P0801
Poster Session III
C. difficile: antimicrobial susceptibility and treatment

SMT19969: A NOVEL AGENT FOR CLOSTRIDIUM DIFFICILE INFECTION - SUMMARY RESULTS FROM IN VITRO MICROBIOLOGY AND A RANDOMISED DOUBLE BLIND PHASE 1 CLINICAL TRIAL

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Objective: C. difficile infection (CDI) is a leading cause of nosocomial diarrhoea, and new agents that address initial infection and reduce rates of recurrent disease are needed. SMT19969 is a selective antimicrobial in development for the treatment of CDI. The following summarises in vitro microbiology and Phase 1 clinical data.

Methods: MICs were determined according to CLSI guidelines M11-A8 and M7-A9. Time kill assays were performed at 1-20xMIC with CFU counts to 24 hours. PAE assays were performed with either 1 or 3 hours pre-incubation with CFU counts to 24 hours post drug exposure. The primary objective of the Phase 1 was to determine safety and tolerability. 56 healthy male subjects were randomised to 8 groups. Groups A-F received single oral doses of SMT19969 or placebo escalating from 2 to 2000 mg while fasting. Group E evaluated food effect with subjects participating in 2 treatment periods (fasted and fed). Group G-H received 200mg or 500mg of SMT19969 or placebo BID for 10 days. SMT19969 was quantified in plasma and faecal samples. Safety and tolerability were assessed by adverse event (AE) monitoring, vital signs, 12-lead ECG, clinical laboratory evaluation and physical examination. Gut bacteria were cultured and quantified from Groups G and H faecal samples on days -1, 4 and 10.

Results: SMT19969 showed potent inhibition of *C. difficile* (MIC_{90}=0.125-0.25 mg/L) against 133 clinical isolates. Against 350 Gram-positive and -negative anaerobic and aerobic bacteria, SMT19969 was more selective than fidaxomicin, vancomycin or metronidazole comparators, with limited activity against most microorganisms including *Bacteroides, Bifidobacteria, Eggerthella, Finegoldia,* and *Peptostreptococcus* species (MIC_{90} >512, >512, >512, 64 and 64 mg/L, respectively). SMT19969 showed bactericidal activity with >5log reduction in CFU/mL at 24 hours, and a pronounced PAE with no recovery of growth following 3 hours pre-incubation. In the completed Phase 1 study oral administration of SMT19969 was considered safe and well tolerated. No subjects were excluded from the analysis. AEs were mild with no dose dependent relationship and a similar rate of AEs between placebo and SMT19969 subjects. No clinically significant findings from clinical laboratory, ECGs or other assessments were observed. Plasma levels of SMT19969 were at or just above the limit of detection (Group G range=0.103-0.243ng/mL; Group H range=0.102-0.305ng/mL). There were no significant changes in gut flora bacteria except for total clostridia with mean reductions from day -1 to day 10 for Group G and H of 5.7 and 4.5 CFU/mL, respectively.
Conclusions: These data demonstrate that SMT19969 is a potent, bactericidal and selective inhibitor of *C. difficile*. Phase 1 results show that SMT19969 is safe and well tolerated with repeat administration, and has minimal impact on gut flora. Further assessment of SMT19969 in CDI patient trials is warranted.