Abstract 648
Sunday 10th June 2018
ASM Microbe Atlanta

# DDS-03: A Highly Potent and Selective Novel Small Molecule Series to treat Multi-Drug Resistant *Neisseria gonorrhoeae*

T. Avis, E. B. M. Breidenstein, C. Coward, N. Khan, C. S. Mason, **P. Meo**;
Summit Therapeutics, Merrifield Centre, Rosemary Lane, Cambridge, CB1 3LQ, UK.

Summit Therapeutics
paul.meo@summitplc.com
+44 (0)1223 394200

**Background:** The emergence and spread of multi-drug resistance to antibiotics used against the Gram-negative bacterial pathogen, *Neisseria gonorrhoeae*, the causative agent of the sexually transmitted infection gonorrhea has resulted in a dramatic loss of effective regimens for the condition. Currently, ceftriaxone (injectable) is the only viable monotherapy option available. A robust pipeline of novel antibiotics is required to provide a sustainable defence against *N. gonorrhoeae* infections worldwide.

To this end, Summit is developing new mechanism oral pathogen specific antibiotics for the treatment of *N. gonorrhoeae*. Here we report on a novel chemotype with excellent levels of activity and remarkable selectivity associated with a novel mechanism of action as established using our Discuva Platform. The DDS-03 chemotype and mechanism is distinct to our other compound series targeting *N. gonorrhoeae*, SMT-571 (see poster #647).

**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 at established service providers. Mechanism of action studies were performed using Summit's proprietary transposon and bioinformatics based technologies.

**Results:**

- DDS-03 series exhibits excellent activity across *N. gonorrhoeae* clinical isolates (WHO Panel), including the highly resistant WHO-X Japanese strain.
- Examples from the DDS-03 series show no shift or a 2-fold shift in the presence of 4% serum.
- A panel of 96 clinical isolates, accessed through the NIAID preclinical services, returned MIC values of 0.01 µg/ml.
- DDS-03 series exhibits remarkable pathogen specificity.
- This series is bactericidal and exhibits low levels of mutational frequency (~$2.8x10^{-8}$ – $3x10^{-9}$) → defined mutants do not exhibit cross-resistance to azithromycin and doxycycline.
- Examples from the DDS-03 series do not show any evidence of synergy or antagonism in combination with azithromycin and doxycycline.

| *ACTIVITY* | FA1090 | WHO-M | WHO-L | WHO-N | WHO-O | WHO-G | WHO-F | WHO-K | WHO-X |
|---|---|---|---|---|---|---|---|---|---|
| MIC (µg/mL) | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 |

**Table 1:** DDS-03a is active against multi-drug resistant *N. gonorrhoeae* clinical isolates (WHO Panel).

| Compound | $MIC_{90}$ | Number of Isolates |
|---|---|---|
| DDS-03b | 0.01 µg/mL | 96 |

**Table 2**: DDS-03 series exhibits potent activity across *96* clinical isolates (supported by NIAID).

| Genus | Species | Strain | MIC (µg/ml) | |
|---|---|---|---|---|
| | | | DDS-03c | Ciprofloxacin |
| *Staphylococcus* | *aureus* | BAA 1720 | >64 | >32 |
| *Staphylococcus* | *epidermidis* | NRS7 | >64 | 8 |
| *Bacillus* | *thuringiensis* | ATCC 35646 | >64 | 0.25 |
| *Enterococcus* | *faecalis* | ATCC 51299 | >64 | 0.5 |
| *Enterococcus* | *faecium* | NCTC 8619 | >64 | 4 |
| *Enterobacter* | *cloacae* | NCTC 13464 | >64 | 0.25 |
| *Enterobacter* | *aerogenes* | DSM 12058 | >64 | >32 |
| *Moraxella* | *catarrhalis* | DSM 11994 | >64 | ≤0.06 |
| *Acinetobacter* | *calcoaceticus* | DSM 16962 | >64 | 0.125 |
| *Acinetobacter* | *junii* | DSM 14968 | >64 | 0.125 |
| *Acinetobacter* | *ursingii* | DSM 16037 | >64 | 1 |
| *Salmonella* | *enterica* | NCTC 6017 | >64 | ≤0.63 |
| *Pseudomonas* | *aeruginosa* | EUP_10.1 | >64 | 0.25 |
| *Proteus* | *mirabilis* | DSM 30116 | >64 | ≤0.63 |
| *Providencia* | *rettgeri* | DSM 1131 | >64 | ≤0.63 |

| Genus | Species | Strain | MIC (µg/ml) | |
|---|---|---|---|---|
| | | | DDS-03c | Ciprofloxacin |
| *Escherichia* | *coli* | ATCC 25922 | >64 | ≤0.63 |
| *Haemophilus* | *influenzae* | A1 1246001 | >64 | - |
| *Legionella* | *pneumophilia* | ATCC 33152 | >64 | 0.5 |
| *Neisseria* | *gonorrhoeae* | ATCC 49226 (DSM 9189) | ≤0.125 | 0.004 |
| *Streptococcus* | *pneumoniae* | 4478-07 | >64 | - |
| *Streptococcus* | *pyogenes* | EUP_112 | >64 | - |
| *Lactobacillus* | *rhamnosus* | ATCC 53103 | >64 | - |
| *Neisseria* | *meningitidis* | ATCC 13077 (DSM 10036) | ≤0.125 | - |
| *Clostridium* | *difficile* | ATCC 43255 | >64 | - |
| *Clostridium* | *perfringens* | ATCC 8237 | >64 | - |
| *Peptostreptococcus* | *anaerobius* | DSM 20357 | >64 | - |
| *Bacteroides* | *fragilis* | ATCC 25285 | >64 | - |
| *Clostridium* | *innocuum* | DSM 1286 | >64 | - |
| *Roseburia* | *faecis* | DSM 16840 | >64 | - |
| *Bifidobacterium* | *bifidum* | ATCC 11863 | >64 | - |

**Table 3:** A representative from the DDS-03 series has been profiled against a panel of 30 bacteria.

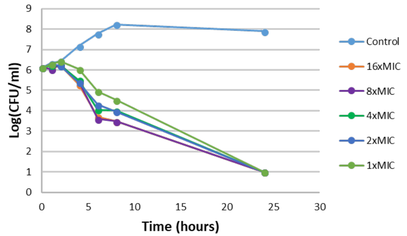


**Figure 1:** Time-kill studies confirmed a bactericidal killing profile against the multi-drug resistant clinical isolate WHO-M.

| Compound | FoR (4xMIC) | |
|---|---|---|
| | 24h | 48h |
| DDS-03e | $3.77x10^{-8}$ | $>2.9x10^{-7}$ |
| DDS-03f | $2.88x10^{-9}$ | $2.88x10^{-9}$ |
| DDS-03g | $2.65x10^{-9}$ | $3.57x10^{-8}$ |

**Table 4:** DDS-03 series exhibit low levels of mutational frequency.

| RBC | Cytotox | Mitotox | GSH (50 µM) | Ames (25 µM) |
|---|---|---|---|---|
| >200 µM | >100 µM | Negative | Negative | Negative |

**Table 5:** The DDS-03 chemotype has a clean ADME and toxicology profile.

## *Discuva Technology: Target Identification*

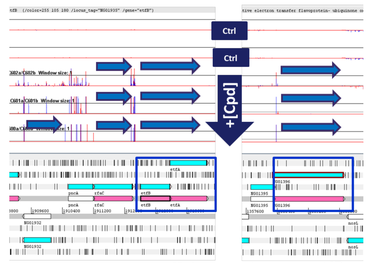


**Figure 2:** Discuva Technology identified the electron transfer proteins (etf) A/B/D as the mechanism of action for the DDS-03 series.

- Single dose pharmacokinetic (SDPK) studies where compounds were administered 1mg/kg IV and 10mg/kg PO have returned highly favourable oral $C_{Max}$/MIC ratios for representative examples from the series.
- DDS-03 series has a clean toxicology profile in RBC, cytotoxicity and mitotoxicity.
- DDS-03 series is negative in Ames assay and no adducts were observed in a glutathione incubation assay in the presence and absence of S9 fraction.
- Our Discuva Platform identified the electron transfer proteins (etf) A/B/D as the mechanism of action for the DDS-03 series which was further confirmed by whole genome sequencing of the resistant mutants.

**Conclusions:** Summit Therapeutics is developing a small molecule oral antibiotic with exceptional levels of potency, selectivity and a novel mechanism of action for the treatment of N. gonorrhoeae infections. The series is undergoing further optimization.

**Acknowledgment:** NIH National Institute of Allergy and Infectious Diseases