Poster# 04502

SMT-738: A Novel Small-Molecule Inhibitor of Bacterial Lipoprotein Targeting Enterobacteriaceae

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INTRODUCTION

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 these Gram-negative bacteria. Of particular concern are Carbapenem-Resistant Enterobacteriaceae (CRE) and Extended-Spectrum β-Lactamase (ESBL)-producing Enterobacteriaceae. Consequently, Enterobacteriaceae are listed as serious or urgent threats by the World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC) (Reference 1). Enterobacteriaceae are a family of Gram-negative bacteria responsible for causing infections across multiple indications, including urinary tract, bloodstream infections and hospital-acquired pneumonias. To address this urgent unmet medical need, Summit Therapeutics identified and is developing SMT-738, a preclinical candidate against a clinically unexploited target (bacterial LolCDE complex involved in lipoprotein transport) that is selective towards Enterobacteriaceae. SMT-738 has the potential to treat infections caused specifically by Enterobacteriaceae at key infection sites including the bloodstream, lungs and the urinary tract.

METHODS

Antimicrobial activity was performed according to CLSI/EUCAST guidelines. *In vitro* mutation frequencies, kill kinetics, and *in vivo* proof-of-concept studies were performed using standard protocols. 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 24 h on a sub-group of mice. 24 h post-infection, SMT-738 was administered *via* IV infusion route QD (once daily) or BID (twice daily) over 3 days. At 96 h post-infection, mice were euthanized and bacterial burden in the kidneys, bladder and urine were determined. Ciprofloxacin (10 mg/kg IV bolus, twice daily every 12 h 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. 2 h post-infection, SMT-738 was administered *via* IV infusion route QD or BID. Mice were euthanised 26 h post infection and lung tissue samples were determined for bacterial burden. Ciprofloxacin (10 mg/kg IV bolus, BID) was used as the reference.

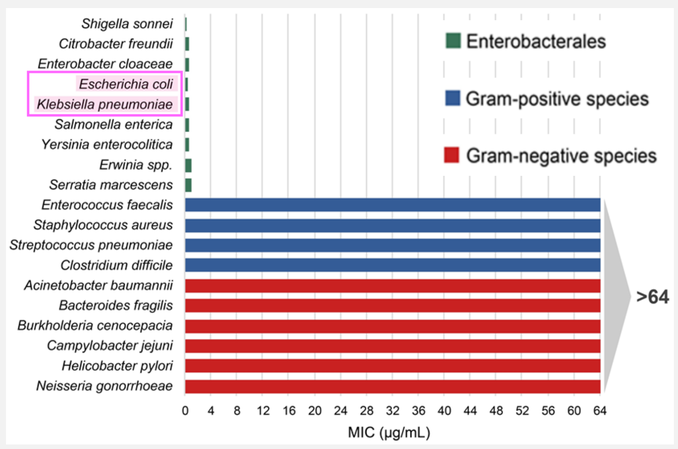
RESULTS

Microbiology

- SMT-738 has narrow spectrum activity and is active against most Enterobacterales spp (including MDR *E. coli* and *K. pneumoniae*) with MIC_{90} values of 1 µg/mL and 2 µg/mL respectively (**Figure 1A & 1B**).
- SMT-738 is rapidly bactericidal (>3log_{10} reduction in bacterial burden; 2 h for Uropathogenic *E. coli* (UPEC) and 3-4 h for *K. pneumoniae*) (**Figure 2**), has a low propensity for resistance development (frequency of resistance ~10^{-9}-10^{-10}) and displays no cross-resistance with existing classes of antibiotics.

Figure 1: Minimum Inhibitory Concentration (MIC) Determination for SMT-738

A) Activity Against Enterobacterales (Reference 2)

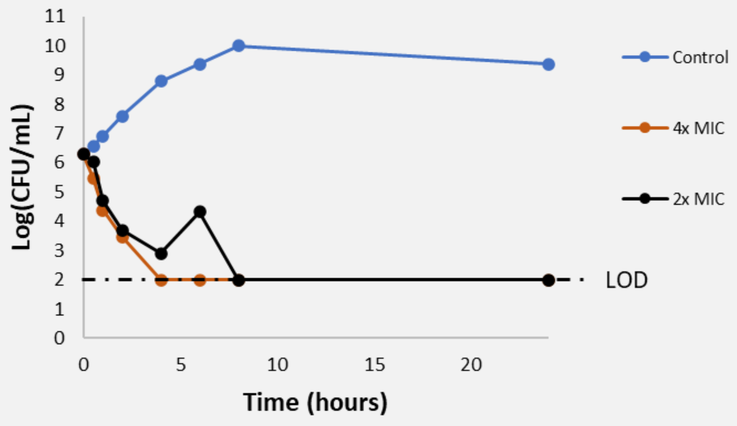


B) Global MDR Isolates of *E. coli* and *K. pneumoniae*

	Global Isolates (n=200) MIC_{90} (µg/mL)		NDM Indian Isolates (n=30) MIC_{90} (µg/mL)	
	E. coli	*K. pneumoniae*	*E. coli*	*K. pneumoniae*
SMT026738	1	2	1	1
Amoxicillin/Clavulanate (Augmentin)	>32	>32	>32	>32
Piperacillin/Tazobactam (Zosyn)	>32	>32	>32	>32
Ceftazidime/Avibactam (Avycaz®)	1	2	>32	>32
Meropenem/Vaborbactam (Vabomere®)	1	>8	>32	>32
Colistin	0.5	16	1	16

NDM: New Delhi Metallo β-lactamase

Figure 2: Time-Kill Curve Uropathogenic *E. coli* NCTC13441

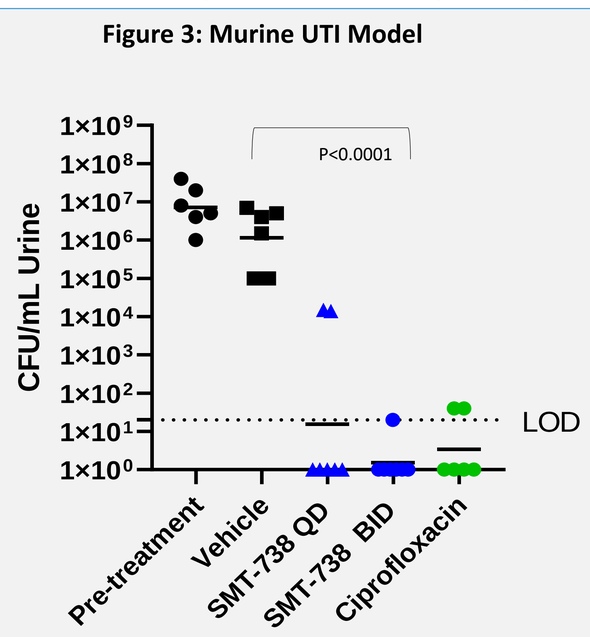


MIC: 0.39 µM

In Vivo Models

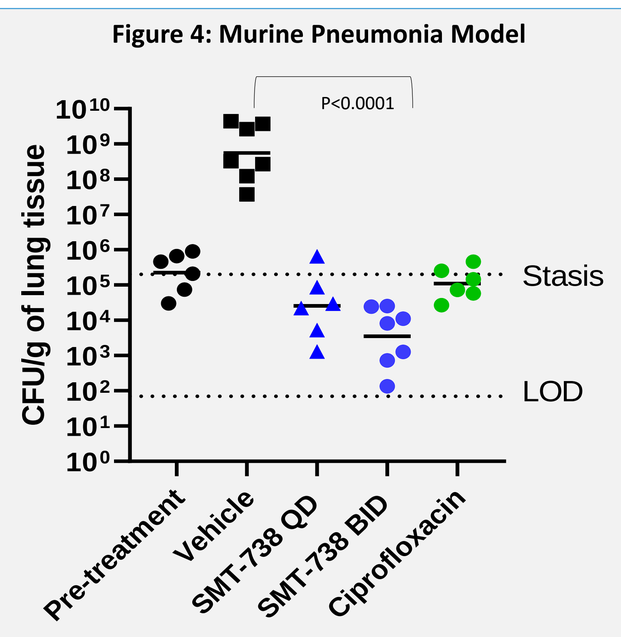
- SMT-738 administered at 20 mg/kg by 60 min IV infusion maintained levels in the blood and distributed to key infections sites, including kidneys and lungs, and was eliminated unchanged in the urine.
- *In vivo* efficacy studies demonstrated that SMT-738 significantly reduced the bacterial burden in murine animal models of urinary tract infections (UTI), septicaemia and pneumonia. In the UTI model, the bacterial burden after 96 h was below the Limit of Detection (LOD) in the urine after QD or BID administration of SMT-738 (**Figure 3**). The bacterial burden after 9 h in the septicaemia model was below the limit of detection (not shown here). In the pneumonia model, a 4-5 log_{10} reduction in CFU was observed compared to the vehicle control after 26 h in the lungs (**Figure 4**).
- A preliminary 7-day rat toxicity study at 150 mg/kg administered by 60 min IV infusion resulted in a profile that supports the further development of SMT-738. This data is in line with data from a battery of *in vitro* toxicity assays.

Figure 3: Murine UTI Model



SMT-738 was administered QD 20 mg/kg or BID 20 mg/kg over three days by 60 min IV infusion. *E. coli* UTI89 (MIC 0.5 µg/mL) was used to raise the infection. Bacterial burden in urine after 96 h shown. LOD (Limit of Detection). Animals with burden below limit of detection were assigned a value of 1 for graphical and statistical purposes.

Figure 4: Murine Pneumonia Model



SMT-738 was administered QD 20 mg/kg or BID 20 mg/kg by 60 min IV infusion. *K. pneumoniae* ATCC 43816 was used to raise the infection (MIC 0.5 µg/mL). Bacterial burden in lung shown after 26 h. LOD (Limit of Detection)

CONCLUSIONS

The discovery of Summit's preclinical candidate SMT-738, represents a promising advance in the development of novel drug candidates to treat infections caused by highly resistant Enterobacteriaceae including CRE. We are developing SMT-738 as a potential Enterobacteriaceae drug of choice to address clinically challenging infections.

DISCLAIMER

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Combating Antibiotic-Resistant Bacteria

SMT-738 is an investigational compound that is not approved by and regulatory body.

REFERENCES

1) CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta (DOI: http://dx.doi.org/10.15620/cdc:82532

2) Avis *et al*, 2021. Drug Discovery Today Sept, 26(9), 2198-2203

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