

CRS0540: Oral/IV Gram-positives CRS3123: *C. difficile* Infection CRS3123 is in Phase 2 development for the treatment of C. difficile infection CRS0540 is in IND-enabling preclinical development as a novel oral/IV agent for the treatment of Gram-positive infections, including those caused by antibiotic-(CDI), enrolling patients (trial registration: NCT04781387). CRS3123 is a diaryldiamine that inhibits methionyl-tRNA synthetase (MetRS) and thereby resistant pathogens such as MRSA, PRSP, and VRE. CRS0540 is a thiadiazole blocks growth (MIC₉₀=1 μ g/mL), toxin production, and sporulation. Its low oral urea compound that inhibits PoIC, the catalytic subunit of the DNA polymerase bioavailability results in little systemic exposure but high accumulation (>1,000 essential for DNA replication. It is a bactericidal agent with no pre-existing µg/g) in the gut, where the drug exerts its action. CRS3123 demonstrated a resistance and a low (10⁻⁹) spontaneous resistance frequency. CRS0540 has favorable safety profile in Phase 1 SAD/MAD studies. An attractive feature of demonstrated efficacy in several mouse models, including MRSA soft tissue and CRS3123 is its narrow spectrum of activity due to the phylogeny of the MetRS bloodstream infection, pneumococcal and MRSA lung infection, and an anthrax nasal challenge model. AUC/MIC is the PK/PD index. Fig. 2. Efficacy in the CDI Hamster Model Fig. 6. Pharmacophore Structure of CRS0540, a Guanosine Mimic, and co-Crystal Structure of PolC with DNA-primer Template and Bound Natural Substrate dGTP 100 **Guanosine Mimic CRS3123** Lipophilic Surface Pocket in PolC Bindine LHS 50 RHS 25 CRS3123 Untreated Vancomycin donors acceptor RNA 30 20 25 10 15 35 Days Fig. 7. Activity of CRS0540 Against Drug-resistant Gram-positive Pathogens for 5 Minimum Inhib Strain CRS0540 S. aureus NRS384 (CA-MRSA, PVL+) S. aureus NRS119 (Levo-R, Lzd-R) Type 1: Susceptible S. epidermidis NRS8 (MRSE) S. pneumoniae \sim S.aureus S.aureus C. difficile S. pyogenes 🔍 S. pyogenes F758883 (Azi-R) 5. pneumoniae MDR-1 (PRSP, MDR) E. faecalis S. pneumoniae F1064366 (Levo-R) E. faecium Type 2: Not-susceptible E. faecalis F1111404 (VRE) E. faecium F1111434 (VRE) L. monocytogenes ATCC 15313 0.5 NT B. anthracis Ames All Gram-negatives Fig. 8. Efficacy of CRS0540 in Mouse Models of Infection E.coli MRSA (Tissue) P. aeruginosa M. catarrhalis CRS0540 Bacteroides Prevotella 💻 Untreated Actinomyces* Bifidobacterium **ANAEROBES** (normal gut microbiome) 200 mg/kg (2h, 14h) MRSA (Blood) Fig. 4. Effect of CRS3123 on Normal Gut Microbiota (Data from Phase 1 MAD Study) /errucomicrobia 100 mg/kg (1h, 5h) Synergistetes Proteobacteria CRS0540 Placebo Firmicutes Untreated Bacteroidetes Actinobacteria 200 mg BID Minimal changes Phase 2 doses **Days Post Infection** 400 mg BID Modest changes Fig. 9. CRS0540 Concentration-Time Profiles and Time-Kill Curves Against Intracellular Listeria monocytogenes Growing in Macrophages in a Hollow Fiber System 600 mg BID Moderate changes, but no phyla lost ----- R2 10000-— R4 8000--o- R5 --- R6 --- R7 0 1 4 7 9 12 18 29 6000-Treatment (10 days) Post, days 4000-2000 10 12 14 16 18 20 22 2 Time in hours Follow Up Period*** Treatment Period TOC/FUV1 FUV2 Fig. 10. Multi-organism (S. aureus) PK/PD Target Studies with CRS0540 Day 12 Day 17 Day 70 Day 40 Randomization In-person Last treatment Day 10** and first dose clinic visit Emax 6.50 ED50 116 N 1.25 R² 0.94 Red arrows indicate follow-up phone contact. Group A CRS3123 200 mg po bid for 10 days _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Group B CRS3123 400 mg po bid for 10 days Group C

target, which largely spares the beneficial gut microbiota.









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Addressing the AMR Challenge: Antibiotics with a Novel Mode of Action in Development to Treat Infections Caused by C. difficile, Gram-positive Pathogens, and Mycobacteria

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fAUC/MIC





itory Concentration, MIC (µg/mL)						
TET	GENT	LZD	VANC	IMI		
>16	≤0.25	2	0.5	8		
>16	>16	>16	1	>16		
0.5	>16	1	8	0.5		
>16	4	1	≤0.25	≤0.25		
>16	>16	0.5	≤0.25	1		
>16	16	1	≤0.25	≤0.25		
0.5	>16	2	>16	4		
>16	>16	2	16	>16		
NT	NT	NT	NT	NT		
NT	NT	NT	NT	NT		
	Concent TET >16 >16 0.5 >16 >16 >16 0.5 >16 0.5 >16 NT NT	Concentration, N TET GENT >16 ≤0.25 >16 >16 0.5 >16 >16 4 >16 >16 >16 16 >16 >16 >16 >16 17 >16 NT NT NT NT	Concentration, WIC (µg/m TET GENT LZD >16 ≤0.25 2 >16 >16 >16 0.5 >16 1 >16 4 1 >16 >16 0.5 >16 16 1 >16 >16 1 >16 >16 1 >16 >16 2 >16 >16 2 NT NT NT NT NT NT	Concentration, WIC (μ g/mL)TETGENTLZDVANC>16 ≤ 0.25 20.5>16>16>1610.5>1618>1641 ≤ 0.25 >16>160.5 ≤ 0.25 >16161 ≤ 0.25 >16161 ≤ 0.25 0.5>16216>16NTNTNTNTNTNTNT		





Lung Emax 6.0 ED50 10.4 R² 0.85 _____

fAUC/MIC

CRS039
CRS0393 is a benzothiazo TB infections. It is a back transporter essential for ce potent <i>in vitro</i> activity again and is also active against effective in killing intracellu indicate that CRS0393 is a was well tolerated and eff <i>abscessus</i> , with a >3 Log ₁₀
Fig. 11. Synthesis of Lead Co
CI S NH_2 HO HO E
Fig. 12. MIC Profiles of CRS03 Over 100 analogs of CRS03 CRS0393 is the lead comport CRS0470 is the amine vers CRS0482 is a des-methyl vers CRS0499 has improved action
Species
Rapid growers <i>M. abscessus</i> ATCC 19977 <i>M. abscessus</i> 1 <i>M. abscessus</i> 21 <i>M. abscessus</i> 79 <i>M. abscessus</i> 103 <i>M. abscessus</i> massiliense 119 <i>M. chelonae</i> 93 <i>M. fortuitum</i> 41
<i>M. peregrinum</i> ATCC 700686 Slow growers ^b
<i>M. avium</i> 101 <i>M. intracellulare</i> 1956 <i>M. chimera</i> 1501948
 ^a Range of 9 test occasions (different b ^b 7H9 medium used for MIC testing of s the compounds, MIC values measure Mueller-Hinton broth used according t
Fig. 13. PK Profiles of CRS03
1000000
Centration (ng/g) 000001 (ng/g) (00001 (ng/g))
$1\frac{1}{0}$ 5 10
Tim
Fig. 14. Efficacy of CRS0393 / Intracellular <i>M. absce</i> THP-1 Macrophages
$ \begin{array}{c} \bullet & 64 \ \mu g/mL & \bullet & 4 \ \mu g/mL \\ \hline \bullet & 32 \ \mu g/mL & \bullet & 2 \ \mu g/mL \\ \hline \bullet & 16 \ \mu g/mL & \bullet & 1 \ \mu g/mL \\ \hline \bullet & 8 \ \mu g/mL & \bullet & Control (control) \\ \end{array} $
abscessus CFU/mI
≥ 0 0 1 Davs
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3: NTM/TB Infection

le amide in preclinical development to treat NTM and tericidal agent targeting MmpL3, a mono-mycolate ell wall biosynthesis in mycobacteria. CRS0393 has nst rapid-grower NTM (MIC range ≤0.03 - 0.5 µg/mL) M. avium and M. tuberculosis. CRS0393 was found ular mycobacteria in human macrophages. PK data suitable for oral or inhaled administration. CRS0393 ficacious in a mouse lung infection model with M. reduction in CFU.



393 and Closely Related Backup Compounds. 393 have been generated and analyzed for antimicrobial activity. ound for development

sion of CRS0393, on average 2-fold less active. version of CRS0393 and is equally active against rapid-growers. tivity against slow-grower NTM strains.

CRS0393 ^a	CRS0470	CRS0482	CRS0499
0.015-0.06	0.06	0.03-0.06	0.12
0.03-0.12	0.03-0.12	0.03-0.06	0.12
0.015-0.06	0.03-0.06	0.015-0.03	0.12
0.03-0.06	0.06-0.12	0.03-0.06	0.06
0.015-0.25	0.06-0.5	0.015-0.25	1
0.03-0.12	0.06-0.5	0.03-0.12	0.5
0.015-0.25	0.015-0.5	0.03-0.12	0.25
0.06-0.25	0.25	0.12-0.25	0.25
0.015-0.12	0.015-0.06	0.03-0.25	0.12
2-4	2	16	0.5
2-4	1	>64	0.5

2-4 patches tested at different dates)

slow-grower NTM contains 5 mg/mL albumin. Due to the high protein binding of ed in this 7H9 broth for slow grower NTM tend to be several-fold higher than in to CLSI for rapid grower NTM.

0.5





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