CRS3123: A Narrow Spectrum Agent for Treatment of *C. difficile* Infection (CDI)

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CRS3123 is a methionyl-tRNA synthetase inhibitor in development for treatment of *Clostridioides difficile* Infection (CDI). It exhibits excellent biochemical potency (K_i = 20 pM vs *C. difficile* MetRS) and is highly selective for Type 1 MetRS. This target selectivity imparts an exceedingly narrow spectrum which spares commensal gut flora while markedly inhibiting *C. difficile* growth, toxin production and spore formation. Target selectivity furthermore contributes to its excellent safety profile in Phase 1 and Phase 2 human clinical studies. CRS3123 inhibits formation of methionyl-adenylate and demonstrates competitive inhibition with the methionine substrate and uncompetitive (co-operative) inhibition with the ATP substrate. We have solved the three-dimensional structure of CRS3123 and a non-hydrolyzable ATP analog bound to CDMetRS. The ternary complex elucidates the structural basis for the narrow spectrum of CRS3123 and features an induced fit spanning two adjacent hydrophobic binding pockets on MetRS. CRS3123 showed minimal perturbation of normal gut flora in healthy human subjects in Phase 1 studies. In recently completed Phase 2 studies, CRS3123 showed promising results with comparable clinical cure rates at the test of cure visit at day 12 in all three treatment groups in the Intent to Treat population, including 28/29 (97%) in patients receiving one of two dosage levels of CRS3123 versus 13/14 (93%) in those receiving vancomycin. In addition, CRS3123 exhibited exceptionally low rates of recurrence. We will present an update on this novel agent focusing on unpublished data ranging from the structural underpinnings of narrow spectrum to exciting topline data from Phase 2. CRS3123 has the potential to become the next-generation CDI treatment option, reducing the use of vancomycin to treat CDI. Experts in the field consider vancomycin as a suboptimal drug to treat CDI due to its broad-spectrum of activity and its propensity to generate vancomycin-resistant enterococci (VRE), contributing to the AMR problem.