#2002
Tue 12/6/22

Phase 2 Clinical Trial Design for CRS3123, a Novel Narrow-Spectrum Agent in Development to Treat *C. difficile* Infections

Urs A. Ochsner[1], Joshua Day[1], Wendy Ribble[1], Teresa Hoang[1], Cliff Mason[1], Katherine Johnson[1], Xicheng Sun[1], Stacie Bell[1], Vicki Abbas[1], Mary A. DeGroote[1], Thale C. Jarvis[1], Jon Bruss[2], Nebojsa Janjic[1]

[1]Crestone, Inc., Boulder, CO; [2]Alarus Development International, Pagosa Springs, CO, USA

ABSTRACT

Clostridioides difficile **infection (CDI) remains the leading cause of hospital-associated diarrhea and is increasingly seen in the community, particularly among the elderly. Disruption of healthy gut microbiota, typically from use of broad-spectrum antibiotics, is a major predisposing factor for CDI. Infection occurs via spores that are abundant in the environment and, after germination in the gut, produce disease-causing toxins. CDI treatment has been dominated by broad-spectrum antibiotics such as metronidazole and vancomycin which are associated with recurrence rates as high as 40%. Narrow spectrum agents such as CRS3123 hold much promise as improved treatment options for CDI.**

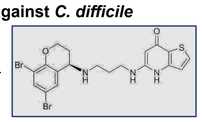
CRS3123 is a novel small molecule that inhibits methionyl-tRNA synthetase. As a protein synthesis inhibitor, CRS3123 blocks *C. difficile* growth, toxin production and spore formation. CRS3123 was found to be safe and well-tolerated in Phase 1 trials. Fecal concentrations reached levels of 1000 µg/ml, with very limited systemic uptake. CRS3123 exhibited minimal perturbation of normal intestinal microbiota. No effects of CRS3123 were observed against important commensal anaerobes including Bacteroides, Bifidobacteria and commensal Clostridia. The narrow spectrum of CRS3123 is largely explained by the phylogeny of the MetRS target, which exists in at least two types. Only bacteria with the type 1 enzyme are susceptible, which includes *C. difficile*. In contrast, bacteria with the type 2 enzyme are not affected by CRS3123, and this includes all Gram-negative bacteria.

A Phase 2 clinical study is ongoing at sites in the USA and in Canada, enrolling patients with either a primary episode or first recurrence of CDI. Treatment arms are CRS3123 200 mg PO BID, CRS3123 400 mg PO BID, and vancomycin 125 mg PO QID. Patients are treated for 10 days and followed for an additional 60 days post-treatment to assess the safety and efficacy and Health-Related Quality of Life outcomes of CRS3123. Exploratory endpoints include evaluation of the effects of CRS3123 on the microbiology, fecal biomarkers of inflammation, the metabolome and the microbiome.

CRS3123 Exhibits Key Attributes for an Optimal CDI Therapeutic

Excellent potency against *C. difficile*

- Novel structure
- MIC_{90} = 1 µg/mL
- Activity against hypervirulent strains (ribotypes 027, 078)
- Narrow spectrum with high specificity for *C. difficile*



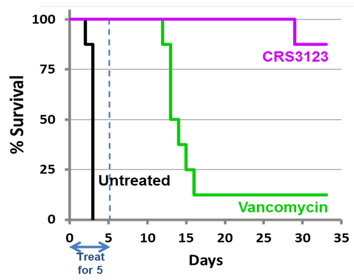
Novel mode of action: MetRS (protein synthesis)

- Inhibition of growth
- Inhibition of toxin production
- Inhibition of sporulation
- No pre-existing resistance
- No induction of resistance to other antibiotic classes

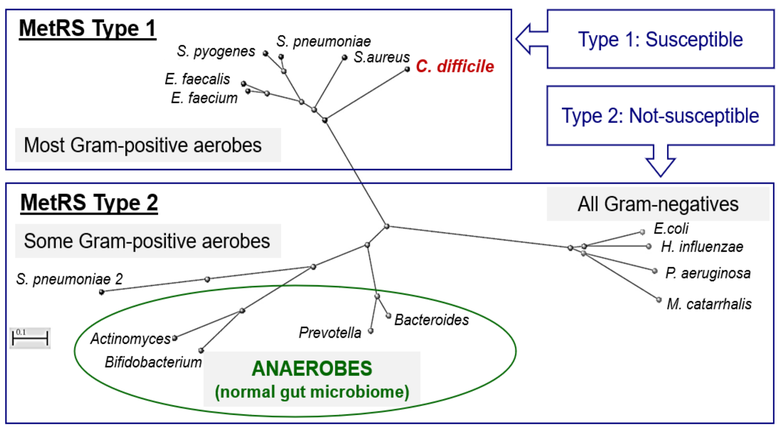
CRS3123 Is Superior to Vancomycin *In Vivo* (Hamster)

Golden Syrian hamster model

- Hamsters pretreated with clindamycin (day -1)
- One day later, hamsters inoculated with *C. difficile* ATCC 43596 (day 0)
- High inoculum model (1.6 x 10^7 CFU per hamster)
- Oral dosing commences the following day (day 1) BID for 5 days
- More than 99% of CRS3123 remains in the gut



Phylogeny of MetRS Explains the Spectrum of Activity of CRS3123)



CRS3123: Safe and Well-Tolerated in Phase 1 Clinical Trials

Single Ascending Dose (DMID10-0008)

- 5 cohorts: 100, 200, 400, 800, 1200 mg; 8 subjects per cohort (6 active, 2 placebo)
- https://clinicaltrials.gov/ct2/show/NCT01551004

Multiple Ascending Dose (DMID10-0009)

- 3 cohorts: 200, 400, 600 mg; 10 subjects each (8 active, 2 placebo, BID dose for 10 days
- https://clinicaltrials.gov/ct2/show/NCT02106338

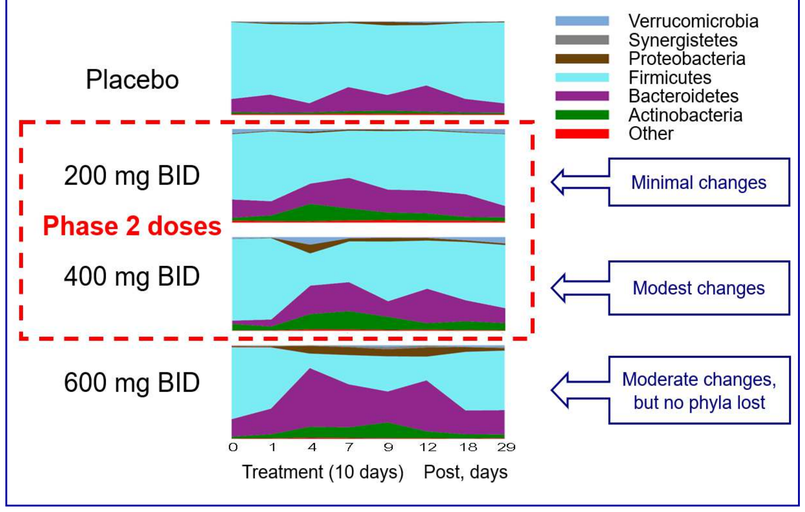
Most adverse events mild, no serious adverse events

Low impact on gut microbiome

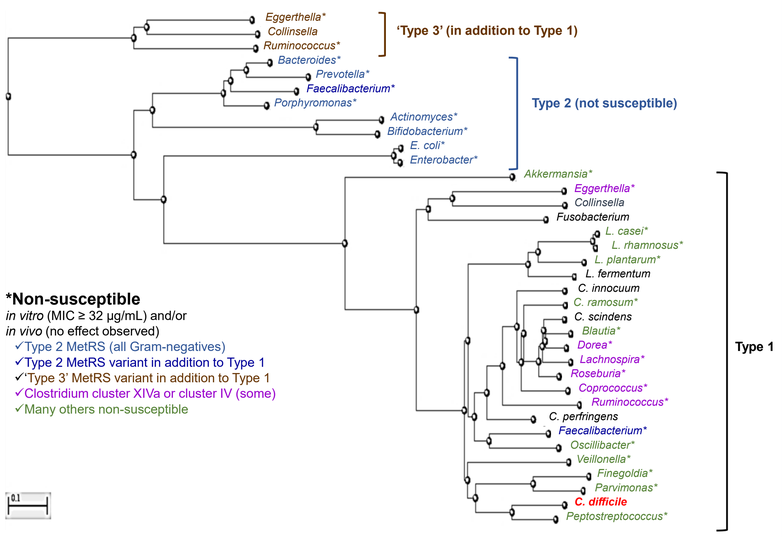
- High selectivity confirmed in human gut
- High concentrations of CRS3123 observed in gut
- Low systemic exposure

Results warranted progression to Phase 2 with favorable drug profile

Effect of CRS3123 on Normal Gut Microbiota (Phase 1 MAD Study)



MetRS Phylogeny and Types in Normal Gut Microbiota

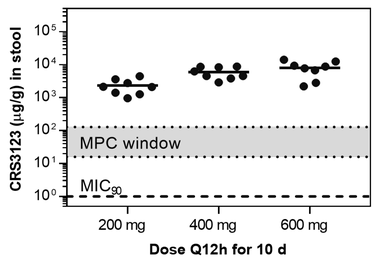


High Levels of CRS3123 Attained In the Gut

CRS3123 levels (Phase 1 data)

- More than 1000-fold above MIC (good for efficacy)[1]
- More than 10-fold above MPC (good for preventing resistance)[2]
- Informed dose selection for Phase 2 study

[1]MIC: minimum inhibitory concentration
[2]MPC: mutant prevention concentration



Phase 2 Protocol Overview and Trial Design

Phase 2 Study 19-0021: A Randomized, Double-Blind Evaluation of CRS3123 Versus Oral Vancomycin in Adult Patients with *C. difficile* Infection

Participants randomized 1:1:1 into 3 treatment arms

- Treatment Arm A (n = 30-36): CRS3123 200 mg PO BID
- Treatment Arm B (n = 30-36): CRS3123 400 mg PO BID
- Treatment Arm C (n = 30-36): Vancomycin 125 mg PO QID

Treatment period: 10 days

30 sites (USA and Canada)

N = 90-108 patients

Phase 2 Trial: Inclusion/Exclusion Criteria

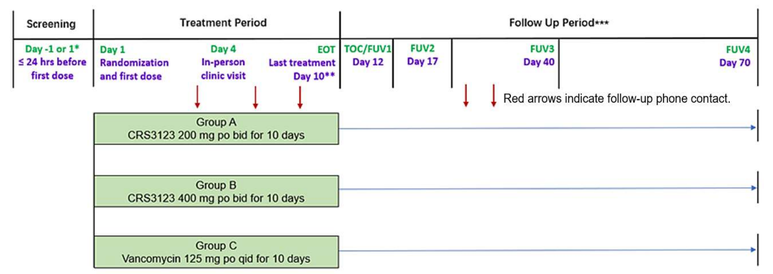
Key Inclusion

- Adults ≥ 18 years of age
- Participants with a primary episode or first recurrence of CDI are eligible
- Stool positive for *C. difficile* GDH **plus** toxin A and/or B, using the Abbott/Alere QUIK CHEK COMPLETE or any other FDA-approved toxin test

Key Exclusion

- Inflammatory bowel disease
- Recent CDI episode within 3 months non-responsive to vancomycin
- Life-threatening CDI
- Immunodeficiency
- Severe hepatic impairment

Phase 2 Study Design Schematic



Phase 2 Study Endpoints

Primary Endpoints

- Rate of clinical cure at test-of-cure
- Safety and tolerability of CRS3123

Secondary Endpoints

- Rate of clinical cure (Day 12-14)
- Rate of total relief of symptoms of CDI
- Time to resolution of diarrhea
- Rate of recurrence of CDI (through FUV4)
- Rate of global cure (no recurrence)

Exploratory Endpoints

- Quantitative *C. difficile* toxin production
- Vancomycin-resistant *Enterococcus* (VRE) culture and identification
- *C. difficile* spore enumeration
- *C. difficile* culture and antimicrobial susceptibility testing
- PCR Ribotyping
- Toxin A/Toxin B titer by cell culture neutralization assay (CCNA)
- Effects of treatment on fecal inflammation biomarkers
- Effects of treatment on fecal microbiome
- Metabolomics

SUMMARY AND CONCLUSIONS

CRS3123

- Narrowest spectrum – like precision medicine
- Selective inhibition of *C. difficile* → *faster recovery of gut microbiota?*
- Inhibition of toxin production → *reduced disease severity?*
- Inhibition of spore formation → *reduced recurrence?*

Why another *C. diff.* drug?

- Improved patient outcomes
- More options for physicians to treat *C. diff.* patients
- Improved economics of CDI therapy
- Potential for shorter hospital stays, fewer re-admissions, fewer clinic visits

ACKNOWLEDGMENTS

Funding:
NIAID Contracts HHSN272200800026C (Phase 1) and 75N93056C00019 (Phase 2, ongoing)

References:

Critchley *et al.* (2009). J Antimicrob Chemother 63, 954-963.
Ochsner *et al.* (2009). J Antimicrob Chemother 63, 964-971.
Citron *et al.* (2009). J Antimicrob Chemother 63, 972-976.
Nayak *et al.* (2017). Antimicrob Agents Chemother 61:e02760-16.
Lomeli *et al.* (2019). Antimicrob Agents Chemother 64:e01395-19.