Abstract 56
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SMT026571 : The Development of a Novel Oral Antibiotic to Treat Multi-Drug Resistant *Neisseria gonorrhoeae*

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Background: The emergence and spread of multi-drug resistance to antibiotics used to treat gonorrhoea 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 antibiotic class, with its activity profile and novel Mechanism of Action (MoA), has potential advantages over current and novel therapies. The lead candidate, SMT026571 (SMT-571), was chosen because of its potential to satisfy the Target Product Profile (TPP), recommended by the World Health Organisation (WHO) and Drugs for Neglected Disease initiative (DNDi)[1], for an oral agent to treat multi-drug resistant gonorrhea.

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.

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

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

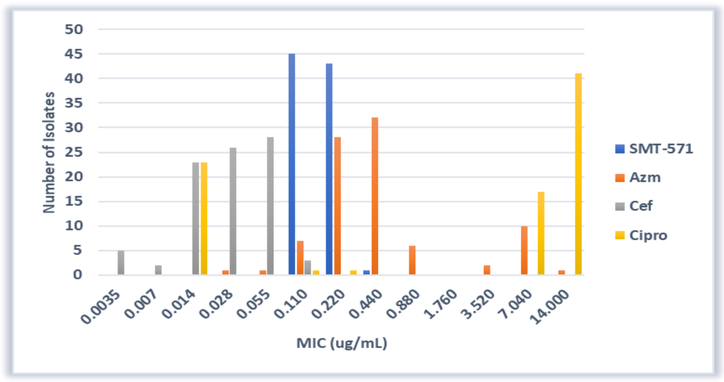


Figure 1: MIC determination across a panel of clinical isolates of *N. gonorrhoeae* (NIAID preclinical services)

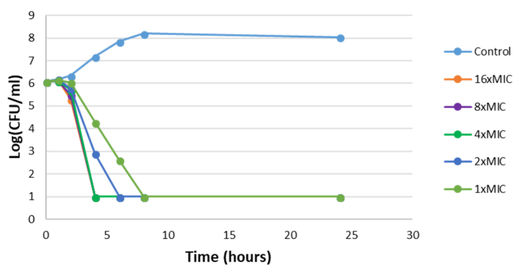


Figure 2: Time kill studies confirmed a rapid bactericidal profile against the clinical strain WHO-M

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

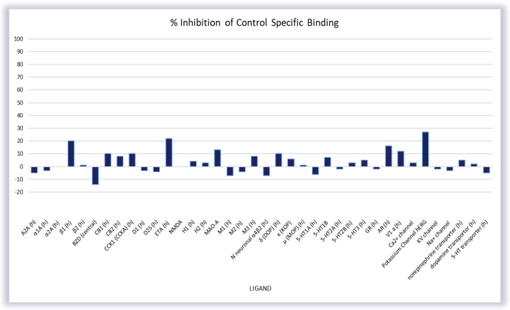
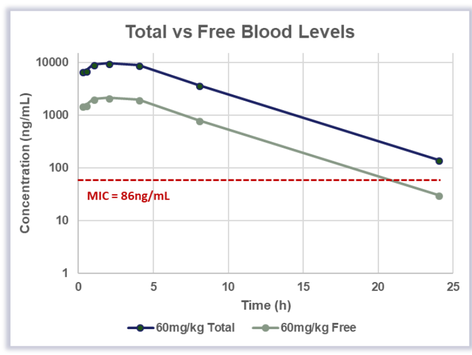


Figure 3: CEREP safety panel displays no polypharmacology

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

Table 6: SMT-571 displays good oral PK properties



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

Table 7 : In mice a single oral dose (60mg/kg) demonstrates coverage of each pharmacodynamic index up to 24h

Results:

- SMT-571 returned agar 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.
- 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), 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 new small molecule antibiotic with a novel mechanism of action that has the appropriate *in vitro* and *in vivo* characteristics required of an oral treatment for *N. gonorrhoeae*. The objective is to nominate SMT-571 as a preclinical candidate during the second half of 2018, and advance it through IND-enabling studies.

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