

Oral Administration of SOR102 Delivers Anti-TNF/IL-23 Activity Directly to Colonic Tissue and Drives Clinical and Pharmacodynamic Responses in Ulcerative Colitis Patients

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INTRODUCTION

Emerging evidence from ulcerative colitis (UC) suggest that dual blockade of IL-23 and TNF α is superior to either agent alone.¹ SOR102 is a novel, orally delivered, bispecific antibody construct containing two humanized single domain antibodies (SDA) targeting TNF α and IL-23p19 connected by a trypsin-labile linker, enabling monomer separation within the small intestine and inhibition of TNF α and IL-23 activity within GI tissue with minimal systemic exposure. SOR102 SDAs were engineered for stability to intestinal and inflammatory proteases, enabling oral dosing.² The Phase 1, first-in-human study (SOR102-101; NCT06080048) had 3 parts. Parts 1 and 2 enrolled healthy subjects (results presented previously).³ Part 3 was a Phase 1b randomized, double-blind, placebo-controlled study in patients with mild to severe UC. Part 3 safety, efficacy, and immunogenicity results were reported in detail previously.^{4,5} Here, we present Part 3 biodistribution and tissue pharmacodynamic (PD) results, and their correlation with clinical results.

SORRISO PLATFORM

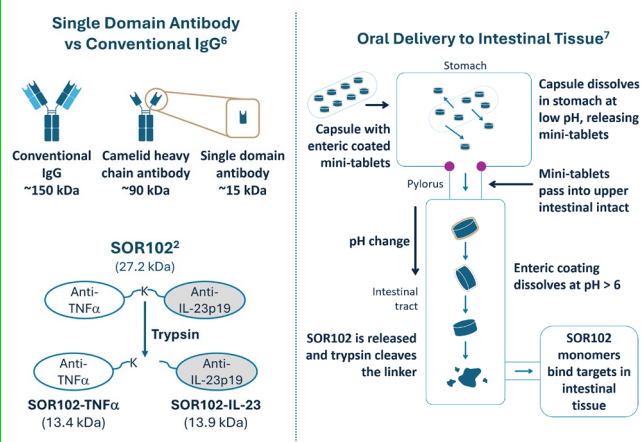


Figure 1. SOR102 Mechanism of Action. SOR102 has picomolar affinity to TNF α and IL-23p19 and can bind both targets simultaneously. Both domains of SOR102 are humanized and protease-resistant, conferring stability during transit through the GI tract. The trypsin-labile linker is cleaved by endogenous trypsin, releasing active SOR102 monomers to independently engage each target in tissue.

METHODS

Patients with a Mayo endoscopy score (ES) of ≥ 2 , a rectal bleeding score (RBS) of ≥ 1 and stool frequency score (SFS) of ≥ 1 were randomized 1:1:1 to receive SOR102 810mg QD, SOR102 810mg BID, or placebo for 6 weeks. Patients underwent baseline and end-of-treatment sigmoidoscopies and biopsy collection for disease scoring and exploratory pharmacodynamic (PD) endpoints. The primary objective was safety and tolerability of SOR102. Secondary objectives were the concentration of SOR102 and monomers in serum, urine and feces, and anti-drug antibodies (ADA). Serum and ADA data were presented previously.⁵ Exploratory efficacy endpoints included Mayo Score (MS) and modified MS (MMS) clinical response, symptomatic remission, clinical remission, and change from baseline in MS, MMS, UC-100 score, SFS, and RBS, among other previously-reported endpoints.⁴ Safety and efficacy were evaluated in patients who received at least 1 dose of SOR102 or placebo (intention-to-treat; ITT). Efficacy was also evaluated in patients who completed the study (Per Protocol; PP). Exploratory colonic tissue PD endpoints included measurement of SOR102 monomers, cytokine protein levels and gene expression changes. Serum cytokine protein levels were also assessed. PD outcomes are reported for the PP population.

BASELINE DEMOGRAPHICS AND SAFETY RESULTS

- 22 patients were randomized (ITT; Table 1), 17 patients completed the study Per Protocol (QD n=6, BID n=5, Placebo n=6). Reasons for discontinuation: worsening of UC (n=2), study schedule non-compliance (n=2) and consent withdrawal (n=1).
- Median MS was 8 (range 6-11) with >90% patients advanced therapy-naïve.
- No clinically significant changes in safety laboratory parameters, dose-limiting toxicities, or events suggestive of pronounced immunosuppression
- All but one TEAE were mild to moderate
- 1 severe and serious TEAE of worsening UC requiring hospitalization was not considered related to treatment. This TEAE occurred during follow-up in a SOR102 BID patient
- 4 QD and 2 BID patients developed ADA responses after SOR102 dosing (anti-SOR102-TNF only, n=1; anti-SOR102-IL-23 only, n=2; ADA against both monomers n=3). Most titers were low ($\leq 1:240$) and not associated with safety or clinical response⁵

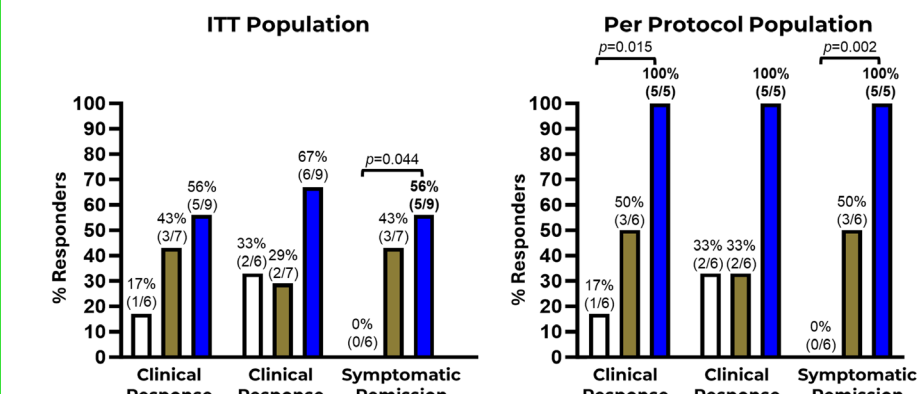
Table 1. Baseline Demographics				
	Placebo (N=6)	SOR102 810mg QD (N=7)	SOR102 810mg BID (N=9)	Total (N=22)
Age, years	53 (17)	49 (18)	49 (16)	50 (16)
Sex, female	3 (50)	2 (29)	7 (78)	12 (55)
Extensive Disease (Pancolitis)	2 (33)	2 (29)	1 (11)	5 (23)
Full Mayo score (MS)	8 (6, 9)	9 (6, 10)	7 (6, 11)	8 (6, 11)
Modified Mayo score (MMS)	6 (4, 7)	7 (5, 8)	5 (4, 9)	6 (4, 9)
Number (%) of patients MES=3	1 (17)	6 (86)	5 (56)	12 (55)
FCAL, median	453.5 (69, 6001)	1559.0 (322, 3893)	1302.0 (12, 5483)	1226.0 (12, 6001)
CRP, median	2.90 (2.9, 157.8)	7.30 (5.3, 56.5)	5.80 (2.9, 38.6)	5.60 (2.9, 157.8)
Prior use of biologics	0 (0)	2 (29)	0 (0)	2 (9)
Concomitant UC meds at baseline				
None	0 (0.0)	1 (14)	1 (11)	2 (9)
Corticosteroids	1 (17)	1 (14)	2 (22)	4 (18)
Aminosalicylates	5 (83)	6 (86)	8 (89)	19 (86)

Data are n (%), mean (SD), or median (min, max); FCAL=fecal calprotectin; CRP=C-reactive protein

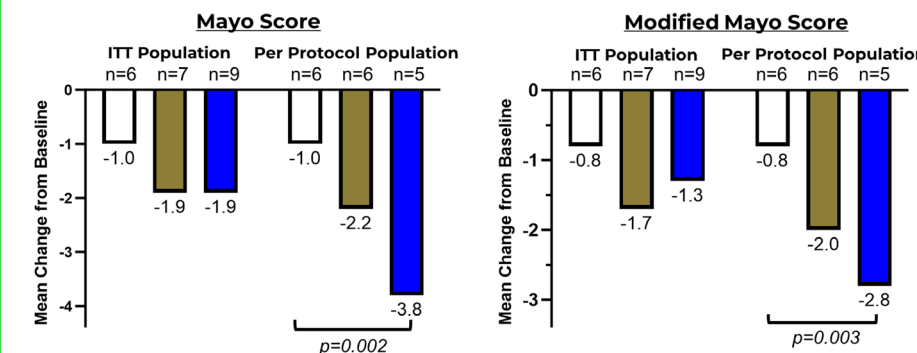
* One patient received adalimumab, and one patient received mirikizumab, both in clinical trials

RESULTS 1 – CLINICAL EFFICACY OF SOR102

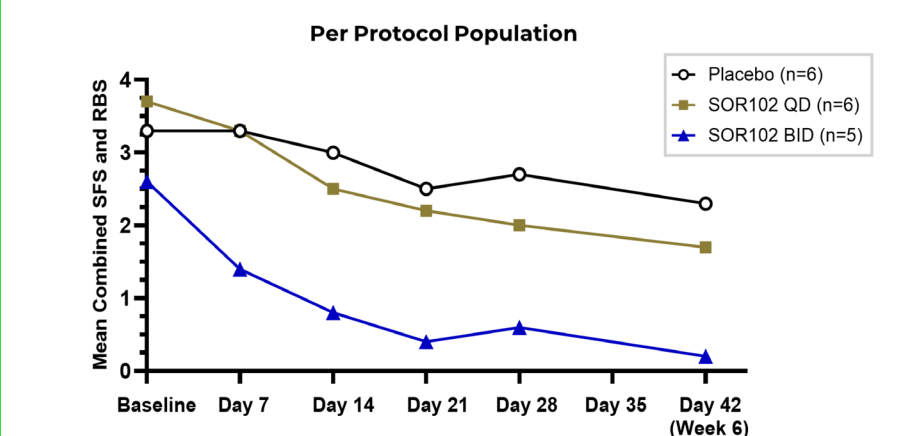
A. Proportion of Patients Achieving Clinical Response and Symptomatic Remission



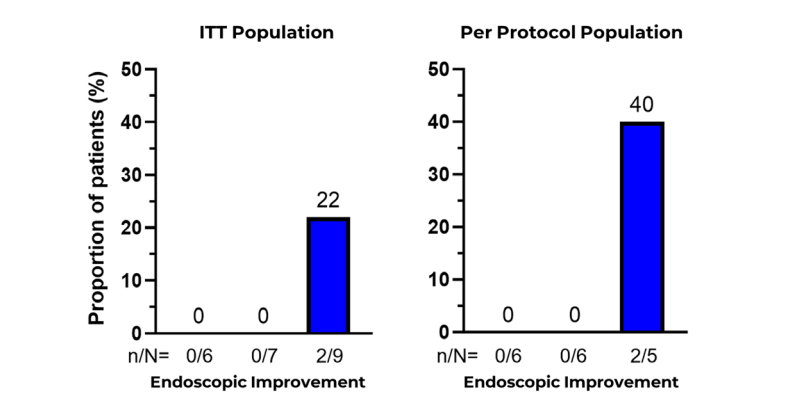
C. Mean Change from Baseline in Mayo Score and Modified Mayo Score



E. Mean Change from Baseline in Combined SFS and RBS



B. Proportion of Patients Achieving Clinical Remission



D. Mean Change from Baseline in UC-100 Score

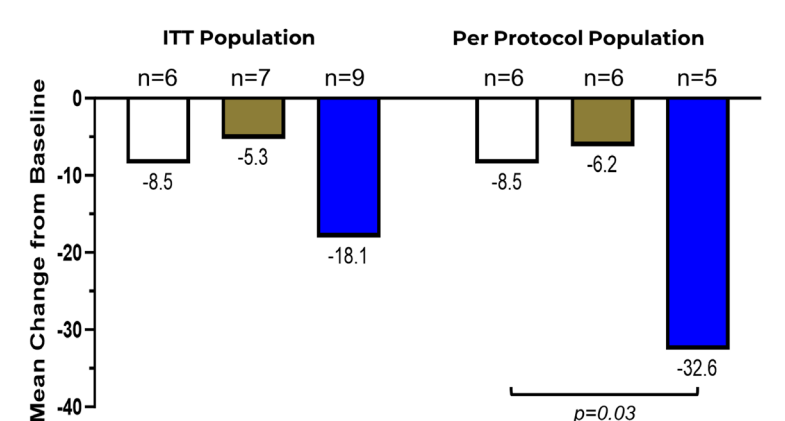


Figure 2. Exploratory efficacy outcomes in patients with UC. A. Higher rates of clinical response by MS and MMS, and symptomatic remission were observed in the SOR102 BID group for both the ITT and PP populations. B. Only patients in the SOR102 BID group reached clinical remission by endoscopic improvement. C. A dose-dependent effect was observed for the PP population in change from baseline for MS and MMS, with the SOR102 BID group showing the largest decrease in both. D. The SOR102 BID group showed the largest decrease in UC-100 score in both the ITT and PP populations. E. The SOR102 BID group showed a rapid and sustained decrease in SFS and RBS over the treatment period. Panels A-D: ITT population dataset uses the last observation carried forward (LOCF) method to assess end-of-treatment (EOT) scores for patients who did not complete treatment. LOCF used the last observation for each individual subscore to arrive at an EOT compound score in the case of MS, MMS, and UC-100. Panel A,B: Fisher's Exact Test. Panel C ITT: Fisher's Exact Test. Panel C PP, Panel D: ANCOVA.

RESULTS 2 – FECAL RECOVERY OF ACTIVE SOR102 AND MONOMERS

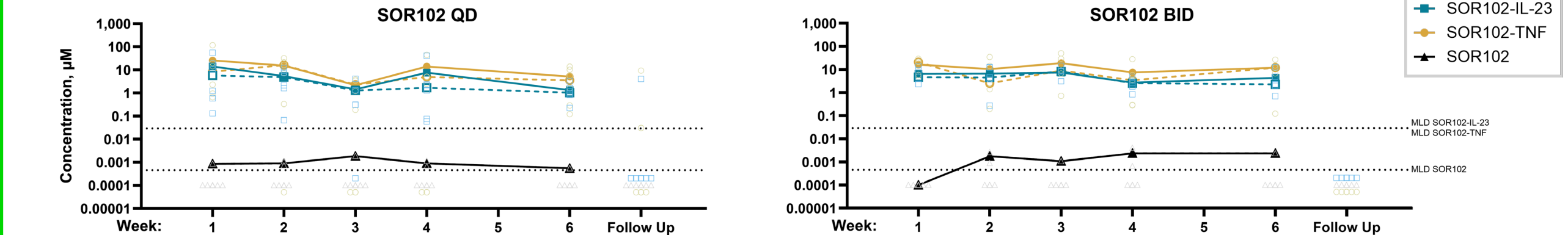


Figure 3. Fecal recovery of active, i.e. cytokine-binding, SOR102 and its monomers from patients with UC who completed treatment Per Protocol. Fecal concentrations for all analytes were determined using assays that required binding of active SOR102 and monomers to target cytokine(s). SOR102-TNF and SOR102-IL-23 were quantified at levels up to 4 orders-of-magnitude higher than SOR102. Serum and urine were assayed for SOR102 and monomers at Weeks 1-6. Active SOR102-IL-23 was only quantified at low levels in the serum of a single QD patient⁵ and active SOR102-TNF was only quantified in 13 urine samples across QD n=3 and BID n=4 patients. No SOR102 was quantified in any sample. All panels: Open symbols denote all individual samples collected and analyzed. Horizontal dotted lines denote the minimum level of detection (MLD) of each analyte. Open symbols below the SOR102 MLD line represent samples negative for the analyte with the corresponding shape/color. Solid lines denote mean values and dashed lines denote median values calculated from samples with detectable levels of each respective analyte. If all samples at a specific timepoint were negative for an analyte, the mean and median lines are below the MLD. Note that SOR102 mean and median lines overlap. Mean and median values were not calculated for the follow-up time point.

RESULTS 3 – PHARMACODYNAMIC EFFECTS OF SOR102 ON CYTOKINE PROTEIN LEVELS AND GENE EXPRESSION MODULES IN COLONIC TISSUE

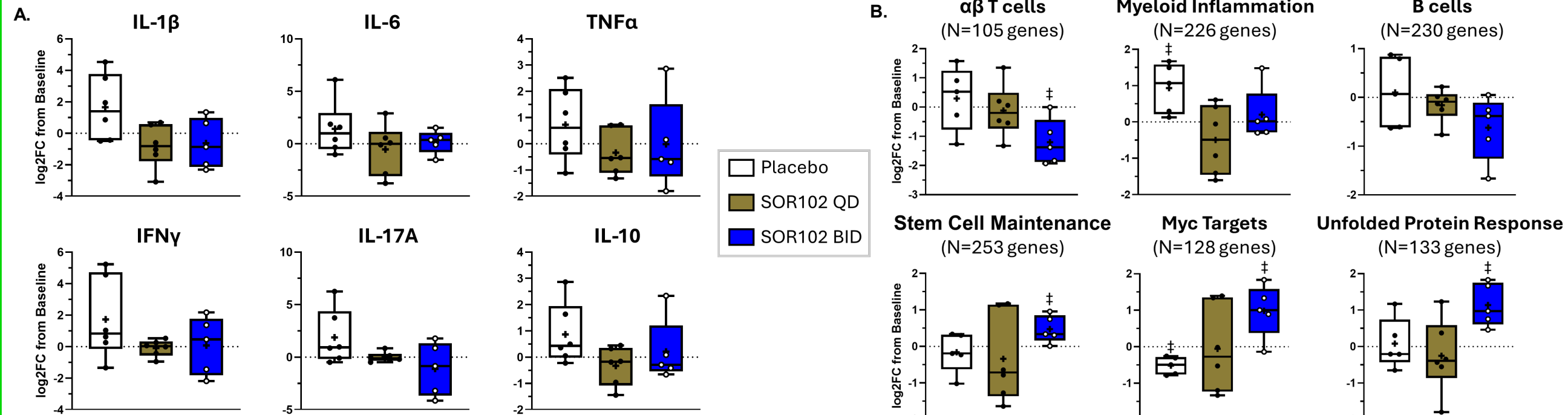


Figure 4. Change from baseline for pathologic cytokine proteins and gene expression modules in colonic biopsy homogenates from patients with UC. A. Log2 fold-change (Log2FC) of cytokine protein concentrations in biopsy homogenates from baseline to end of treatment (day 42, EOT). Serum cytokines were examined weekly and showed no consistent changes over the treatment period. B. Log2FC of gene correlation network (GCN) analysis module scores in biopsy homogenates from baseline to EOT. $\dagger$ $p < 0.05$ between baseline and EOT within treatment group. All panels: boxes indicate median and interquartile range while whiskers represent the min and max values in each dataset. Mean values are denoted as "+". Each point corresponds to a unique patient. Horizontal dotted line indicates Log2FC of 0 (no change from baseline to EOT) while values below the line indicate a decrease from baseline to EOT. QD n=6; BID n=5; Placebo n=6 for cytokines, n=5 for GCN.

RESULTS 4 – TISSUE PENETRATION OF SOR102 MONOMERS

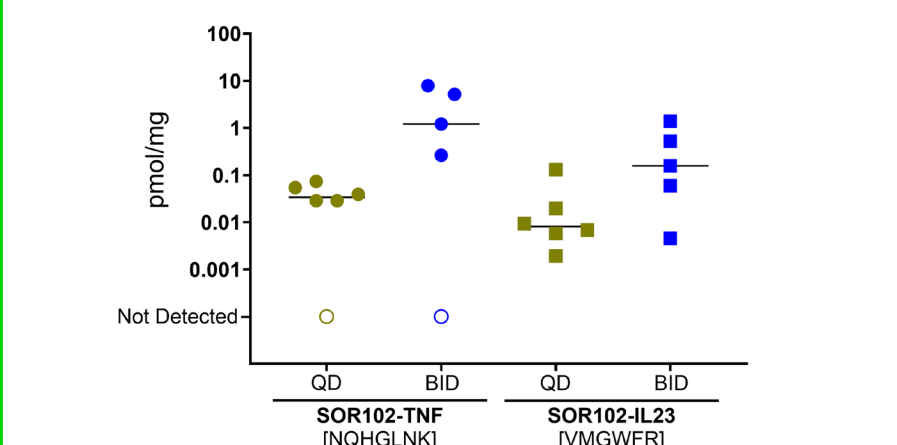


Figure 5. Levels of SOR102-TNF and SOR102-IL-23 at end of treatment in colonic biopsy homogenate samples from patients with UC. Displayed values represent pmol of a representative peptide for SOR102-TNF (NQHGLNK) and SOR102-IL-23 (VMGWFR), measured by targeted mass spectrometry, per mg of total protein in biopsy homogenates (rather than neat tissue). Closed symbols denote samples with detectable monomer peptides while open symbols denote samples with no detectable monomer peptides. Lines denote medians of each peptide. Samples with no peptide detected are included in the median value calculation as "0".

CONCLUSIONS

- SOR102 was safe and well tolerated.
- SOR102 BID demonstrated strong and consistent activity across multiple clinical and tissue PD endpoints in patients with UC.
- High and sustained levels of active monomers in feces confirmed SOR102 is efficiently cleaved by trypsin and cytokine-binding activity is maintained after oral dosing in patients with UC.
- Levels of SOR102 monomers in sigmoid colonic tissue increased with oral dose, with minimal systemic exposure.
- Increases in colonic tissue IL-1 β , IL-6, TNF α , IFN- γ , IL-17A, and IL-10 were observed with placebo, whereas decreases or no change were observed with SOR102.
- Gene modules associated with inflammatory immune cell types ($\alpha\beta$ T cells, myeloid cells, B cells) decreased in both SOR102-treated groups compared to placebo, while modules associated with regenerative pathways (stem cell maintenance, Myc targets, unfolded protein response) increased with SOR102 BID.

PRESENTER CONFLICTS OF INTEREST

V.J. (Presenter) reports potential conflicts of interest with AbbVie, Alimentiv, Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Avoro Capital, Bristol Myers Squibb, Celltrion, Eli Lilly, Endpoint Health, Entera, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Glaxo, Innovent, JAMP Pharma Group, Janssen, Merck, Melinta, Mylan, Pandion, Pandox, Pfizer, Protonix, Promethix Biosciences, Reliance Biopharma, F. Hoffmann La Roche, LtdGenentech, Novartis, Sandoz, Second Genome, Shire, Sorriso, SynGene, Takeda, Toronto Dominion Securities, Teva, Tivoli, Vertex, Vividion.

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