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L0029 Pharmacodynamic Assessment of VRT001-C (Oral Ceftriaxone) vs. Intravenous Ceftriaxone Against *Escherichia coli* in the Neutropenic Murine Thigh Infection Model

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Background: Stealth Targeted Nanoparticles (STN) is a platform technology which employs a polymeric backbone and a targeting moiety for the oral delivery of poorly bioavailable drugs that belong to Biopharmaceutical Classification System (BCS) Class III and IV. Ceftriaxone, a model BCS Class III drug, was chosen for proof-of-concept studies as it is a widely used injectable-only cephalosporin with potent broad-spectrum activity and oral bioavailability of <1%. The objective of this study was to assess the *in vivo* efficacy of VRT001-C compared to intravenous (IV) ceftriaxone against *Escherichia coli* in a neutropenic murine thigh infection model.

Materials/methods: 51 Cyclophosphamide-induced neutropenic BALB/c mice were infected intramuscularly in both thighs with 1.6×10^6 CFU/thigh with *E. coli* (ATCC 35218; TEM-1 positive; Ceftriaxone MIC of 1µg/mL). Treatment mice received either ceftriaxone (100mg/kg administered IV bolus) or VRT001-C (100mg/kg and 200mg/kg administered orally). Three mice each were euthanized at 0, 3, 6, 9 and 12 hours (h) respectively in all groups and thigh muscle was homogenized, serially diluted, plated on permissive media with CFU counted after 24h incubation. Changes in $\log_{10}$ CFU/thigh homogenate at each time point were compared with 0h control to assess efficacy.

Results: The mean (±SD) $\log_{10}$CFU/thigh at 0h was 6.95±0.31. The maximal reduction of 1.72±0.09 $\log_{10}$CFU/thigh was observed with IV Ceftriaxone (100mg/kg) at the 6h time point, compared to 1.99±0.18 and 1.99±0.42 log-reduction in bacterial burden with VRT001-C (100mg/kg) and VRT001-C (200mg/kg) at the 6h and 3h time points respectively. All three dosing regimens exhibited a relatively similar pharmacodynamic (PD) profile until 9h with a statistically significant reduction in bacterial burden compared to the 0h control. However, VRT001-C at 200mg/kg was the only dose which maintained a ≥1-$\log_{10}$ reduction until 12h.

Conclusions: Orally administered VRT001-C showed potent *in vivo* efficacy with ≈2-$\log_{10}$ reduction in bacterial burden against *E. coli* in neutropenic mice thigh infection model. The high PD effect observed with the oral delivery of ceftriaxone is indicative of high systemic bioavailability and tissue concentration at the infection site. These results encourage further development of VRT001-C and exploration of STN platform for the oral delivery of other poorly bioavailable drugs.