

# A first clinical trial of a novel narrow spectrum kinase inhibitor TOP1288 in patients with ulcerative colitis

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## Background

- TOP1288 a novel narrow spectrum kinase inhibitor (NSKI), selectively targets key kinases fundamental to inflammatory cell signalling in innate and adaptive immune responses: p38-alpha, Src and Syk.
- Through synergistic effects on these kinases TOP1288 is a potent inhibitor of the inflammatory cascade and offers therapeutic potential in ulcerative colitis and Crohn's disease with minimal systemic absorption which could provide a significant safety advantage over current therapies.
- In healthy subjects TOP1288 (evaluated up to 400mg total daily rectal dose for 4 days) is well tolerated, with measurable drug levels in colonic biopsies in a pharmacologically relevant range but with minimal systemic exposure. Positive signals for target engagement and biological effects were also seen.<sup>1</sup>
- The present phase 1b study was designed to evaluate TOP1288's safety, tolerability, PK and PD in ulcerative colitis patients with active disease.

## Methods

- Subjects (n=6) aged 18-55 years with active ulcerative colitis (total Mayo Clinic Score 5-10; sigmoidoscopy subscore  $\geq 1$ ) experiencing rectal bleeding and receiving oral 5-ASA ( $\leq 2.4$ g/day) were randomized double blind to TOP1288 200mg or placebo rectal solution once daily for 4 days.
- Subjects were resident in a phase 1 accredited clinical trials' unit for assessments.
- Safety parameters were assessed and serial blood samples collected to measure TOP1288 plasma concentrations.
- Subjects had sigmoidoscopy at baseline and (on Day 5) approx. 24 hours after final dose to obtain biopsies from the recto-sigmoid area to measure TOP1288 concentration and selected inflammatory biomarkers.

## Results (i)

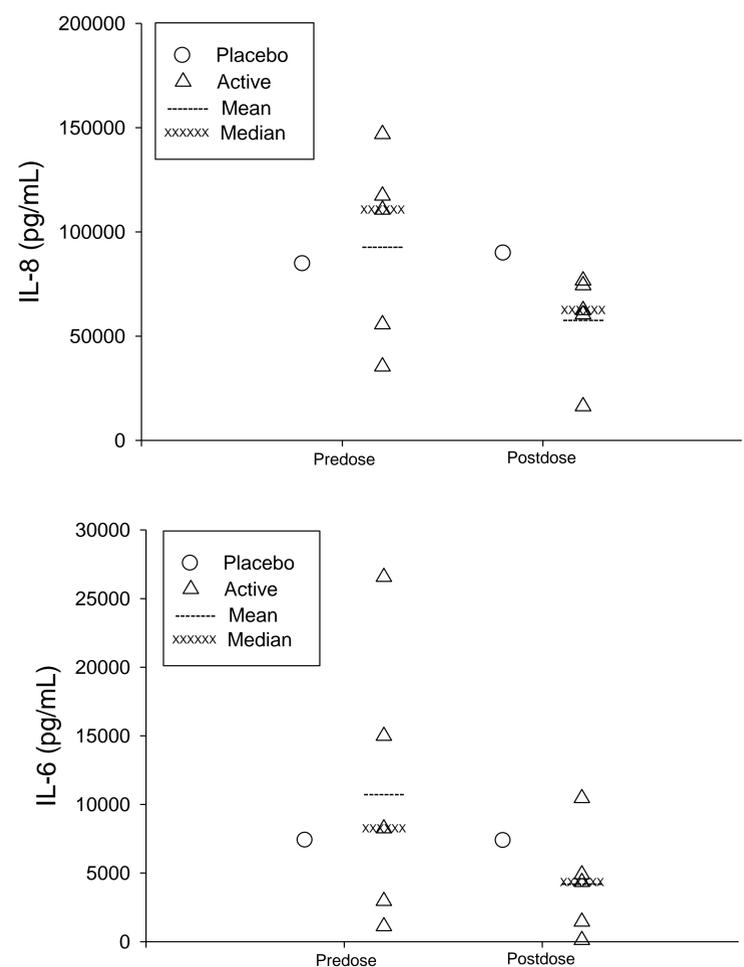
- TOP1288 was well tolerated with no clinically significant findings of note. No Serious Adverse Events (SAEs), or AEs leading to study discontinuation were reported.

## Results (ii)

- Plasma exposure was above the limit of quantification in only 2 subjects and measurable drug concentrations were very low ( $<0.134$  ng/mL).
- Colon tissue exposure approx. 24 hours after final dose was detected in most (4/5) subjects (0.2-1.2 ng TOP1288/mg protein).

## Results (iii)

- 4 days of TOP1288 treatment inhibited IL-8 and IL-6 release from unstimulated whole colonic biopsies: IL-8 median reduced from 111 ug/mL pre-dose to 62 ug/mL post-dose (placebo 85 ug/mL pre-dose; 90 ug/mL post-dose) and IL-6 from 8 ug/mL pre-dose to 4 ug/mL post-dose (placebo 7 ug/mL pre-dose; 7 ug/mL post-dose). (Figure 1).



**Figure 1.** Observed Individual, Mean, and Median unstimulated IL-8 and IL-6 Cytokine Release from Whole Colonic Biopsies

## Conclusions

In this first study in subjects with active ulcerative colitis :

- The NSKI TOP1288 was well tolerated.
- Measurable drug levels were detected in colonic biopsies in a pharmacologically relevant range
- As anticipated based upon pre-clinical and prior phase 1 data, minimal systemic exposure was seen following 4 days of dosing .
- Positive signs of biological activity were demonstrated suggesting a normalization of dysregulated cytokine pathways.
- TOP1288 promises to be an efficacious new therapy for UC patients free from systemic side effects often seen with other non gut restricted therapies.

Reference:

- 1 Rowley A, Duggal A, Taylor M, Foster M, Solanke Y, Sirohi S, Walshe C A, Webber S, Irving P M, Travis S. A First-in-Human Randomized Double-Blind Placebo-Controlled Clinical Trial of a Novel Narrow Spectrum Kinase Inhibitor. *Gastroenterology* 2016; 150 (4), Supplement 1: S776.

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