P0798
Poster Session III
C. difficile: antimicrobial susceptibility and treatment

SMT19969 FOR CLOSTRIDIUM DIFFICILE INFECTION (CDI): COMPARATIVE EFFICACY COMPARED TO FIDAXOMICIN AND VANCOMYCIN IN THE HAMSTER MODEL OF CDI

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Objectives: CDI continues to cause significant impact to the healthcare system and new agents are required. SMT19969 is a novel antimicrobial shown to have potent growth inhibition of C. difficile and be associated with a highly selective spectrum of activity. The objectives of following study was to assess the comparative efficacy of SMT19969, fidaxomicin and vancomycin in the hamster model of CDI with infection by C. difficile ribotypes 027, 078 and 012. Plasma and GI concentrations of SMT19969 following single and repeat administration in infected hamsters was studied.

Methods: For efficacy and PK studies, hamsters were preconditioned orogastrically with clindamycin (30 mg/kg) on day -1, followed on day 0 by gavage with *C. difficile* spores (100-1000 CFU). For PK, hamsters (N=3 per time point) were administered SMT19969 as single or BID 12.5 or 25 mg/Kg doses. Animals were euthanized 1, 4, 8, 12 and 24 hours post dosing, the GI tract sectioned and SMT19969 quantified in stomach, small intestine, cecum and colon. Plasma samples were analysed for SMT19969 at 1, 4, 8, 12 and 24 hours post dosing. Three independent efficacy studies were performed with C. difficile ribotypes 027, 078 or 012. On day 1 animals were dosed with either SMT19969 (12.5 and 25 mg/Kg BID), vancomycin (10 mg/Kg BID), fidaxomicin (1 and 2.5 mg/Kg BID) or vehicle for 5 days (N=10 per group). Hamsters were monitored until day 28. Endpoints included daily weight, temperature and survival measurements. Faecal samples were collected on days 1, 7, 12, and 19 for quantitative counts of *C. difficile*.

Results: Administration of SMT19969, fidaxomicin or vancomycin at all doses resulted in 100% survival by day 5 following infection with all C. difficile strains. 100% mortality was observed by day 3 in vehicle treated animals. Following infection with ribotype 027 onset of mortality was observed in vancomycin treated animals on day 13 with 10% survival recorded by day 28. Superior long term survival was observed in SMT19969 and fidaxomicin treated animals with day 28 survival rates of 95% for both treatments. Comparable results were observed following infection with ribotypes 078 or 012. Concentrations of SMT19969 in the caecum and colon remained greatly in excess of MIC for 12 hours after a single dose with negligible systemic exposure observed. On multi-dosing GI levels remained above the MIC throughout.

Conclusions: These data show that SMT19969 is highly effective in the hamster model of CDI against multiple strains of C. difficile including hyper virulent ribotype 027 and 078 isolates. Oral administration resulted in GI concentrations >1000 fold above MIC with minimal plasma exposure even in the inflamed GI tract. Further development of SMT19969 for CDI is warranted.