

In-Vitro Activity of SMT-571 & Comparators Against Clinical Isolates & Reference Strains of *Neisseria gonorrhoeae*

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Basic Science & Translational Research

Introduction

The emergence and spread of multidrug resistance to antibiotics used to treat gonorrhoea has resulted in a dramatic loss of effective regimens for the condition.¹ Currently, the extended spectrum cephalosporin, ceftriaxone, is the only viable monotherapy option available, however, resistance to this last line treatment is now emerging globally. Summit Therapeutics is developing a novel first-in-class oral antibiotic, with activity against, *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 mechanism of action (MoA), has potential advantages over current and novel therapies. The lead candidate, SMT-571, was chosen due to its potential to satisfy the Target Product Profile (TPP), recommended by the World Health Organization and the Drugs for Neglected Disease Initiative,² for an oral agent to treat multi-drug resistant gonorrhoea, including multi-drug resistant strains. Herein, we assessed the *in vitro* activity of a novel small molecule antimicrobial (SMT-571) with a new mechanism of action against a large collection of *N. gonorrhoeae* clinical isolates and reference strains including numerous MDR and XDR gonococcal isolates.

Methods

MICs (mg/L) of SMT-571 were determined by agar dilution according to current CLSI guidelines.³ The MICs of ceftriaxone, cefixime, azithromycin, ciprofloxacin, spectinomycin, tetracycline, and ampicillin were determined using the Etest method (AB bioMérieux, Marcy l'Etoile, France).

Results

Antimicrobial, isolate group (n)	MIC range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	Modal MIC (mg/L)	S/I/R ^a (%)
SMT-571					
<i>all isolates</i> (262)	0.064–0.125	0.125	0.125	0.125	ND
<i>consecutive isolates</i> (100)	0.064–0.125	0.064	0.125	0.064	ND
<i>selected isolates</i> (128)	0.064–0.125	0.125	0.125	0.125	ND
<i>reference strains</i> (34)	0.064–0.125	0.125	0.125	0.125	ND
Ceftriaxone (262)	<0.002–4	0.008	0.064	0.004	96/ND/3
Cefixime (262)	<0.016–8	<0.016	0.25	<0.016	89/ND/11
Azithromycin (262)	0.016 to >256	0.5	2	1	44/14/42
Spectinomycin (262)	4 to >1024	16	16	16	98/ND/2
Ciprofloxacin (262)	<0.002 to >32	2	>32	>32	40/0/60
Ampicillin (262)	<0.016 to >256	0.5	4	1	27/59/14
Tetracycline (262)	0.125–256	2	16	4	22/18/60

ND, not determined due to lack of interpretative criteria.

MICs were determined using an agar dilution technique for SMT-571 and using the Etest method for the additional antimicrobials.

aS, susceptible; I, intermediately susceptible; R, resistant. EUCAST clinical breakpoints were applied for all antimicrobials, with the exception of SMT-571

Table 1: MIC range, MIC₅₀, MIC₉₀ and modal MIC values of SMT-571 and therapeutic antimicrobials

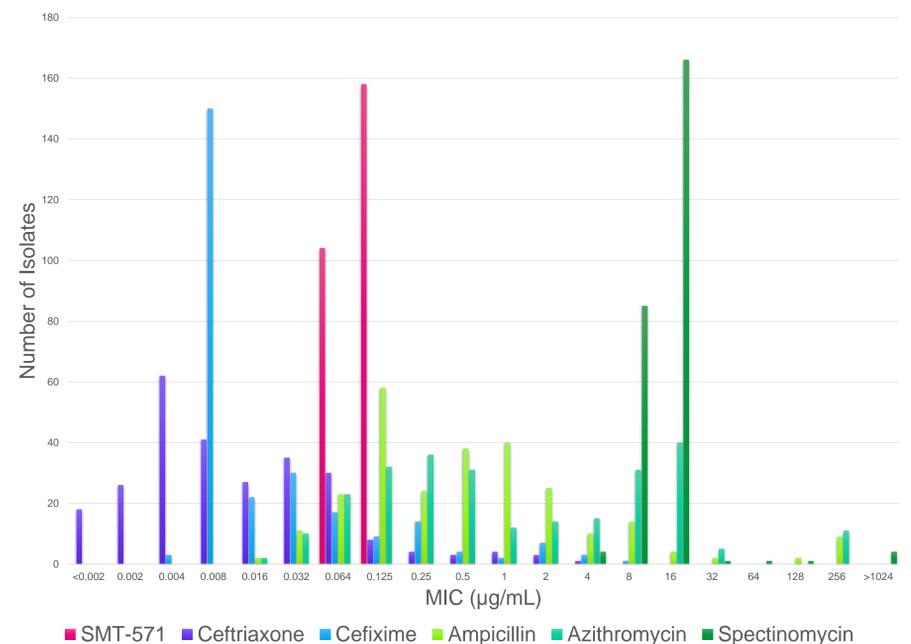


Figure 1: MIC distributions of SMT-571 and comparators

This study is the first broad evaluation of the *in vitro* activities of the promising new-mechanism novel small-molecule antimicrobial SMT-571 against a large geographically, temporally and genetically diverse collection of clinical *N. gonorrhoeae* isolates and international reference strains, including various types of high-level resistant, MDR and XDR gonococcal isolates.⁴ The susceptibility results for SMT-571 and seven antimicrobials currently or previously recommended for the treatment of gonorrhoea are summarised in Table 1. The isolates evaluated against SMT-571 have been further subdivided into separate groups (all isolates, consecutive isolates, selected isolates and international reference strains) for clarity (Table 1). SMT-571 displayed potent *in vitro* activity against all the tested *N. gonorrhoeae* isolates (n = 262). The MIC ranged from 0.064 to 0.125 mg/L and the MIC₅₀, MIC₉₀ and modal MIC were all 0.125 mg/L. With the exception of the extended spectrum cephalosporins (ceftriaxone and cefixime), the modal MIC, MIC₅₀ and MIC₉₀ of the additional antimicrobials tested were all substantially higher than those observed for SMT-571 (Figure 1). No cross-resistance or correlation between the MICs of SMT-571 and the MICs of any of the other tested currently or previously used antimicrobials was observed, with the Spearman's rank correlation coefficient ranging from 0.024 to 0.261 when comparing the MICs of SMT-571 and the MICs of the additional antimicrobials (data not shown).

Conclusion

SMT-571 is a novel small molecule antibiotic targeted towards the treatment of gonorrhoea. Through its novel mechanism of action it has demonstrated high *in vitro* activity against a large collection of gonococcal international reference strains and clinical isolates, including numerous MDR and XDR isolates as well as ceftriaxone resistant strains. It has demonstrated the appropriate *in vitro* and *in vivo* characteristics required of a single oral dose treatment for *N. gonorrhoeae* and is currently undergoing IND-enabling studies ahead of Phase 1 clinical assessment.

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References:

- Unemo *et al.*, *Clin Microbiol Rev.*, 2014; 27: 587–613
- Alirol *et al.* (2017), *PLOS Medicine*, 14(7): e1002366
- www.clsi.org
- Jacobsson *et al.*, *JAC*, 74, 6, 1591–1594

