ECCO 2018 Abstract

A novel phase 1 trial design to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of TOP1288, a Narrow Spectrum Kinase Inhibitor, delivered topically to the colon via oral administration

Adele Rowley[1], Mike Taylor[1], Ajay Duggal[1] Martyn Foster[1], Sameer Sirohi[1], Yemisi Solanke[1], Claire Walshe[1], Matthew Fyfe[1], Steve Webber,[1] Simon Travis[2]

[1]Topivert Pharma Ltd, London, United Kingdom, [2]Oxford University Hospitals Trust, Translational Gastroenterology Unit, Oxford, United Kingdom

Background

TOP1288 is a topically acting, narrow spectrum kinase inhibitor that selectively targets key kinases (p38apha, Src family kinases and Syk) involved in inflammatory signaling in cells of the innate and adaptive immune systems. TOP1288 has minimal systemic absorption, is free from systemic or local toxicities and has potential to provide a safe and efficacious, chronic dosing treatment for Inflammatory Bowel Disease (IBD) as demonstrated by a prior study with a rectal formulation[3,4]. Combining an innovative trial design with bespoke assays of target engagement and immune responses in serial colon biopsies, this phase 1 study evaluates the safety, tolerability and local pharmacokinetics/pharmacodynamics of orally administered TOP1288.

Methods

Single and multiple doses of TOP1288, formulated as a granule for oral suspension, were administered to healthy male volunteers (n=36) in a phase 1, randomized, double-blind, placebo-controlled study. Safety parameters were assessed and serial blood samples taken for PK analysis. Subjects in Cohorts 1 and 2 received a single dose (200mg BID or 1g BID) (n=7) of TOP1288 or matching placebo (n=3). Cohort 3 subjects received multiple oral doses of TOP1288 (200mg BID, Days 1-3, then 600mg BID Days 4-7) (n=10) or placebo (Day 1 through Day 7) (n=6). To confirm delivery of solubilized TOP1288 to the colon, multiple biopsies were obtained via serial sigmoidoscopies in the same patients up to 36 hours after last dose for measurement of TOP1288 tissue drug concentrations and temporal target engagement/pharmacodynamic responses.

Results

TOP1288 was well tolerated with no safety concerns. Plasma concentrations were low (<0.4ng/mL) whereas, in all subjects, TOP1288 was readily quantified at pharmacologically relevant concentrations (cohort mean range 124-445 ng TOP1288/mg protein) in biopsies taken from multiple areas in the descending colon, even those taken 36 hours after last dose. Stimulated phosphorylated Lck, a marker of target engagement assessed in isolated lamina propria mononuclear cells (LPMCs), decreased in a dose dependent manner with maximal inhibition at 1 g BID (single dose) and 600 mg BID (multiple dose). IL-8 production from LPMCs, a localized innate immune response to biopsy excision (measured in Cohort 3 only) was similarly inhibited up to 24 hours after last dose in subjects receiving TOP1288 (600mg BID).

Conclusion

TOP1288 is safe and well tolerated with low systemic exposure following oral dosing. Sustained, pharmacologically relevant TOP1288 concentrations are delivered to the colon as measured by direct quantification in tissue samples and biomarker assays. TOP1288 is a promising new oral therapy for the treatment of IBD.

Financial Interests: Topivert Pharma Ltd.
ClinicalTrials.gov Identifier: NCT03071081

Refs (count for 30 characters each):

[3]First-in-Human Randomized Double-Blind Placebo-Controlled Clinical Trial of a Novel Narrow Spectrum Kinase Inhibitor
A. Rowley *et al*. Gastroenterology , Volume 150 , Issue 4 , Page S776, April 2016

[4]A first clinical trial of a novel narrow spectrum kinase inhibitor TOP1288 in patients with ulcerative colitis
M. Taylor *et al*. Journal of Crohn's and Colitis, Volume 11, Issue suppl_1, 1 February 2017, Pages S429–S430

Abstract format

- Title: should be brief and in lower case except for acronyms, names, first letter and after colons. Please do not use commercial names, non-standard abbreviations or author names in the title.
  Please note that the following medical terms should be spelled with capital letters: Inflammatory Bowel Disease, Ulcerative Colitis, Acute Severe Colitis.
  Please note that names of products should be spelled with lower case letters (such as vedolizumab, infliximab, ustekinumab, biosimilars, …).
- Authors' list: Please do not mention academic degrees.
- Structure: Abstracts should be structured in the following four sections:
  - Background: indicates the purpose of the study
  - Methods: describe pertinent experimental procedures
  - Results: summarise the results of the research
  - Conclusion: states the main conclusions
- Maximum length of 2750 characters (excl. title & author block, INCLUDING spaces).
- Content:
  - Please use UK spelling.
  - Please spell out Greek or scientific characters in use insert these from the editor.
  - Abbreviations: may be used if standard or if spelled out and defined at the first use (put in parentheses immediately after the first mention of a term or phrase). Compounds should be mentioned with the generic name, in lower cases.
- Abstracts may include tables, graphics and pictures (incl. in max. count of 2750 characters). Each file inserted into the abstract accounts for 200 characters.
- It is allowed to include references. Please note that each reference accounts for 30 characters.
- The max. size of an image is 1,5 MB.
- In case of complex tables or heavy graphics, please seek help from Smart Abstract (info@smart-abstract.com) minimum three working days before the submission deadline.