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PHASE 1B STUDY OF SOR102, A NOVEL, ORALLY DELIVERED BISPECIFIC ANTI-TNF/ANTI-IL-23 DOMAIN ANTIBODY IN PATIENTS WITH MILD TO SEVERE ULCERATIVE COLITIS

V. JAIRATH[1], S. DANESE[2], G. D'HAENS[3], B. FEAGAN[4], L. PEYRIN-BIROULET[5], B. SANDS[6], P. WEDEL[7], S. BARBAT[7], C. SATTLER[7]

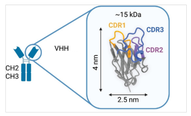
1. Western University, London, ON, Canada.
2. Universita Vita-Salute San Raffaele Facolta di Medicina e Chirurgia, Milano, Lombardia, Italy.
3. Amsterdam UMC Locatie AMC, Amsterdam, Noord-Holland, Netherlands.
4. Alimentiv Inc, London, ON, Canada.
5. Universite de Lorraine, Nancy, Grand Est, France.
6. Icahn School of Medicine at Mount Sinai, New York, NY, United States.
7. Sorriso Pharmaceuticals, Sandy, UT, United States.

INTRODUCTION

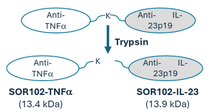
Emerging evidence from ulcerative colitis suggest that dual blockade of IL-23 and TNF is superior to either agent alone[1]. SOR102 is a novel, orally delivered, bispecific antibody construct containing two humanized single domain antibodies (SDA) targeting TNFα and IL-23p19 connected by a trypsin-labile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

SORRISO PLATFORM

Heavy Chain Only VHH Single Domain Antibody[2]

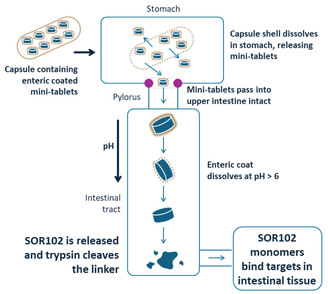


SOR102[3]



SOR102-TNFα (13.4 kDa) **SOR102-IL-23** (13.9 kDa)

Oral Delivery to Intestinal Tissue[4]



SOR102 Mechanism of Action. SOR102 has picomolar affinity to TNFα and IL-23p19, and can bind both targets simultaneously. Both domains of SOR102 are humanized and protease-resistant, conferring GI stability. 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 BID, SOR102 810mg QD, or placebo for 6 weeks. The primary objective was safety and tolerability of SOR102. Secondary objectives were the concentration of SOR102 and monomers in serum, urine and feces, and antidrug antibodies. Exploratory efficacy endpoints were Mayo Clinic Score (MCS) and modified MCS (mMCS) clinical response, symptomatic remission, and mean change from baseline in MCS, mMCS, UC-100 score, stool frequency score (SFS), rectal bleeding score (RBS), fecal calprotectin (FC), C-reactive protein (CRP), and Robarts Histopathology Index (RHI). Safety and efficacy were evaluated in patients who received at least 1 dose of SOR102 or placebo (ITT). Efficacy was also evaluated in patients who completed the study (Per Protocol).

EXPLORATORY EFFICACY RESULTS

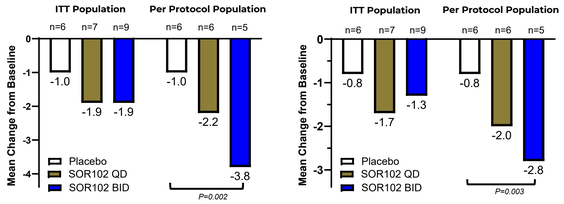
Twenty-two patients were randomized (ITT: SOR102 810mg BID=9; SOR102 810mg QD=7; placebo=6); 17 patients completed the study Per Protocol. Reasons for discontinuation were worsening of UC (N=2), study schedule non-compliance (N=2) and consent withdrawal (N=1). Mean age was 50 yrs; 45% were male. The median MCS was 8 (range 6-11). Most patients were advanced therapy-naive. A summary of baseline characteristics is shown in Table 1.

Table 1. Baseline Demographics

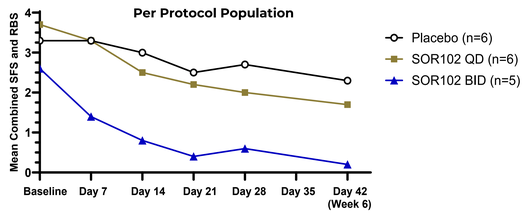
	Placebo (N=6)	SOR102 810mg QD (N=7)	SOR102 810mg BID (N=9)	Total (N=22)
Age, years	53 (17)	49 (18)	49 (16)	50 (16)
Sex, female	3 (50)	2 (29)	7 (78)	12 (55)
Extensive Disease (Pancolitis)	2 (33)	2 (29)	1 (11)	5 (23)
Full Mayo score	8 (6, 9)	9 (6, 10)	7 (6, 11)	8 (6, 11)
Modified Mayo score	6 (4, 7)	7 (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

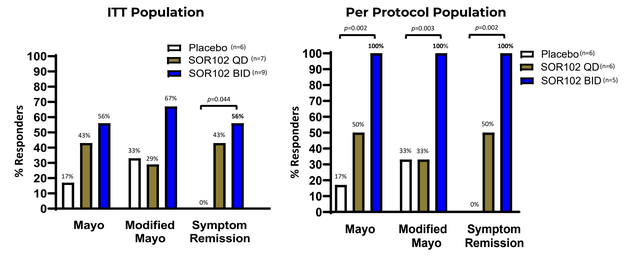
Mean Change from Baseline in Mayo Score and Modified Mayo Score



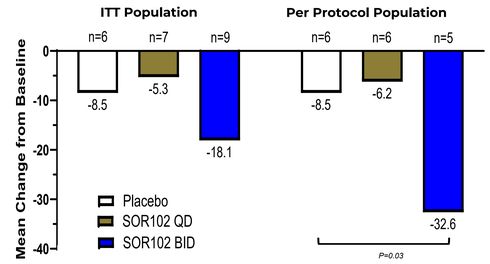
Mean Change from Baseline in Combined SFS and RBS



Proportion of Patients Achieving Clinical Response and Symptomatic Remission



Mean Change from Baseline in UC-100 Score



The Figures show exploratory efficacy results. Higher rates of MCS and mMCS clinical response and symptomatic remission, and greater decreases from baseline in MCS, mMCS, UC-100, combined SFS+RBS, and RHI (figure not shown) were observed in the SOR102 BID arm compared with QD and placebo. There were no significant differences in FC and CRP between the treatment groups.

SAFETY RESULTS

Treatment emergent adverse events (TEAEs) were reported in 57%, 29%, and 50% of patients receiving SOR102 810mg BID, SOR102 810mg QD, or placebo, respectively (Table 2). Most were mild-to-moderate in severity. One AE (SOR102 810mg BID arm) was considered possibly related to SOR102 (abdominal pain of mild severity). One unrelated serious AE of worsening of UC that led to hospitalization was observed in the SOR102 810mg BID arm.

Table 2. Treatment Emergent Adverse Events

	Placebo (N=6)	SOR102 810mg QD (N=7)	SOR102 810mg BID (N=9)	Total (N=22)
Total Number of TEAEs	5	2	6	13
Number of patients with ≥1 TEAE	(50)	2 (29)	5 (56)	10 (46)
Number of patients with TEAEs leading to study discontinuation	0 (0)	0 (0)	2 (22)	2 (9)
Number of patients with ≥1 SAE	0 (0)	0 (0)	1 (11)[1]	1 (5)
Number of patients with SAEs leading to study discontinuation	0 (0)	0 (0)	1 (11)	1 (5)
Number of patients with ≥1 TEAE by maximum severity				
Mild	1 (17)	1 (14)	2 (22)	4 (18)
Moderate	2 (33)	1 (14)	2 (22)	5 (23)
Severe	0 (0)	0 (0)	1 (11)	1 (5)
Number of patients with ≥1 TEAE by relationship to Treatment				
Possibly related	0 (0)	0 (0)	1 (11)[2]	1 (5)
Not related	5 (83)	2 (29)	5 (55)	12 (55)

1. Worsening of UC that led to hospitalization 2. Abdominal pain of mild severity

SERUM PK AND IMMUNOGENICITY RESULTS

Serum PK

- One patient in the SOR102 QD arm had detectable SOR102-IL-23 monomer levels in serum. All other samples were below the lower limits of quantification for SOR102 and monomers.

Immunogenicity

- 2 patients (1 Placebo, 1 QD) were ADA+ for both monomers at Baseline
- 6 patients (4 QD, 2 BID) developed ADA+ responses after SOR102 dosing
  - Anti-TNF monomer only =1, Anti-IL-23 monomer only = 2, Both = 3
- Most ADA titers were low (≤1:240) and not associated with safety or clinical response

CONCLUSIONS

- SOR102 was safe and well tolerated.
- In most samples tested, there were no detectable levels of SOR102 or monomers in serum
- ADA titers were low in most patients and not associated with safety or decreased clinical response.
- Efficacy across multiple endpoints was observed in the SOR102 BID arm compared to QD and placebo, despite the short treatment duration.
- Further clinical development of SOR102 is warranted

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CONTACT INFORMATION

Carlos Sattler (csattler@sorrisopharma.com)