SMT19969 for *Clostridium difficile* Infection: Comparative Efficacy Compared to Fidaxomicin and Vancomycin in the Hamster Model of CDI

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Introduction and Purpose

C. difficile infection (CDI) is a significant cause of mortality and morbidity in the healthcare setting.[1] Current standard-of-care therapy is complicated by recurrent disease, which occurs in up to 30% of patients following initial infection, with risk of further recurrence and disease severity increasing with each subsequent episode.[2] Therapy options are limited, with vancomycin and fidaxomicin being the only FDA approved antibiotics. Phase III trials have shown fidaxomicin to be non-inferior on initial cure when compared to vancomycin and it is associated with reduced rates of recurrent disease.[3]

SMT19969 is a narrow spectrum antibiotic in clinical development for the treatment of CDI. The objective 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, and 012.[4] In addition, plasma and gastrointestinal (GI) concentrations of SMT19969 following single and repeat administration in infected hamsters were studied.

Methods

Animals: Golden Syrian hamsters ~100g. **Bacterial Isolates:** *C. difficile* strains BI1 (ribotype 027) and NCTC 13307 (also called strain 630, ribotype 012) were used in these studies. **Pre-infection:** Hamsters were administered 30mg/kg oral clindamycin 24 hours prior to infection. **Infection:** Hamsters were infected with 100-350 *C. difficile* spores by oral gavage 24 hours post clindamycin. **Preparation of Test Articles and dosing:** SMT19969 and fidaxomicin (prepared from Dificlir tablets), were administered as aqueous suspensions in 0.5% methyl cellulose. Vancomycin (Vancocin) was prepared in water. Hamsters were treated at 10mL/kg by oral gavage. Treatment was initiated 20 hours post infection, and administered twice daily for 5 days. **In life sample collection:** Faecal samples were collected on days 1, 7, 12, 19 and 28 post infection. **Endpoints:** Hamsters with severe hypothermia (<33°C), severe diarrhoea or severe weight loss (>20%) were euthanised and samples of the ileum, caecum and colon contents cultured. All survivors were culled at day 28. **Pharmacokinetics:** Hamsters were infected and treated with 1-5 doses, then euthanized at the appropriate time points with blood, contents of stomach, small intestine, caecum and colon collected for bioanalysis

Results: *In vivo* Hamster Efficacy

- SMT19969 showed superior efficacy to vancomycin following infection with *C. difficile* ribotypes 027 and 012 with 80% to 100% survival 27 days post infection (Figures 1A-B).
- Vancomycin resulted in 100% survival during the course of treatment with typical onset of mortality and recurrent disease on day 11 with 0-10% survival at day 27 (Figures 1A-B).
- Fidaxomicin resulted in 80-100% survival at day 27 following infection with ribotype 027 (Figure 1A).
- Following infection with ribotype 012 fidaxomicin conferred 100% protection during the course of dosing at both high and low regimens. However, onset of mortality was observed from day 7 with 0-40% survival recorded by the end of the study (Figure 1B).
- Increasing the dose of fidaxomicin above 2.5 mg/Kg did not lead to an increase in survival (Figure 1C)

Results: *C. difficile* Burden

- Both SMT19969 and vancomycin resulted in complete clearance of *C. difficile* spores by day 7.
- Spores were recovered in faecal samples on day 7 following fidaxomicin treatment for ribotypes 012 and 027.

Results: Pharmacokinetics

- Following administration of SMT19969 plasma levels were typically below the LOQ (1ng/mL) in infected animals.
- Concentrations of SMT19969 in the colon and caecum remained significantly above MIC to 24 hours following a single dose of 25mg/Kg
- Following BID dosing of SMT19969 at 25mg/Kg enhanced exposure was observed in the colon and caecum of animals.

Drug	Dose (mg/Kg BID)	Median Survival (days) Ribotype 027	Median Survival (days) Ribotype 012	Day 7 Spore Positive Samples Ribotype 027	Day 7 Spore Positive Samples Ribotype 012
SMT19969	12.5	27	27	0/10	0/10
	25	27	27	0/10	0/10
Vancomycin	10	11	12	0/10	0/10
Fidaxomicin	1	27	17	7/10	5/7
	2.5	27	23	0/10	1/9
	12.5	-	10	-	-
	25	-	11	-	-

Table 1: Median Survival (days) and Number of *C. difficile* Spore Positive Faecal Samples Collected on Day 7 Following Infection with *C. difficile* Ribotype 012 and 027

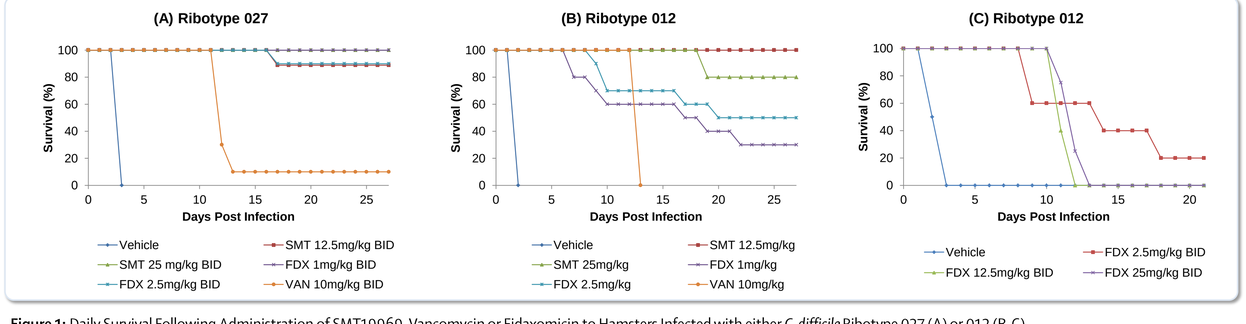

Figure 1: Daily Survival Following Administration of SMT19969, Vancomycin or Fidaxomicin to Hamsters Infected with either *C. difficile* Ribotype 027 (A) or 012 (B-C).

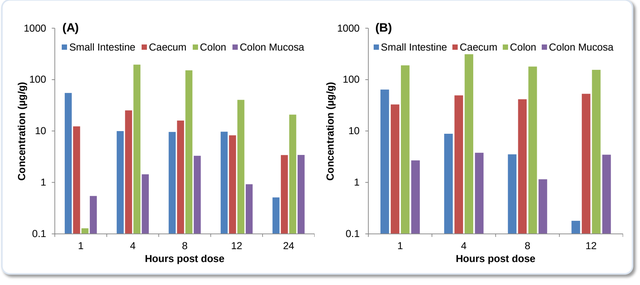

Figure 2: Concentrations (µg/g) of SMT19969 post final dose in sections of GI tract following administration of **(A)** a single dose of 25mg/Kg or **(B)** two doses (q12hrs) of 25mg/Kg.

Conclusions

- SMT19969, fidaxomicin and vancomycin provided 100% protection during dosing and acute infection with ribotypes 012 and 027.
- SMT19969 conferred significant protection from recurrent disease with day 28 survival rates of 90-100% following infection with ribotypes 012 and 027.
- Vancomycin administration resulted in 100% survival during dosing but significant recurrence was observed with both strains with 0-10% survival by the end of the study.
- Against ribotypes 027 recurrence rates for fidaxomicin were comparable to SMT19969 but fidaxomicin was less effective against ribotype 012 infection.
- These data support continued development of SMT19969 as a potential therapy for CDI.

References

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