

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

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Background

- TOP1288 is a topically acting, narrow spectrum kinase inhibitor that selectively targets key kinases (p38alpha, Src family kinases and Syk) involved in inflammatory signalling 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).
- Combining an innovative trial design with bespoke assays of target engagement and inflammatory 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 clinically significant findings of note. No Serious Adverse Events (SAEs), or AEs leading to study discontinuation were reported.
- Plasma concentrations were consistently low (<0.4ng/mL).
- TOP1288 was readily quantified at pharmacologically relevant concentrations in biopsies taken from multiple areas (Fig 1) in the descending colon, even those taken 36 hours (Day 3) after last dose. There was excellent concordance between duplicate samples.

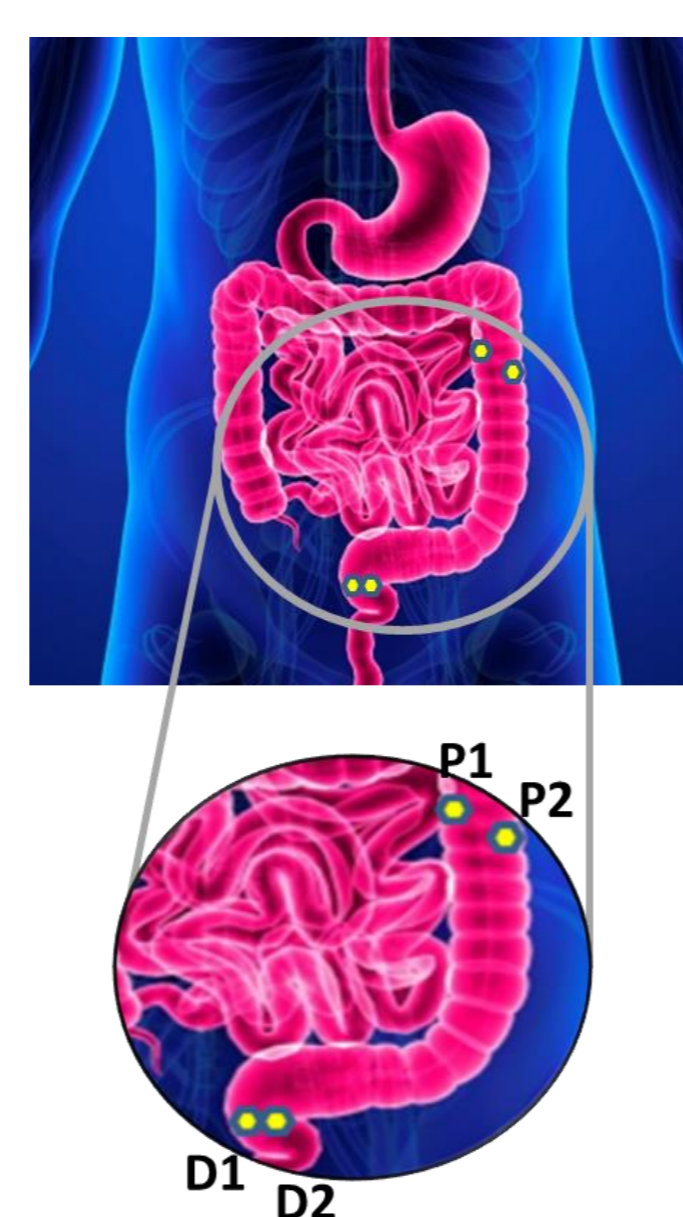


Figure 1. Biopsy sampling strategy. Duplicate biopsies taken proximally (P1/P2) and distally (D1/D2)

Biopsy Location	Statistic	TOP1288 Single Dose				TOP1288 Multiple Dose	
		Cohort 1 200 mg BID (N=7)		Cohort 2 1 g BID (N=7)		Cohort 3 600 mg BID (N=10)	
		Day 2	Day 3	Day 2	Day 3	Day 7	Day 8
Proximal	Mean	222.9	187.4	616.5	642.2	527.8	744.8
	SD	505.1	507.7	779.8	1586.2	431.0	1164.0
	N	14	14	14	14	20	20
Distal	Mean	24.7	69.7	200.7	42.2	303.7	145.5
	SD	41.1	140.2	327.7	58.6	358.3	272.5
	N	14	14	14	14	20	20

Table 1. Colon Tissue Drug Concentrations (ng/mg adjusted for protein concentration) versus excision Location by Treatment and Time Point.

Results

- 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) (Fig 2).

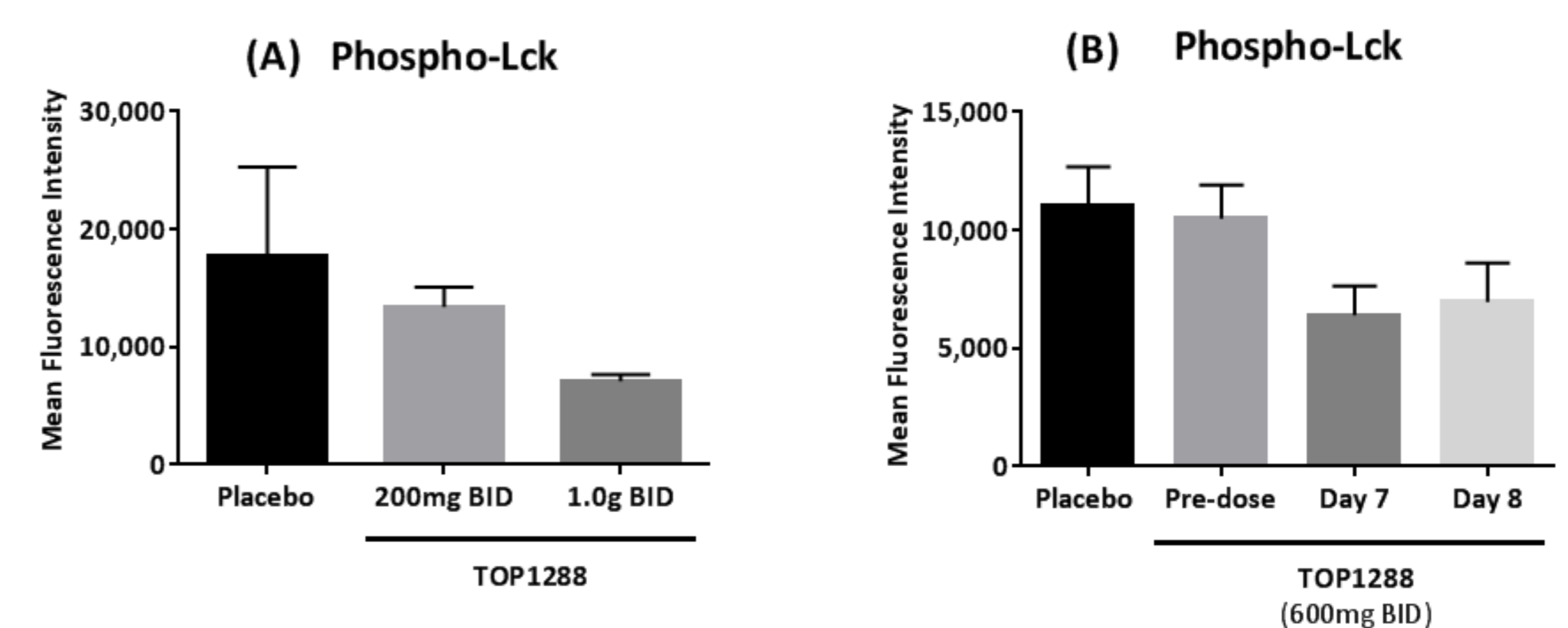


Figure 2. Lck phosphorylation in Lamina Propria Mononuclear Cells isolated from colonic (rectosigmoid) biopsies following (A) single-day or (B) multiple-day oral dosing with TOP1288.

- 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 (Fig 3) in subjects receiving TOP1288 (600mg BID).

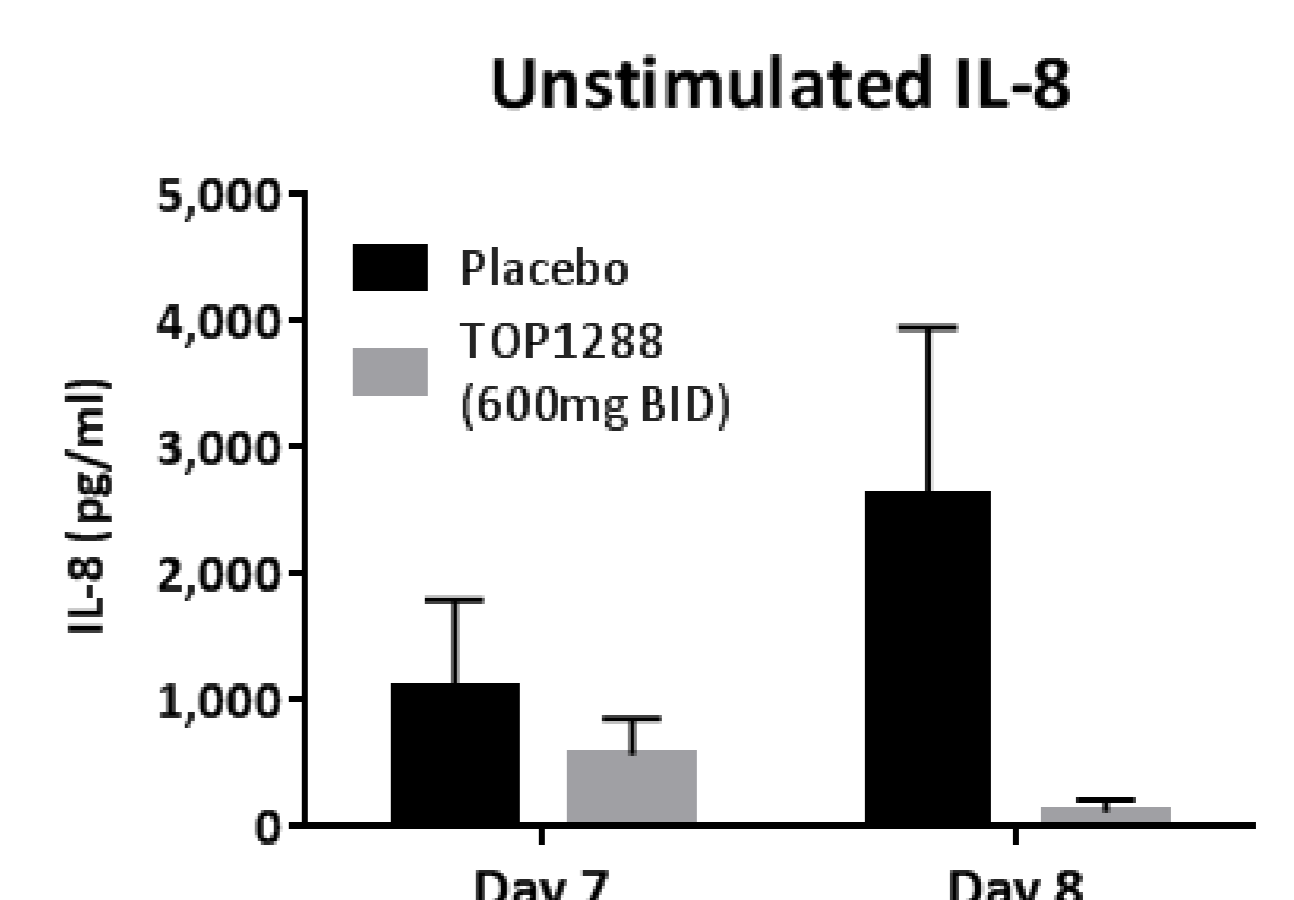


Figure 3. IL-8 release from Lamina Propria Mononuclear Cells isolated from colonic (rectosigmoid) biopsies following multiple-day oral dosing with TOP1288.

Conclusions

- TOP1288 is safe and well tolerated with consistently 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.
- 100-600mg TOP1288 is an appropriate dose range to be explored in a phase 2 PoC trial. Sustained exposure in colon tissue, even after a single dose, supports once daily dosing.
- TOP1288 is a promising new oral therapy for the treatment of IBD.