In vivo Proof-of-Concept for a Novel Small-Molecule Inhibitor of Bacterial Lipoprotein Transport Targeting Enterobacteriaceae

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Background:

Enterobacteriaceae infections are associated with increasing treatment failure rates due to the rise of antimicrobial resistance towards the broad-spectrum antibiotics currently used to treat this Gram-negative bacteria. Of particular concern are Carbapenem-Resistant Enterobacteriaceae (CRE) and Extended-Spectrum β-Lactamase (ESBL)-producing Enterobacteriaceae as resistance rates due to these classes [of antibiotics] continues to rise. Consequently, Enterobacteriaceae are listed as serious or urgent threats by the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC). To address this urgent unmet medical need, Summit Therapeutics is developing a novel class antibiotic series (DDS-04[1]) designed as a precision Enterobacteriaceae therapy that overcomes all pre-existing resistance mechanisms. The DDS-04 series targets the clinically unexploited bacterial LolC/E complex, involved in lipoprotein transport. Our DDS-04 antibiotic series has the potential to treat infections caused specifically by Enterobacteriaceae at key infection sites including the bloodstream, lungs and urinary tract.

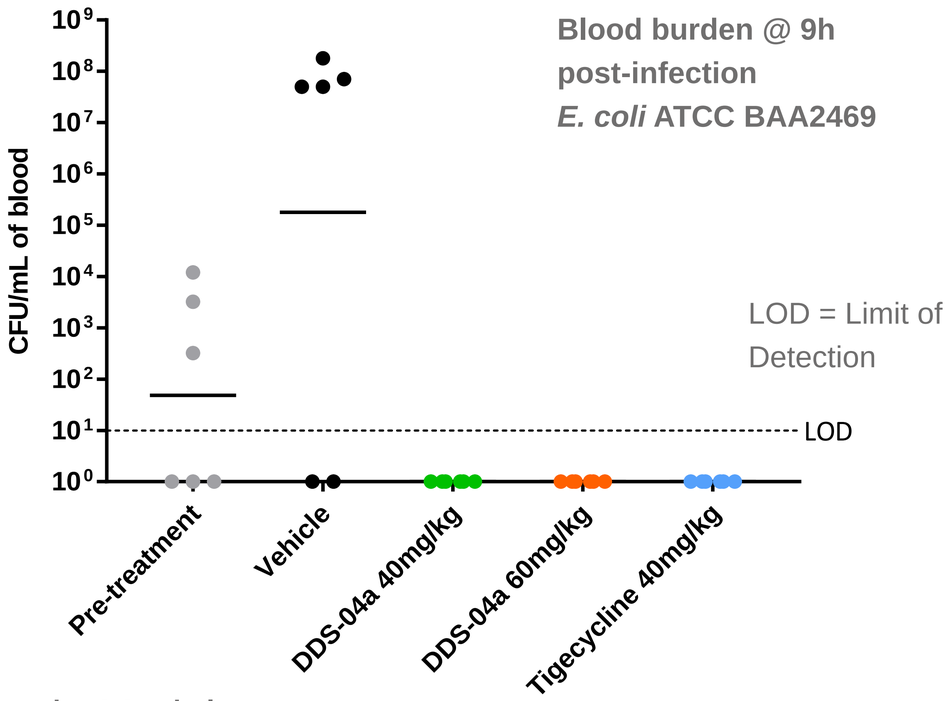
Method:

The septicaemia model represents a non-neutropenic mouse model (CD-1 mice) of peritonitis due to infection with *E. coli* ATCC BAA2469. Pre-treatment bacterial burden was determined 1h post-infection and compound treatment was administered via IV route 3x every 3h starting 1h post-infection. Mice were euthanized 9h post-infection and blood, kidneys, liver, spleen and lungs were analysed. Tigecycline (40 mg/kg, 2 doses at 1h and 7h) was used as the reference. In the urinary tract infection (UTI) model C3H/HeN female mice were pre-conditioned with glucose and then infected with *E. coli* UTI89. Pre-treatment bacterial burden was determined after 24h on a sub-group of mice. 24h post-infection, compound treatment was administered via IV route 3x daily every 8h over 3 days. At 96h post-infection, mice were euthanized and bacterial burden in the kidneys, bladder and urine were analysed. Ciprofloxacin (10 mg/kg, 3x daily every 8h over 3 days) was used as the reference. A neutropenic mouse model of CD-1 mice was used for the pneumonia model. Mice were infected by intra-nasal administration with *K. pneumoniae* ATCC 43816. 2h post-infection, compound treatment was administered via IV route 3x every 8h. Mice were euthanised 26h post infection and lung tissue samples were analysed for bacterial burden. Tigecycline (40 mg/kg, 3x every 8h) administered sub-cutaneous was used as the reference.

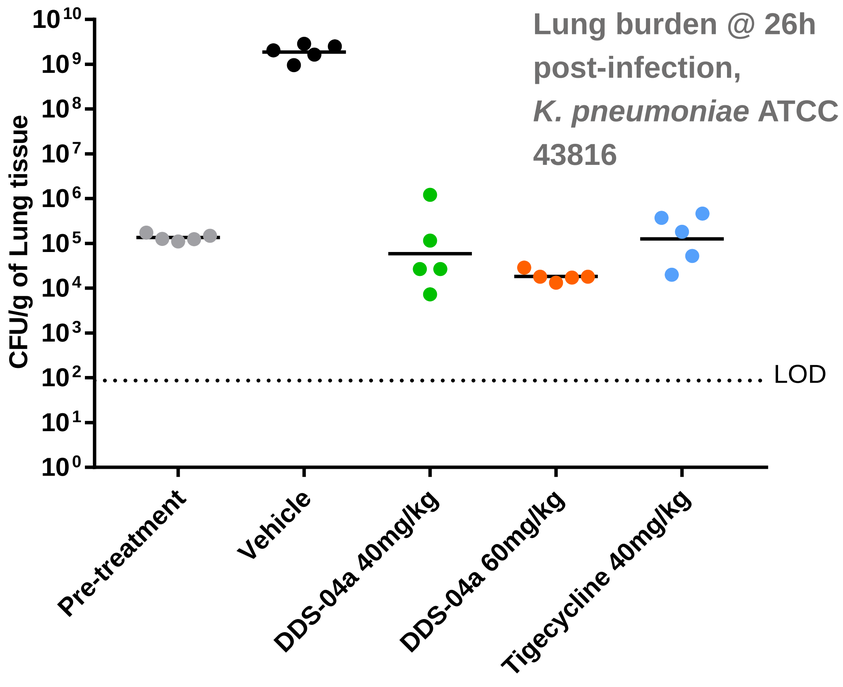
Results:

Following IV dosing at 40 mg/kg and 60 mg/kg, a representative compound from the series (Compound DDS-04a) maintained good C_{max} levels in the bloodstream and was distributed to multiple infection sites including the bladder, kidneys and lungs. *In vivo* efficacy studies using the same doses TID at different intervals demonstrated that the DDS-04 series significantly reduced the bacterial burden in animal models of septicaemia, UTI and pneumonia. In the septicaemia model, the bacterial burden after 9h was below the limit of detection in the blood, the kidneys, the liver, lungs and the spleen. In the UTI model, a significant reduction in colony-forming units (CFU) was observed on Day 4 in the urine, the bladder and the kidneys. In the pneumonia model, a 4.5 $\log_{10}$ reduction in CFU was observed after 26h in the lungs. Efficacy in all 3 models was comparable to the reference antibiotic in each case.

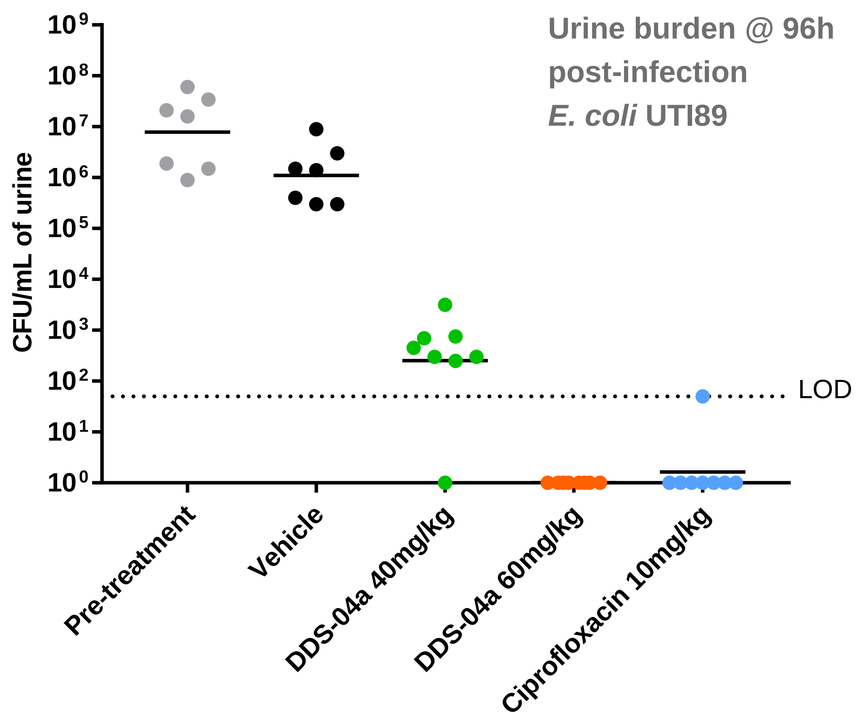
Sepsis Model

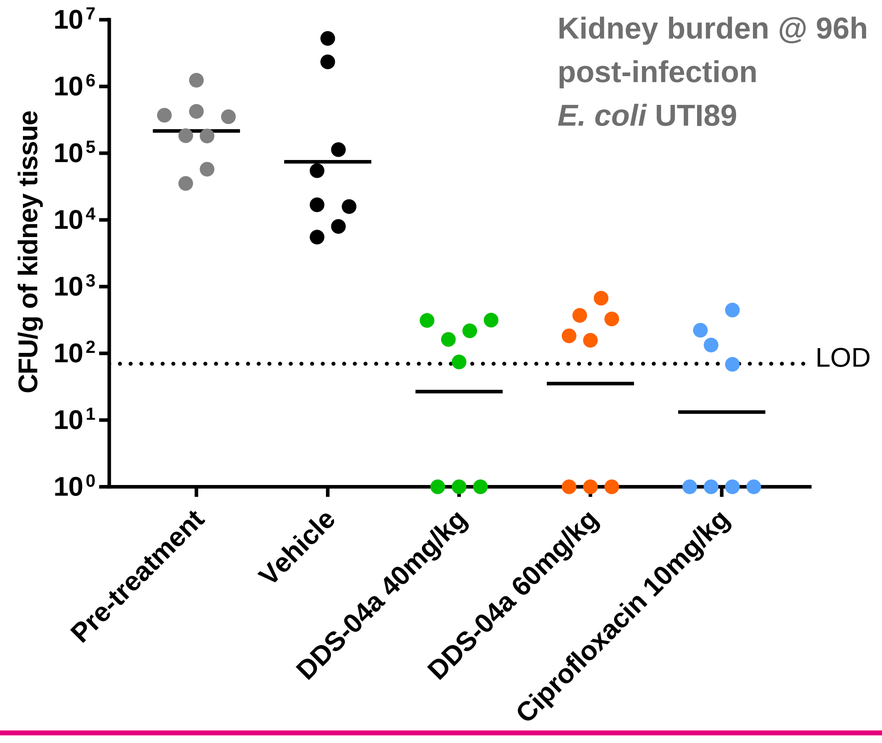


Pneumonia Model



Urinary Tract Infection Model





Conclusions:

Our novel class DDS-04 antibiotic series has demonstrated potential to treat Gram-negative Enterobacteria infections throughout the body. Targeting a clinically unexploited bacterial mechanism, the DDS-04 series has achieved an excellent *in vivo* PD profile across three key Enterobacteriaceae disease models, with comparable efficacy to clinical antibiotics with known resistance challenges. The DDS-04 series continues to progress through lead optimisation with further PD, PK, safety and tolerability studies ongoing.

Acknowledgements: All *in vivo* infection models were completed at Evotec (UK) Ltd (Alderley Park, Macclesfield, UK).

References: 1: DDS-04 series structural information is detailed in WIPO patent application WO 2019/086890 A1