High [V565] was achieved in the ileum and beyond.

In a further study, 3 female cynomolgus monkeys received a single oral dose of 118.6 mg V565, plus 11 mg methylene blue, in 11 minitablets and were culled at 4 hours post dose.

The proximal location for blue staining (Fig. 9) in all three monkeys was observed from the mid-jejunum to the ileum, indicating release of V565 and coverage of the ileal/cecal region onwards.

Gut luminal contents were removed and [V565] was determined by ELISA (Fig. 15). V565 was only observed in the stomach of monkey 1, indicating that the 24% enteric coating is effective.

High micromolar [V565] were observed in the ileum to the upper colon. V565 levels in the lower colon most likely reflect the time of culling.

Luminal V565 concentrations observed here are likely to be therapeutic in IBD as V565 can penetrate to the lamina propria in DSS colitis mice with disrupted epithelia and mucosal healing has been reported in patients with IBD at 67 mM or greater.

Conclusions

V565 is a highly potent inhibitor of human TNFα and is comparable in efficacy to current monoclonal antibody therapies for IBD.

V565 is highly resistant to enteric and microbially-derived intestinal proteases, facilitating oral delivery in man.

High micromolar concentrations were observed in the cynomolgus monkey gut following a single oral dose. These concentrations are orders of magnitude higher than those required in the serum for adalimumab and infliximab to induce mucosal healing in IBD.

V565 is currently in a Phase 2 clinical study (Harbor trial) for Crohn's disease in North America and Europe.