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Abstract (poster session)

SMT19969 - Preclinical safety and pharmacokinetics of a novel antimicrobial for Clostridium difficile infection

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Objectives: SMT19969 is a narrow spectrum antibiotic in clinical development for the treatment of Clostridium difficile infection (CDI). The objectives of the following GLP studies were to assess the toxicology, pharmacokinetics and distribution of SMT19969 to allow initiation of Phase I clinical trials. Methods: SMT19969 was administered orally once daily for 28 days to dogs and rats at doses of 1,000mg/Kg. Animals were monitored daily for general health and food consumption. Blood samples for toxicokinetics and clinical pathology were taken on days 1 and 28. On completion of dosing, all animals were subject to necropsy with organ weights recorded and tissues examined by histopathology. Distribution and excretion of SMT19969 was assessed by quantitative whole body autoradiography (QWBA) and excretion mass balance studies following a single 50mg/Kg oral dose of 14C labelled SMT19969 to rats. Effects on general activity, behaviour, autonomic and motor effects were assessed by IV administration to rats followed by observations based on Irwin's method. Genotoxicity was assessed in vitro in the presence and absence of metabolic activation (S-9 fraction) in bacterial Ames and chromosomal aberration assays. A combined cardiovascular and respiratory (CVR) study in anesthetised dogs was conducted by IV administration. Results: 28 days repeat dosing in both dog and rat at 1,000mg/Kg resulted in no treatment related observation, findings from histopathology of tissue or from any in-life parameters. Following a single oral dose of radiolabelled SMT19969, >99% of radioactivity was excreted in faeces with no radioactivity detected outside of the gastrointestinal (GI) tract indicating minimal systemic exposure. In the Irwin test, IV administration at 3.0 mg/kg produced no behavioural, physiological or body temperature changes when compared to the vehicle controls. No evidence for genotoxicity was observed in the Ames or chromosome aberration assays both in the absence and presence of metabolic activation. No effect on QT prolongation was observed in the dog CVR study. Conclusions: SMT19969 was shown to be well tolerated during GLP toxicology studies and to be retained in the GI tract. These data support the continued clinical development of SMT19969 as a potential therapy for CDI.