Abstract 647
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DDS-01 (SMT-571) : The Development of a Novel Oral Antibiotic to Treat Multi-Drug Resistant *Neisseria gonorrhoeae*

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Background: The emergence and spread of multidrug resistance to antibiotics used to treat gonorrhea infection has resulted in a dramatic loss of effective regimens for the condition. Currently, the extended spectrum cephalosporins (ESCs), ceftriaxone (injectable) and cefixime (oral), are the only viable monotherapy options available. Summit is developing a novel first-in-class oral antibiotic, with activity effective against the Gram-negative bacterial pathogen, *Neisseria gonorrhoeae*, the causative agent of the sexually transmitted infection gonorrhoea. Key to the successful treatment of *N. gonorrhoeae* infections will be new and diverse antibiotics. This new class, with its activity profile and novel MoA, has potential advantages over current and novel therapies. The lead candidate, SMT-571, was chosen because of its potential to satisfy the Target Product Profile (TPP), recommended by the World Health Organization (WHO) and Drugs for Neglected Disease initiative (DNDi)[1], for an oral agent to treat gonorrhea, including multi-drug resistant strains.

Methods: Agar-based MICs were established according to CLSI guidelines with ceftriaxone as a comparator. Agar MICs and mutational frequencies were performed using WHO *N. gonorrhoeae* reference strains. *In vitro* kill kinetic assays were conducted in broth using the multi-drug resistant clinical isolate [WHO-M]. *In vitro* ADME and toxicological assays were run using standardised protocols internally and with established service providers. Intravenous and oral PK studies were performed in CD-1 mice.

Results:

- SMT-571 returned agar dilution MICs of 0.09 µg/mL across a selection of isolates from the WHO *N. gonorrhoeae* reference panel and was not influenced by pre-existing resistance mechanisms.
- A panel of 91 clinical isolates, accessed through NIAID preclinical services, returned an MIC range of 0.1-0.2 µg/mL.
- The series is rapidly bactericidal and displays very low levels of mutational frequency (<8.2 x 10^{-10} @ 4 x MIC) with no mutants identified after 144h at 4 x MIC.

Microbiology

	SMT-571										CTX
ACTIVITY	FA1090	WHO-M	WHO-L	WHO-N	WHO-O	WHO-G	WHO-F	WHO-K	WHO-P	WHO-X	
MIC (µM)	0.35	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	5
MIC (µg/mL)	0.08	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	2.8

Table 1: SMT-571 is active against multi-drug resistant *N. gonorrhoeae* clinical isolates (WHO Panel)

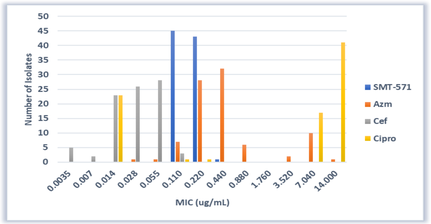


Figure 1: MIC determination across a panel of clinical isolates of *N. gonorrhoeae* (NIAID preclinical services)

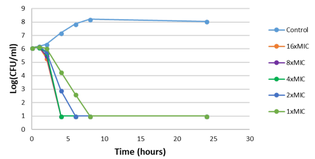


Figure 2: Time kill studies confirmed a rapid bactericidal killing profile against the clinical strain WHO-M

SMT-571 Frequency of Resistance (48h)	
WHO-M	<8.2 x 10^{-10} @ 4 x MIC
WHO-V	<3.1 x 10^{-10} @ 4 x MIC
WHO-X	<8.7 x 10^{-10} @ 4 x MIC

Table 2: SMT-571 Demonstrates a low propensity to resistance generation

ADMET & Pharmacokinetics

RBC	Cytotox	Mitotox	GSH (50µM)	Ames (25µM)	hERG (IC_{50})	human Hep Stability (µL/min/10^6 cells)
>200µM	>100µM	Negative	Negative	Negative	>25µM	2.9 86% @ 120min

Table 3: SMT-571 exhibits a clean toxicological profile with low metabolism

Isoform	CYP3A4	CYP2C8	CYP2C9	CYP2B6	CYP2D6	CYP1A2	CYP2C19
IC_{50} (µM)	>25 µM	>25 µM	>25 µM	>25 µM	>25 µM	>25 µM	>25 µM

Table 4: No Cytochrome P450 inhibition liabilities identified for SMT-571

Species	%PPB
Mouse	78
Rat	54
Dog	63
Human	84

Table 5 : SMT-571 has good PPB across species

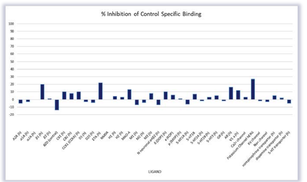
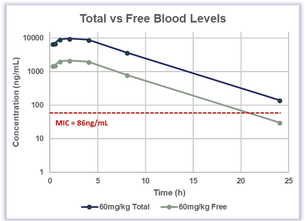


Figure 3: CEREP panel confirms a reduced likelihood of polypharmacology

Table 6: SMT-571 exhibits good Oral PK properties

Species	%F	Cl (mL/min/kg)	Vd (L/kg)	$T_{1/2}$ (h) (IV)	$T_{1/2}$ (h) (PO)	C_{max} (PO) (ng/mL)
CD-1 Mouse	96	17	0.6	0.5	2.0	3017



T>MIC (h)	PO Cmax (ng/ml)	Cmax/ MIC	PO AUC_{0-last} (ng/ml)	AUC/MIC *(fAUC/MIC)*
24	10577	123	90967	1058 (233)

Figure 4: A single oral dose (60mg/kg) of SMT-571 in mice demonstrates coverage of each pharmacodynamic index up to 24h

- SMT-571 has a clean toxicological profile in mammalian haemolysis assays and cytotoxicity assays including HepG2 and mitotoxicity.
- Is negative in Ames assays (S*almonella* and *E. coli*) and no adducts were observed in a glutathione incubation assay in the presence or absence of S9 fraction.
- The compound exhibits good metabolic stability across mouse, rat and dog with a human intrinsic clearance value of 2.9 µL/min/10^6 cells.
- The compound displayed no inhibition against all major cytochrome P450 isoforms with no significant binding being reported at 10µM across a CEREP safety panel.
- Plasma protein binding across mouse, rat, dog, and human species ranged from 54-84% bound.
- SMT-571 displays a highly desirable pharmacokinetic profile in support of oral administration. Following IV/PO dosing in mice (1mg/kg and 10mg/kg respectively Figure 7), SMT-571 was highly orally bioavailable (%F) displaying excellent systemic drug concentration levels (C_{Max}/AUC). In addition to this, SMT-571 gave a volume of distribution (Vd) equal to total body water, and a clearance rate (Cl) indicative of low first pass effects.

Conclusions: SMT-571 represents a potent, novel small molecule antibiotic with the appropriate *in vitro* and *in vivo* characteristics required of an oral treatment for *N. gonorrhoeae*. The objective is select a preclinical candidate during the second half of 2018 to advance SMT-571 into, and through, IND-enabling studies to initiate and complete a First-in-Human (FIH) Phase 1 clinical trial to establish safety and tolerability, in addition to PK, following oral administration.

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1. Alirol et al. (2017), PLOS Medicine 14(7): e1002366