-16	0.03- >8
MIC_{50}	2	0.5	1	0.5
MIC_{90}	4	4	4	2

MTZ; metronidazole; VAN: vancomycin; FDX: fidaxomicin

Effectiveness in a Syrian hamster model



ACX-362E: First in human, phase I clinical trial

- **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*)

Randomized, placebo controlled, 3-part study design

	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
Comparator (n=)	Placebo (n=2)	None	Vancomycin (n=6) Placebo (n=2)
Purpose	Safety and PK (systemic and stool)	Safety and PK (systemic and stool)	Safety, PK (systemic and stool), and microbiome

PK: pharmacokinetics

Safety

Proportion of subjects with any adverse event (AE) in each study period

	Single ascending dose		Food effect	Multiple ascending dose	
Dose	*ACX-362E (n=6)*	*Placebo (n=2)*	*ACX-362E (n=8)*	*ACX-362E (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

##Fed: n=2; Fast: n=1

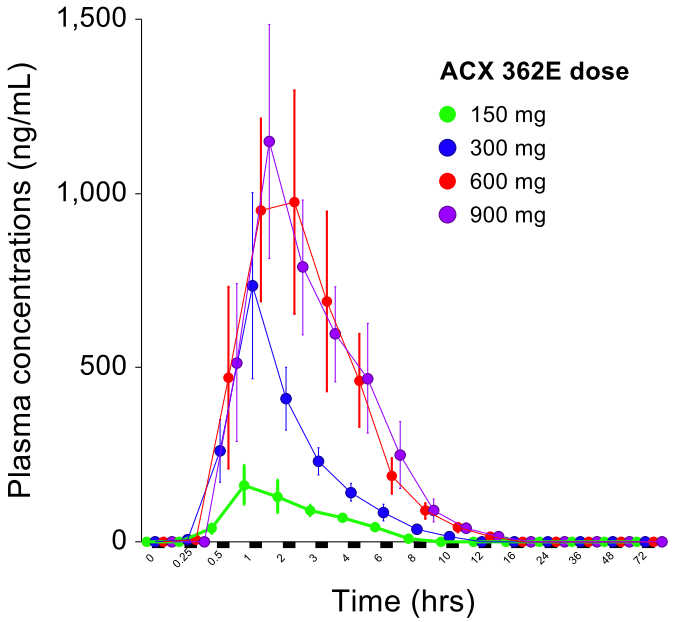
Description of adverse events from MAD study*

DOSE (mg BID x 10 D)	AE DESCRIPTION	Number of events	INTENSITY SCALE
300	COUGH	1	MILD (GRADE 1)
300	CYSTITIS-NON INFECTIVE	1	MILD (GRADE 1)
300	DIZZINESS	1	MILD (GRADE 1)
300	EPIGASTRIC PAIN*	1	MILD (GRADE 1)
300	HEADACHE*	3	MILD (GRADE 1)
300	HEADACHE	1	MODERATE (GRADE 2)*
300	NASAL CONGESTION	1	MILD (GRADE 1)
300	TWITCHING SENSATION	1	MILD (GRADE 1)
450	DYSPEPSIA*	1	MILD (GRADE 1)
450	NAUSEA*	1	MILD (GRADE 1)
450	PROLONGED PR INTERVAL*	1	MILD (GRADE 1)
450	SHORTNESS OF BREATH*	1	MILD (GRADE 1)
450	TACHYCARDIA*	1	MILD (GRADE 1)

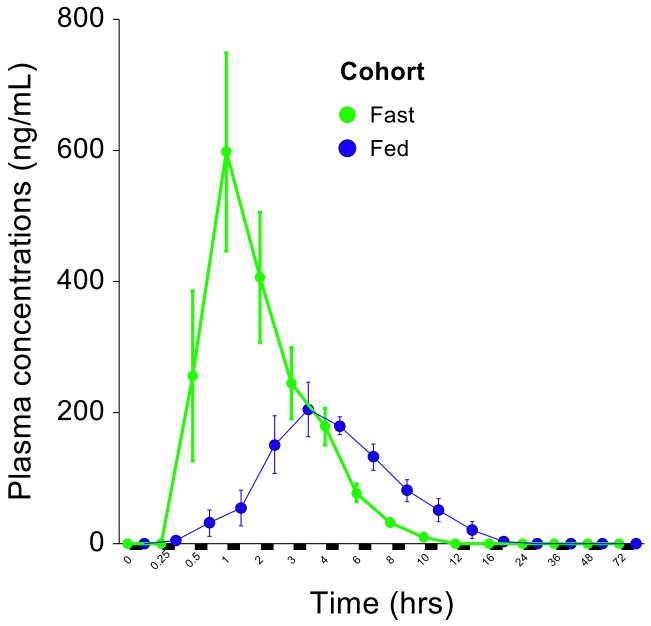
*Possibly or probably related
No AE required a change in therapy or intervention
AEs in placebo group (n=2): Headache, rash, left hand ecchymosis

Plasma Pharmacokinetics

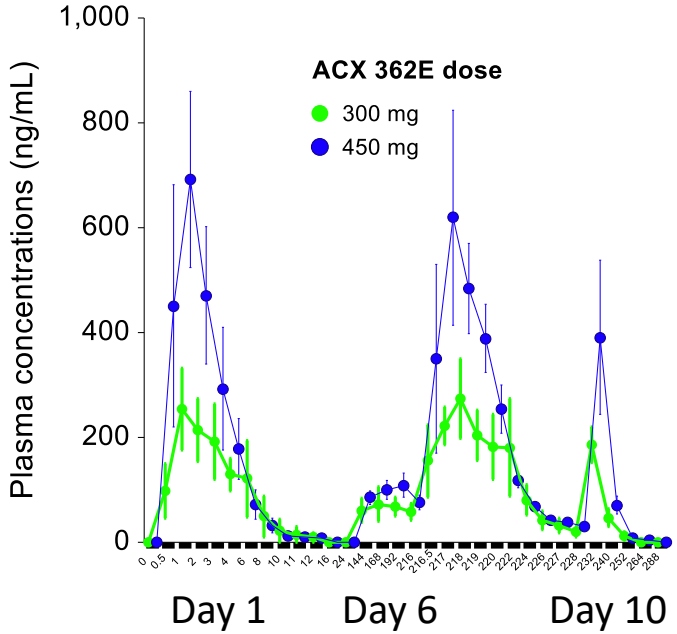
Single ascending dose



Food effect (ACX-362E 300 mg)

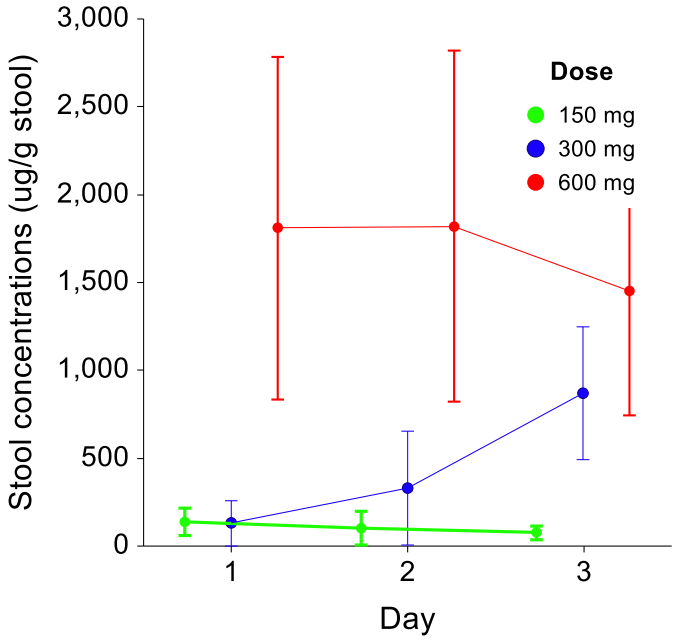


Multiday ascending dose

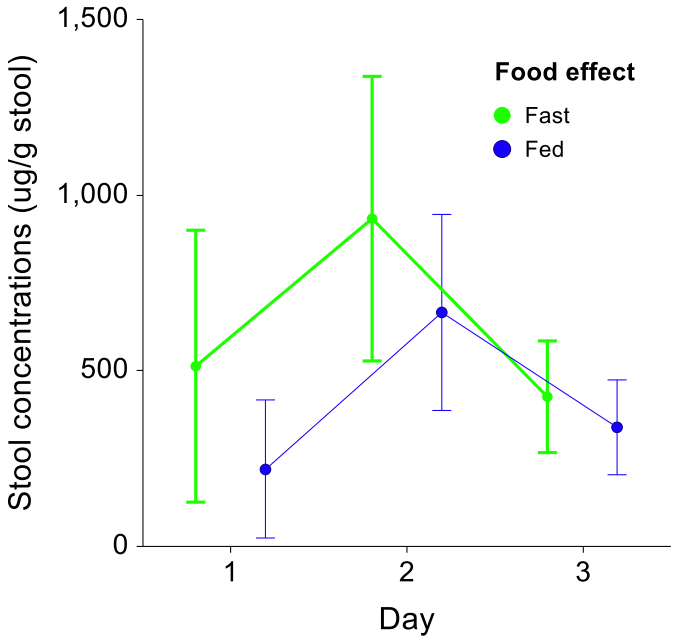


Stool pharmacokinetics

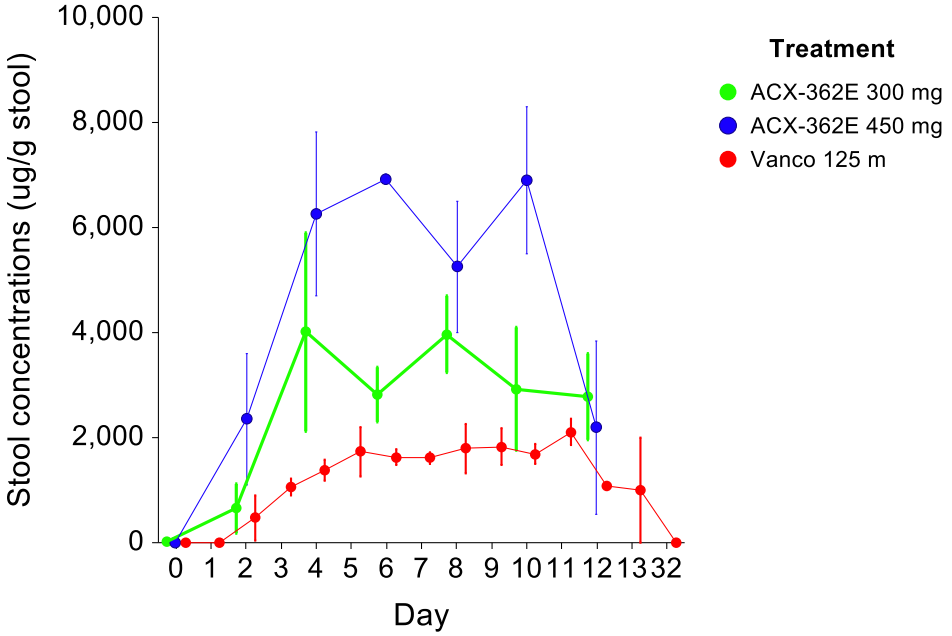
Single ascending dose



Food effect (ACX-362E 300 mg)



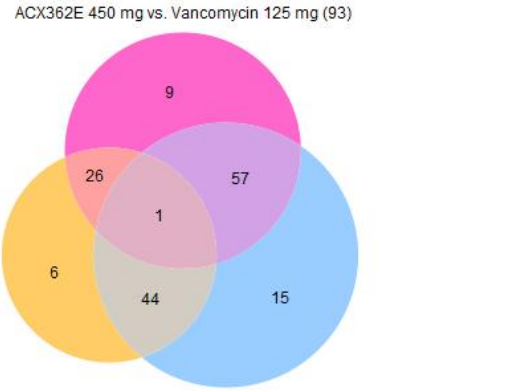
Multiday ascending dose



Metagenomics: Differential abundance & beta diversity

Day 0

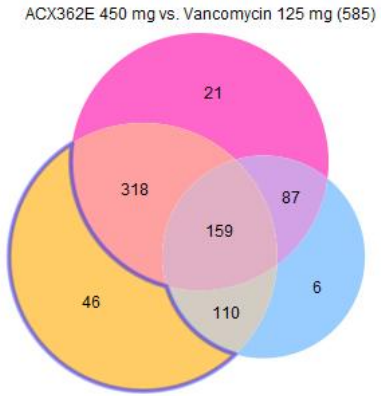
P=0.70



P=1.0 P=1.0

Day 5

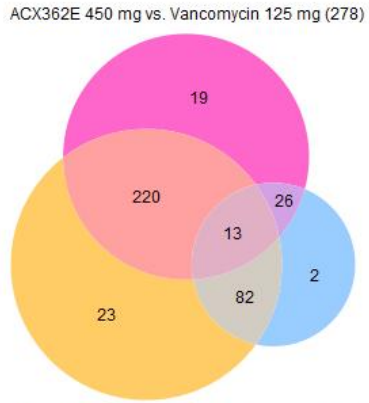
P=0.2



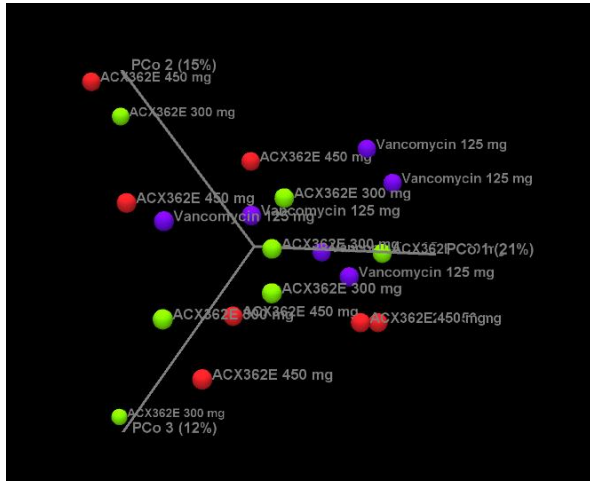
P=0.70 P=1.0

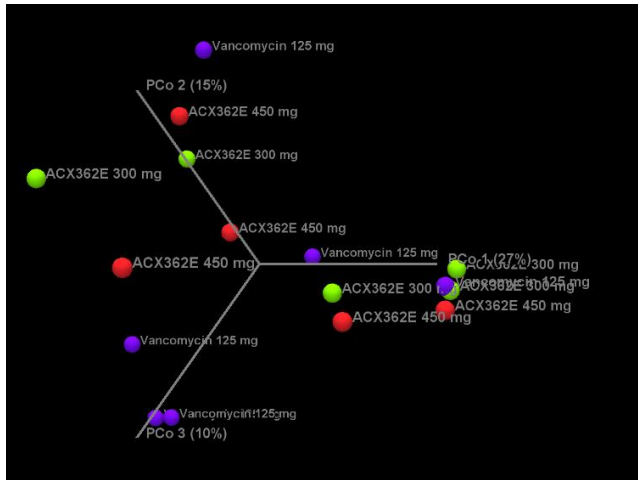
Day 10

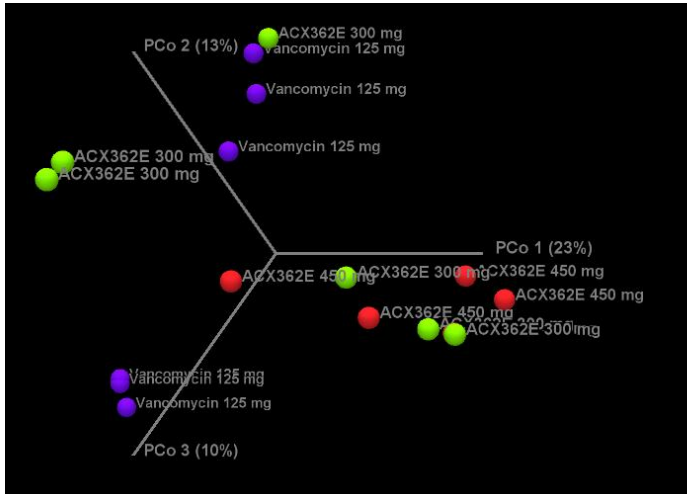
P=0.006



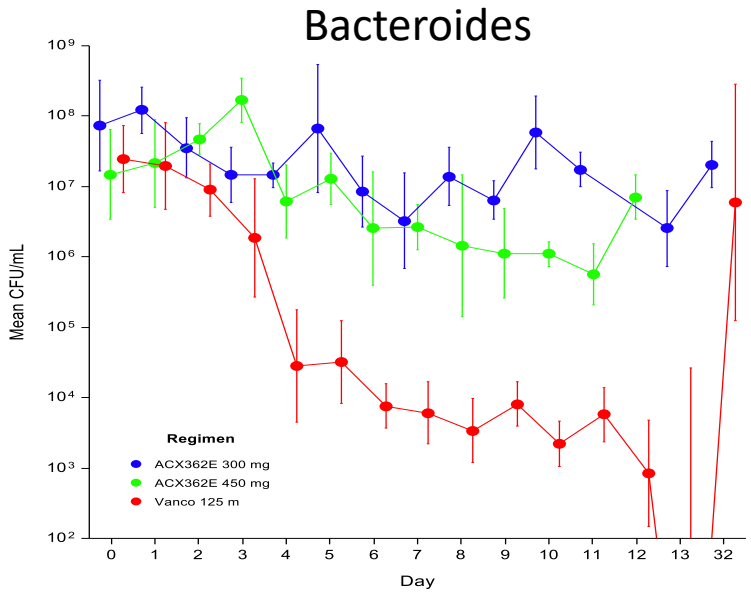
P=0.006 P=0.66

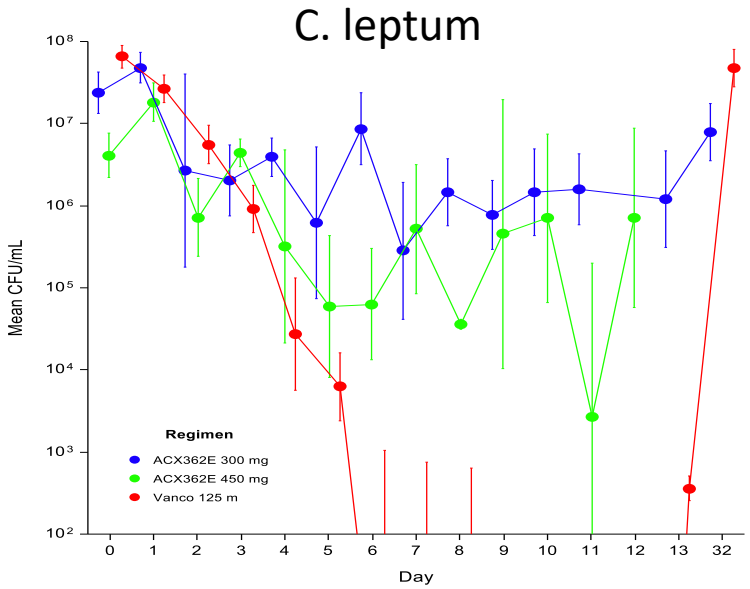


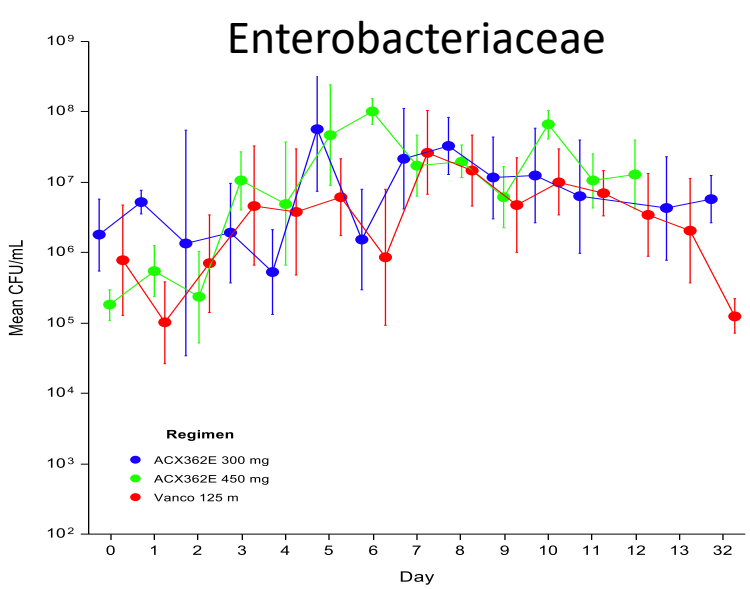


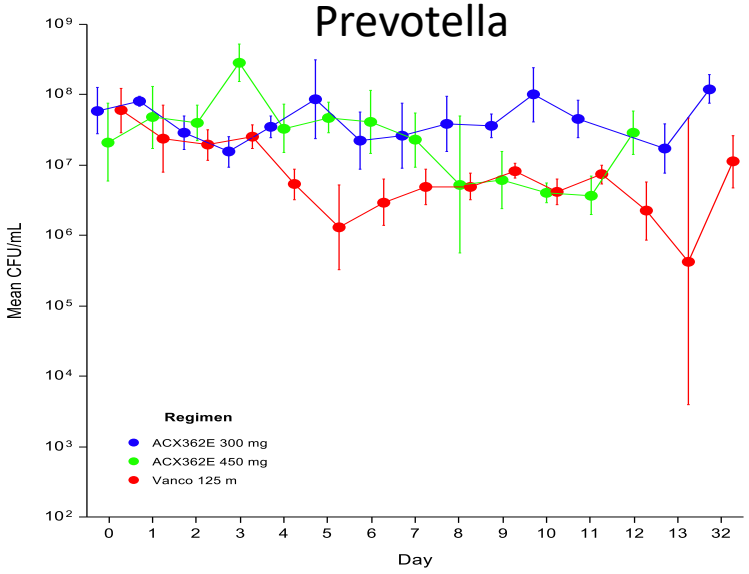


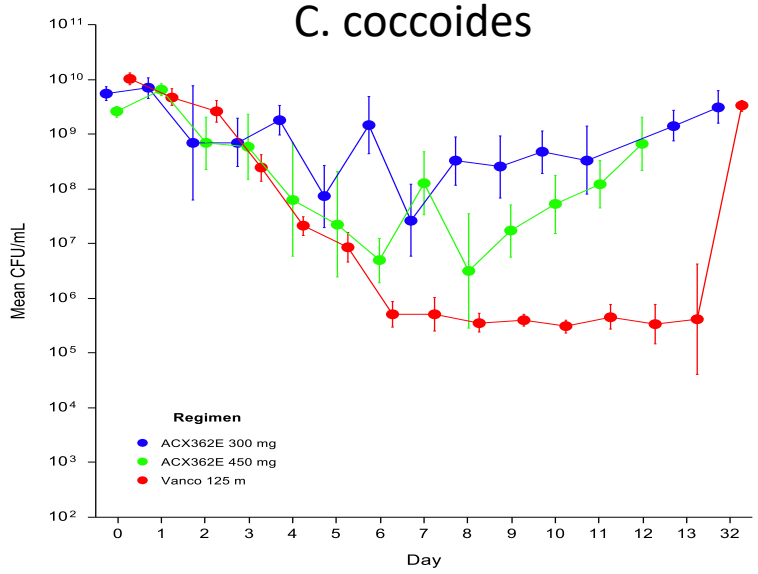
Microbiome analysis (qPCR): Microbiota levels belonging to different taxonomic groups

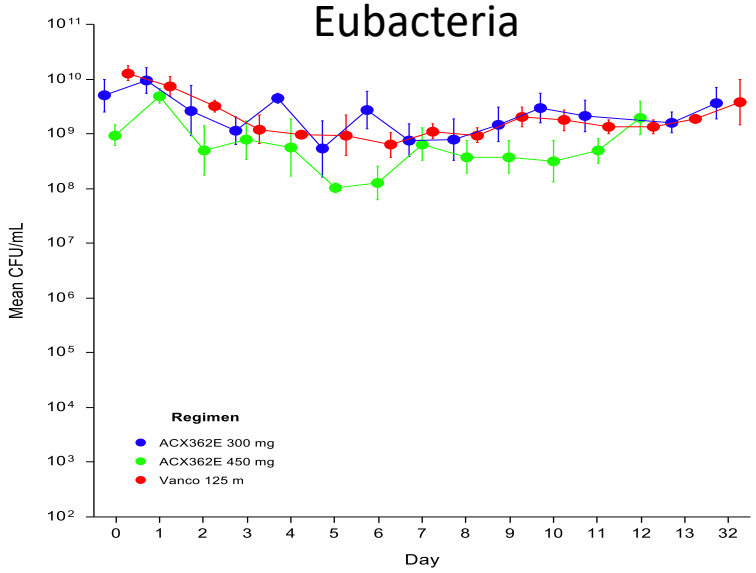












Conclusions: ACX-362E Phase I Clinical Trial

- No safety signals observed
  - AEs were well tolerated, similar to placebo, and transitory
- Ideal pharmacokinetics for a *C. difficile* antibiotic
  - Low systemic concentrations below 1 ug/mL
  - Fecal levels several fold higher than the MIC of *C. difficile* (4,000-6,000 ug/g stool)
- Favorable microbiome profile with less disruption to microbiota than vancomycin
  - Results largely driven by decreased killing of Bacteroidetes and Firmicutes
- Results support continued development of ACX-362E

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