Novel orally delivered bispecific antibody for local GI activity: SOR102, an anti-TNFα/anti-IL-23 antibody in clinical development for treatment of Inflammatory Bowel Disease

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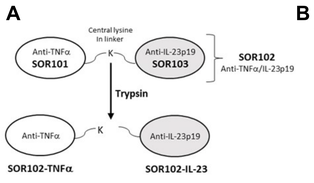
Abstract

TNFα and IL-23 are highly validated targets for inflammatory bowel disease (IBD). However, the approved therapeutics require systemic administration by intravenous (IV) or subcutaneous injection, subjecting patients to increased risk of systemic immunosuppression. Combination systemic TNF/IL-23 inhibition recently demonstrated encouraging clinical efficacy in patients with ulcerative colitis (UC) suggesting additive benefit of inhibiting these two pathways simultaneously, although safety and efficacy of long-term systemic combination therapy is not yet demonstrated. SOR102 is a novel orally delivered biologic that neutralizes TNF and IL-23 activity within GI tissue, limiting systemic exposure and immunosuppression, in a single molecule for manufacturing, storage, and dosing. SOR102 contains two humanized single domain antibodies, SOR101 (anti-TNF) and SOR103 (anti-IL-23p19), connected by a trypsin-labile central linker enabling liberation of the monomers within the small intestine. In contrast to traditional monoclonal antibodies, SOR101 and SOR103 were specifically engineered for high stability among intestinal and inflammatory proteases. SOR102 is formulated into enteric-coated mini-tablets that are encapsulated into size 0 HPMC hard capsules. Mini-tablets are stable in the stomach but disintegrate at higher pH levels in the small intestine to expose SOR102 to intestinal trypsin, liberating anti-TNF and anti-IL-23 monomers to cross the disrupted lining of an inflamed gut and engage TNF/IL-23 within the lamina propria. Thus, SOR102 will deliver simultaneous and durable TNF/IL-23 inhibition within inflamed GI tissue after oral dosing. This SOR102 formulation is stable at room temperature, eliminating cold chain reliance required by injectable therapies. After oral administration of SOR101 and SOR103 to mice, high levels of active SOR101 and SOR103 were detected in the feces, confirming molecular stability throughout the intestinal tract. SOR102 also demonstrates full activity against TNF/IL-23 before and after trypsin cleavage. In ex vivo cultures of colonic biopsies from UC patients, treatment with SOR101 or SOR103 inhibited tissue phosphoprotein levels alone and, to a greater extent, in combination. Systemic exposure after oral dosing of SOR102 is expected to be low and transient since SOR102 monomers have a short elimination half-life from serum after single or multiple IV doses to cynomolgus monkeys (NHPs). Urine recovery data suggest that SOR102 monomers are predominantly cleared by the renal route. Collectively, these data support a low risk of systemic immunosuppression after oral SOR102 dosing in IBD patients. SOR102 is the first orally delivered anti-TNF/anti-IL-23 dual-specific therapeutic and is currently in a Phase I/Ib clinical trial to assess safety, pharmacokinetics and pharmacodynamics in healthy volunteers and UC patients (NCT06080048).

Sorriso Technology



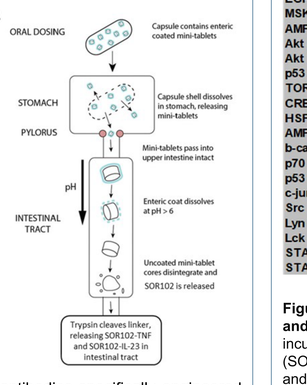


Figure 1. Sorriso molecule summary. (A) SOR101 and SOR103 are single domain antibodies against TNFα or IL-23p19, respectively. SOR102 is a bispecific molecule comprised of SOR101 and SOR103 sequences connected with a trypsin-labile linker due to a lysine residue. SOR102-TNF and SOR102-IL-23 are the trypsin-liberated monomers after exposure of SOR102 to trypsin. (B) Mechanism of oral delivery and release of SOR102.

The Sorriso platform uses single domain antibodies specifically engineered to directly access and maintain activity within inflamed tissue via local delivery routes. Single domains can be dosed individually or linked together in one molecule for multi-target specificity. Humanization and Sorriso engineering results in high stability among intestinal and inflammatory proteases, while scalable production in yeast strains (*S. cerevisiae* or *Pichia pastoris*) allow for an attractive cost of goods and stability at room temperature eliminates cold chain reliance.

Materials and Methods

SOR101, SOR102, and SOR103 were produced and purified from yeast. SOR102 was incubated in pooled human fecal supernatant (HFS) and assessed by SDS-PAGE gel for degradation across time. Inhibition curves of SOR101, SOR102, SOR103, and trypsin-liberated SOR102 monomer arms were assessed by ELISAs whereby SOR molecules competed with biotinylated adalimumab (anti-TNFα IgG1) or interrupted IL-23/IL-23-receptor binding. UC colonic biopsies were collected from patients and incubated with SOR101, SOR103, or both and phosphoarray data were collected. Concentrations of SOR102 and its monomer arms in NHP intestinal contents, feces, and serum were also quantified by ELISA, with additives to limit matrix interference, following oral (intestinal, fecal) or IV (serum) dosing.

For extended methods, see figure legends and associated publication via the QR code.

Results

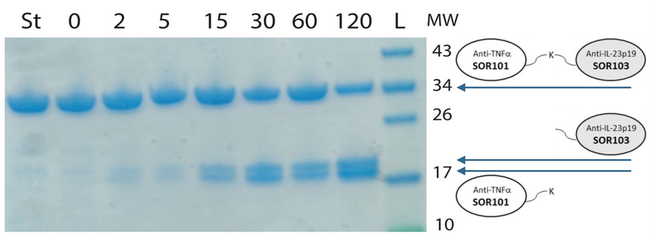


Figure 2. The SOR102 central lysine linker is cleaved in intestinal supernatants. SOR102 was incubated at 37 °C with 1/1,000 diluted human fecal supernatant (HFS). Samples were taken for SDS-PAGE analysis at selected time intervals, shown in minutes (horizontal numbers). Equal volumes were loaded per lane. 'St' is undigested SOR102 standard. L = protein standard EZ-Run Prestained Ladder. MW = Molecular weight in kDa (vertical numbers).

	Average Phosphorylation Signals (N=4 Biopsies / Treatment)			
	ID2A	SOR101	SOR103	Combo
p38alpha	11468	10914	9817	8579
ERK1/2	7413	5062	4727	3620
JNK pan	18007	17209	17001	16040
GSK-3a/b	15038	12609	12469	10723
p53 S392	11176	4947	4767	3428
EGF R	6444	4789	5814	3729
MSK1/2	13269	12154	10176	11458
AMPKa1	6327	3378	4690	2836
Akt S473	8267	5381	5692	4121
Akt T308	14669	5191	6841	4738
p53 S46	15689	7731	7559	6318
TOR	10453	7356	6783	6876
CREB	8140	5208	5218	4216
HSP27	6876	4663	6403	3425
AMPKa2	12011	9836	9029	9946
b-catenin	5664	2916	3325	2049
p70 S6K T389	9591	2780	3339	2331
p53 S15	8124	2958	4135	2416
c-jun	9856	6354	7416	5224
Src	12972	11282	10343	10886
Lyn	8424	5588	4971	4111
Lck	5604	3207	4783	1781
STAT2	13970	10307	9533	11693
STAT5a	10149	6097	6004	5799

	Average Phosphorylation Signals (N=4 Biopsies / Treatment)			
	ID2A	SOR101	SOR103	Combo
p70 S6K T/S	8845	3116	3652	2455
RSK1/2/3	9393	4187	4513	3847
eNOS	6139	2631	3393	2098
Fyn	10874	7592	8347	6552
Yes	10336	6834	6589	6114
Fgr	5466	3110	4688	1920
STAT6	13054	10965	11320	10468
STAT5b	12805	11282	10391	10796
STAT3 Y705	12599	6489	6420	5940
p27	7220	2124	3130	1199
PLC-γ1	9582	4898	6453	5030
Hck	14484	10847	10603	10820
Chk-2	11842	8177	9815	7632
FAK	17638	14255	12589	13825
PDGF Rβ	5608	2914	5006	2780
STAT5a/b	15185	13197	11116	12206
STAT3 S727	7307	3455	4920	2739
WNK1	7394	4956	5607	4047
PYK2	9117	5251	7412	5008
PRAS40	18373	18048	14827	13239
hsp60	5300	1458	2253	2753
∑ n=45	468164	313703	323877	277814

Figure 4. SOR101 and SOR103 inhibit phosphorylation in UC colonic tissue individually and, to a greater extent, in combination. Biopsies from four different UC patients were incubated for 24 h with single domain antibody treatments (Control (ID2A) 225 nM; anti-TNFα (SOR101) 75 nM; anti-IL-23 (SOR103) 150 nM or SOR101 75 nM + SOR103 150 nM combined) and analyzed for the extent of phosphorylation of tyrosine kinase receptors and signalling proteins that are increased in inflamed intestinal tissue. Lysates were analyzed on R&D proteome profiler human phosphokinase arrays and phosphointensity data were averaged for each treatment. Heatmap colors were applied relative to the averaged signal of each phosphoprotein in the final array data set. Red indicates strong phosphorylation signals; Green indicates weak phosphorylation signals. Total phosphorylation values were calculated by summing the averaged spot intensities of all 45 analytes. Studies were performed in accordance with the relevant guidelines and regulations outlined by the approving institutions. All patients took part in the study after giving informed written consent.

Results

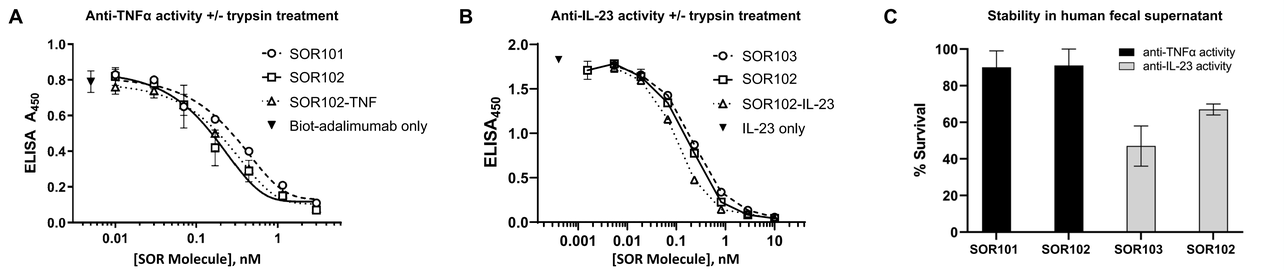


Figure 3. SOR102 and liberated monomer arms retain full anti-TNFα and anti-IL-23 activity after exposure to trypsin and cleavage products are highly resistant to human fecal proteases. (A) SOR102 and the trypsin-liberated SOR102-TNF monomer arm were tested alongside the SOR101 parent in the biotinylated adalimumab competition ELISA for TNF binding activity. Biotinylated adalimumab alone was used as a control. (B) SOR102 and the trypsin-liberated SOR102-IL-23 monomer arm were tested alongside the SOR103 parent in the IL-23/IL-23R ELISA for IL-23 binding activity. IL-23 alone was used as a control. (C) SOR102 and the parent monomers SOR101 and SOR103 were incubated in pooled human fecal supernatant (HFS) for 4 h. This timepoint was selected for accurate observation of differences in stability. Time 0 and 4 h samples were compared for anti-TNFα activity in the biotinylated adalimumab assay (SOR101 and SOR102) or anti-IL-23 activity in the IL-23/IL-23R ELISA (SOR103 and SOR102). The remaining activity in each sample at 4 h was calculated as a survival percentage against the 0 h time point. Error bars +/− SD. N = 3.

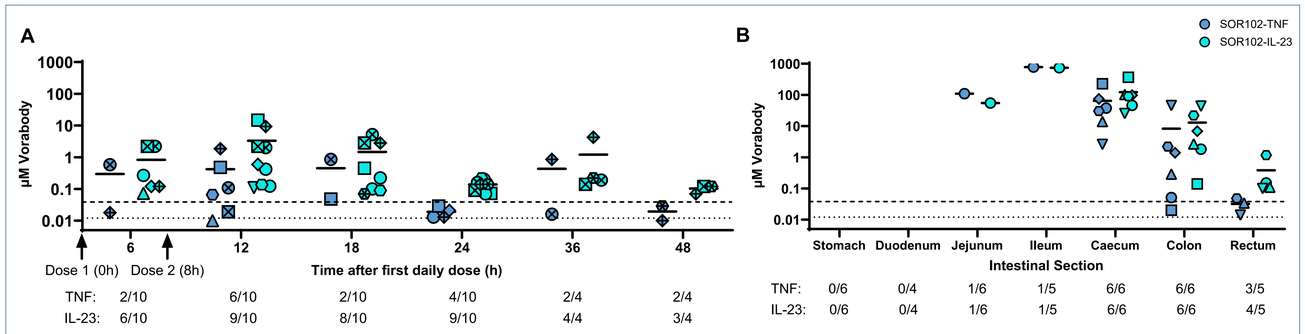


Figure 5. SOR102-TNF and SOR102-IL-23 are detected in intestinal sections and in faeces in cynomolgus monkeys after oral dosing of SOR102. 10 NHPs were dosed orally twice a day for 42 days. On Day 42, fecal samples and intestinal samples were collected and analysed for the presence of SOR102, SOR102-TNF, and SOR102-IL-23. (A) Fecal samples were collected at 6-hour timepoints following the first daily dose of SOR102 for 10 animals during the first 24 hours after dosing and for 4 animals for an additional 24 hours (two 12-hour sample collection time points). 9/10 and 10/10 animals were positive for fecal SOR102-TNF or SOR102-IL-23, respectively, for at least one timepoint (B) The 6 animals that did not have fecal samples collected >24 hours post-first daily dose of SOR102 were given a third oral dose of SOR102 at the 24-hour time point and culled 4 hours after this final dose. Contents were collected from 7 gastrointestinal sections at this 4-hour time point. Concentrations of active SOR102-TNF and SOR102-IL-23 are presented. Intact SOR102 levels were below the assay LLOQ (245nM) in all intestinal samples, therefore fecal samples were not analyzed. Horizontal lines indicate the average LLOQ across all assay plates (SOR102-TNF = 0.012 µM, dotted; SOR102-IL-23 = 0.039 µM, dashed). Black lines in each group indicate mean values. Numbers located below the x axes indicate the number of samples positive for each analyte vs the total number of samples collected for the indicated fecal time point or intestinal sample type. Each animal is represented as a unique symbol. Symbols are consistent across both panels.

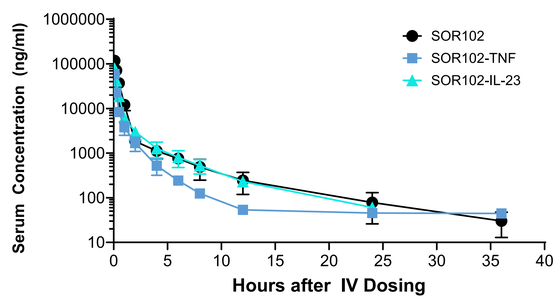


Figure 6. SOR102, SOR102-TNF, and SOR102-IL-23 are rapidly cleared from the serum in cynomolgus monkeys. SOR102 or a mixture of the two trypsin-liberated monomer arms (SOR102-TNF or SOR102-IL-23) were administered intravenously to NHPs (n=3 per group), and the serum concentration of each molecule was measured for the first 36 hours post-administration by ELISA.

Summary/Conclusions

SOR102 is the first orally-delivered anti-TNFα/anti-IL-23 dual-specificity domain antibody for the treatment of IBD.

- SOR102 is cleaved by HFS and NHP gut matrices into its monomer arms
- SOR102-TNF and SOR102-IL-23 monomer arms are stable and retain target binding efficacy after exposure to trypsin, HFS, and NHP gut matrices
- SOR101 and SOR103 in combination decrease protein phosphorylation in UC patient biopsies, confirming the benefit of dual targeting
- SOR102 and its monomer arms show rapid serum clearance, suggesting low risk of systemic exposure in IBD patients.

SOR102 is currently in a Phase I/Ib clinical trial (NCT06080048) to assess safety in humans.

Disclosures

All authors are current employees of Sorriso Pharmaceuticals.
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