A first-in-human randomized double-blind placebo-controlled clinical trial of a novel narrow spectrum kinase inhibitor

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Background

- Current treatments for inflammatory bowel disease (IBD) are ineffective in many patients and are limited by serious side effects and safety concerns.
- TOP1288 is a novel narrow spectrum kinase inhibitor (NSKI) that selectively targets kinases (p38-alpha mitogen activated protein kinase, Src family kinases (Src and Lck) and Syk)).
- Through its synergistic effect on these kinases TOP1288 is a potent inhibitor of the inflammatory cascade impacting both innate and adaptive pathways. Data from *in vivo* and *in vitro* models of ulcerative colitis (UC) indicate an efficacy profile that is superior to steroids with the advantage of minimal systemic absorption.
- As such, TOP1288 provides potential for a promising efficacy profile with a significant safety advantage over current therapies.
- This randomized, double-blind, placebo controlled study was designed to evaluate the safety, tolerability and pharmacokinetics of TOP1288 single and multiple ascending doses (SAD and MAD) in healthy volunteers and exploratory markers of target engagement.
- This first-in-human study was conducted with a rectal formulation and a phase 1 study is planned with an oral formulation.

Methods

- 61 healthy subjects aged 18-55 years were randomized to receive single doses of 1, 10, 100, 200mg or 200mg bid and multiple doses (4 days) of 10, 50, 200mg or 200mg bid of TOP1288 or placebo administered as a rectal solution in successive cohorts (4 subjects TOP1288:2 placebo, per SAD cohort; 6:2, MAD).
- Safety parameters were assessed and serial blood samples were collected for measurement of TOP1288 concentration in plasma.
- All subjects had a flexible sigmoidoscopy following bowel preparation at baseline and approximately 24 hours after final dose to obtain colon biopsies from the recto-sigmoid region for measurement of:
  i. TOP1288 concentration.
  ii. IL-8 production in lamina propria mononuclear cells (LPMCs)

Results (1)

- TOP1288 was well tolerated with no clinically significant findings of note. No Serious Adverse Events (SAEs), or AEs leading to study discontinuation were reported. No trends were observed for clinical laboratory values, vital signs, and ECGs.

Results (2)

- Minimal plasma exposure occurred in a small minority of subjects and measurable drug concentrations were very low (<0.42 ng/mL 0-72 hours post first dose) and the maximum concentration reached in any subject (0.416 ng/mL) was 10,000 fold below the limit set by preclinical safety studies (4780 ng/mL). Where concentrations were quantifiable T_{max} was between 1.5 hours and 4 hours after dose administration.
- Colon tissue levels, approximately 24 hours following final dose were measurable in the majority of subjects in the higher dose cohorts (0.2-29.1 ng TOP1288/mg protein).

Results (3)

- Upregulation of IL-8 release was observed in LPMCs isolated from postdose biopsies of the placebo group (Figure 1). The level of IL-8 was markedly reduced in subjects receiving TOP1288 (Figure 2).

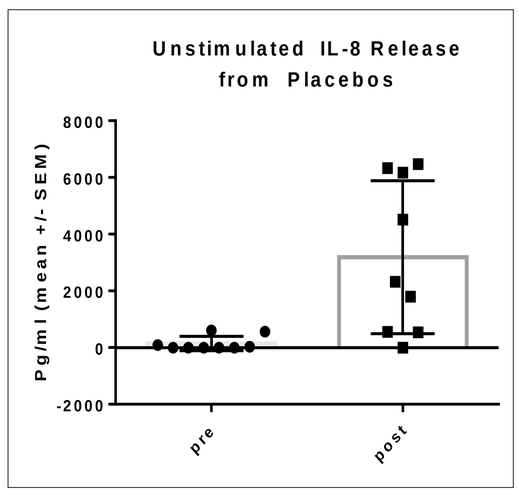

Figure 1. An injury response and upregulation of IL-8 release is observed in LPMCs isolated from post-dose biopsies in the SAD study due to the short time between pre and post dose biopsy excision (24hr). [This response was not observed in the MAD study as it is believed the 4 day window between pre and post dose biopsies allowed for tissue healing].

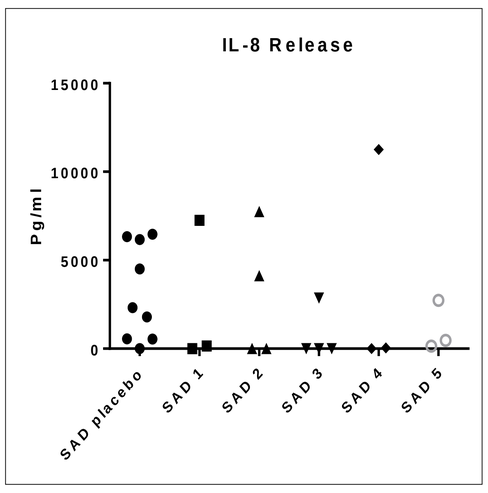

Figure 2. TOP1288 inhibits IL-8 release in isolated LPMCs in higher dose cohorts.

Conclusions

In this first-in-human study:

- TOP1288 was well tolerated.
- Levels of TOP1288 measurable in colonic biopsies were in a pharmacologically relevant range (based on pre-clinical data) even though patients had received bowel preparation and endoscopy prior to the measurement.
- There was minimal systemic exposure of TOP1288 after rectal administration.
- Positive signals of target engagement and biomarker response were seen, in particular IL-8 response.
- Overall, the results are highly promising and support future investigation of TOP1288 as a novel minimally absorbed treatment for patients with ulcerative colitis.

ClinicalTrials.gov ID: NCT02463045

Funding: Topivert Pharma Ltd