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First In Human Study Of SOR102, A Novel, Orally Delivered Bispecific Anti-TNF/Anti-IL-23 Domain Antibody In Clinical Development For The Treatment Of Inflammatory Bowel Disease

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Disclosure of Conflicts of Interest

VJ has received consulting/advisory board fees from AbbVie, Alimentiv, Arena pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Avoro Capital, Bristol Myers Squibb, Celltrion, Eli Lilly, Endpoint Health, Enthera, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, Gilde Healthcare, GlaxoSmithKline, Genentech, Gilead, Innomar, JAMP, Janssen, Merck, Metacrine, Mylan, MRM Health, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus Biosciences, Reistone Biopharma, Roche, Roivant, Sandoz, Second Genome, Sorriso, Synedgen, Takeda, TD Securities, Teva, Topivert, Ventyx, Vividion; speaker's fees from, Abbvie, Ferring, Bristol Myers Squibb, Galapagos, Janssen, Pfizer, Shire, Takeda, Fresenius Kabi

CS and **PW** are employees of Sorriso Pharmaceuticals

EW and **CG** are employees of MAC Clinical Research

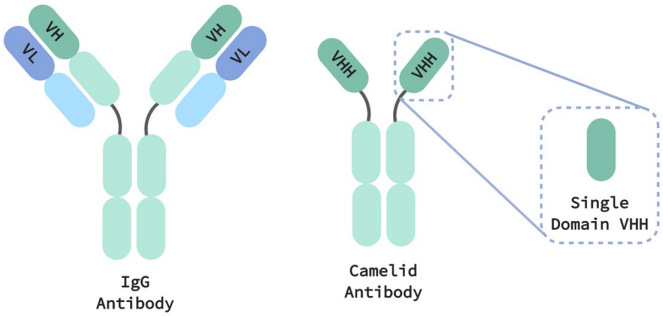
Therapeutic ceiling in IBD

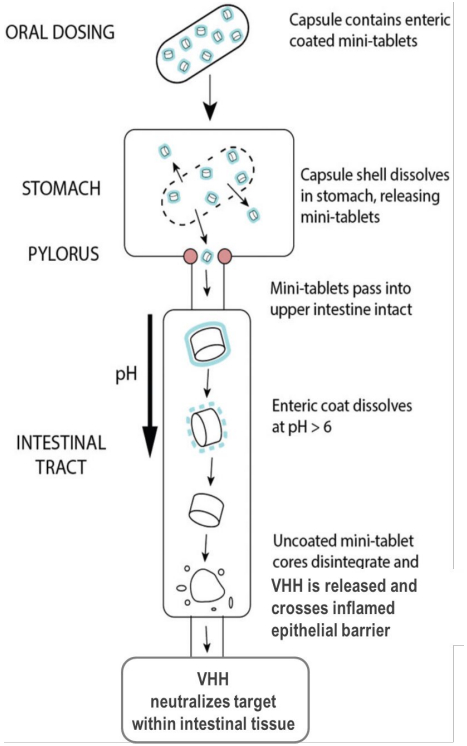
- Multiple pathways drive the immune-mediated inflammatory process
- Limited remission rates for advanced therapies when used as single agents
- Mechanistic failure can develop over time for a single advanced therapy agent
- Advanced therapies used in succession tend to be less effective
- Emerging evidence from ulcerative colitis suggest that dual blockade of IL-23 and TNF was superior to either agent alone[1]

1. Feagan BG et al. Lancet Gastroenterol Hepatol 2023

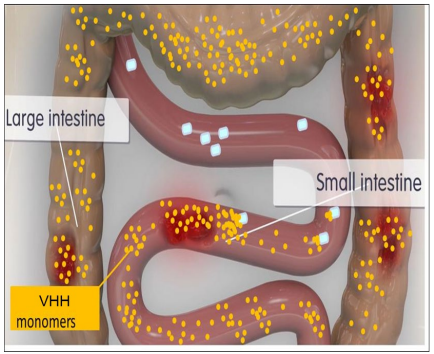
Orally Delivered, Protease-Resistant Single Domain Antibodies (VHHs)

- Structure: Humanized single domain antibodies
- Size: 12-15 kDa
- Stability: Intestinal protease-stable; high stability at room temperature and 37°C
- Affinity: High potency & specificity; can link several domains for multi-specificity; Local tissue delivery
- Locally delivered and functional within tissue





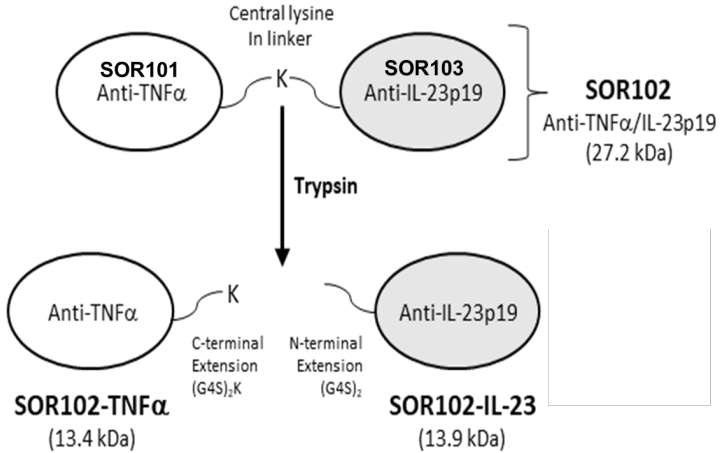
VHH is dosed orally for IBD tissue delivery and activity



https://www.twistbioscience.com/blog/science/how-llama-antibodies-may-help-us-fight-coronavirus; Crowe JS et al. Drug Dev Ind Pharm 2019

Oral SOR102 Delivers Anti-TNFα + Anti-IL-23 VHHs Directly to GI Tissue

- SOR102 combines two monomers (SOR101 and SOR103) of anti-TNFα and anti-IL-23 specificities into a single molecule
- SOR102 binds TNFα and IL-23p19 with high affinity, without interference from one another
- Endogenous trypsin cleaves the linker, releasing active monomers in small intestine



Design Benefits

- Increased efficacy through simultaneous blockade of two clinically validated pathways of IBD
- A single product for manufacture, formulation, and development
- No requirement for both targets to be co-located within tissue
- Anticipated minimal systemic immunosuppression, enabling long-term treatment

Roberts KJ et al. Scientific Reports 2021; Crowe JS et al. Scientific Reports 2018; Roberts et al, 2024 DDW Poster Abstract Su1737

Study Design and Objectives

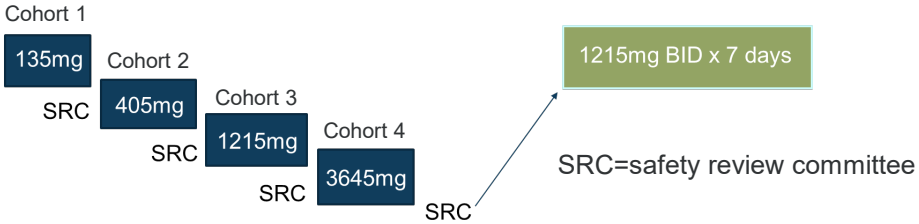
SOR102-101 (NCT06080048) is a Phase 1, first in human study that consists of 3 parts. Parts 1 and 2 enrolled healthy subjects (HS) age 18-55 years and evaluated single ascending (SAD) and multiple doses (MD) of SOR102, respectively.

Part 1
SAD, healthy volunteers – safety, tolerability, PK (serum & faeces)

- Single center, subjects confined
- n=32
- 4 cohorts (8 pts/cohort)
- Males and females
- Blinded, placebo-controlled
  - 6 SOR102
  - 2 PLB

Part 2
MD, healthy volunteers – safety, tolerability, PK (serum, urine & faeces)

- Single center, subjects confined
- n=10
- 1 cohort – SOR102 x 7days
- Males and females
- Randomized, blinded, placebo-controlled
  - 8 SOR102
  - 2 PLB



SRC=safety review committee

Objectives of Parts 1 and 2:

- To evaluate the safety and tolerability of SAD (Part 1) and MD (Part 2) of SOR102
- To evaluate the concentration of intact SOR102 and its monomers (SOR102-TNF and SOR102-IL-23) in serum and faeces (Parts 1 and 2) and urine (Part 2)[1]
- To evaluate the incidence of anti-drug antibodies (ADA) (Part 2).

1. PK method: antigen-binding ELISA (detects active SOR102 and monomers)

SOR102 is Safe and Well-Tolerated

No safety or tolerability concerns noted at single doses up to 3,645mg or multiple doses of 1,215mg BID

-No serious adverse events

-No clinically significant laboratory, ECG, vitals, or physical exam findings

-No subjects discontinued

Part 1: One TEAE considered related to study drug (Cohort #1)

Cohort / Dose	Event	Duration	Severity	Causality
C1 / 135mg	Diarrhea	~17 hours	Mild	Probably related
C1 / 135mg	Dysmenorrhea	~2.5 days	Moderate	Not related
C1 / 135mg	Flatulence	~12 hours	Mild	Not related
C2 / Placebo	Headache	~4 hours	Mild	Not related
C2 / Placebo	Catheter site pain	~5 hours	Moderate	Not related
C2 / 405mg	Dysmenorrhea	~12 hours	Moderate	Not related

Part 2: No adverse events

TEAE: treatment-emergent adverse event

Systemic Exposure Of SOR102 And Its Monomers Was Not Observed; Low-Level ADA Signal in 3 of 40 Samples Tested

Serum PK

- No detectable levels of SOR102 or monomers in serum in Parts 1 and 2

Immunogenicity

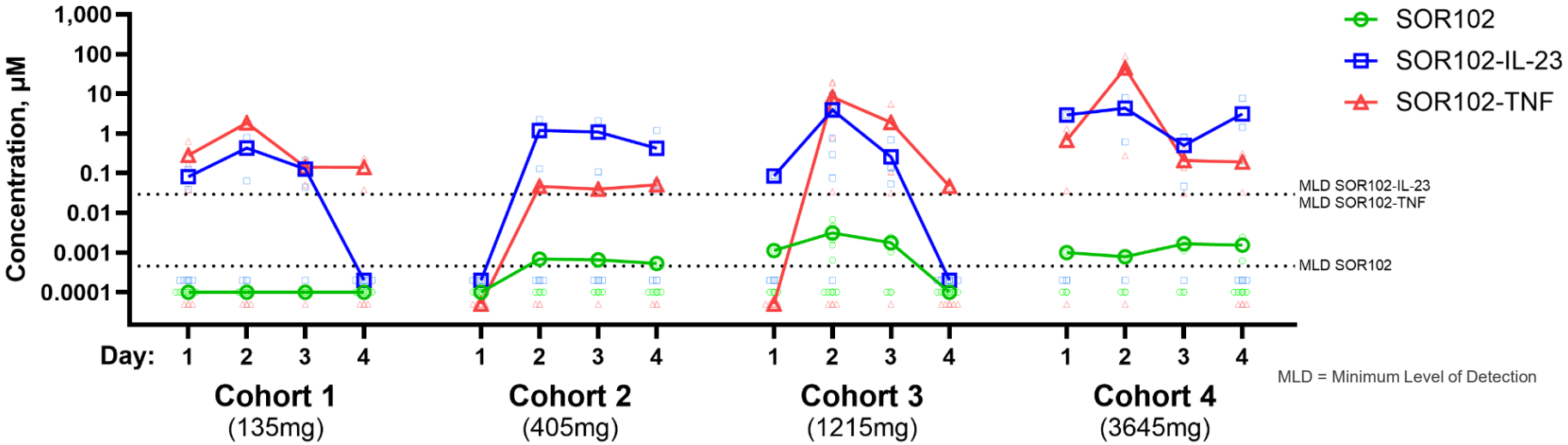
- Most samples negative for ADA
- Low level assay signal detected in:
  - 2 of 20 samples for SOR102-IL-23 (1 pre-, 1 post-dose from a single subject)
  - 1 of 20 samples for SOR102-TNF (1 post-dose in a different subject)

ADA= anti-drug antibodies

SOR102 Is Efficiently Separated Into Active Monomers After Oral Dosing, Resulting in High Monomer Concentrations in Stool

Stool: Part 1 - Single ascending dose – SOR102 and Monomer Faecal Concentrations

- Intact SOR102 stool concentrations were approximately 1000x lower than SOR102 monomer concentrations
- Monomers were detected in stool in all dose cohorts
- Monomer concentrations increased with each ascending dose, peaking on Day 2 and 3 after administration; furthermore, in this time period, most stool samples tested showed detectable monomer levels

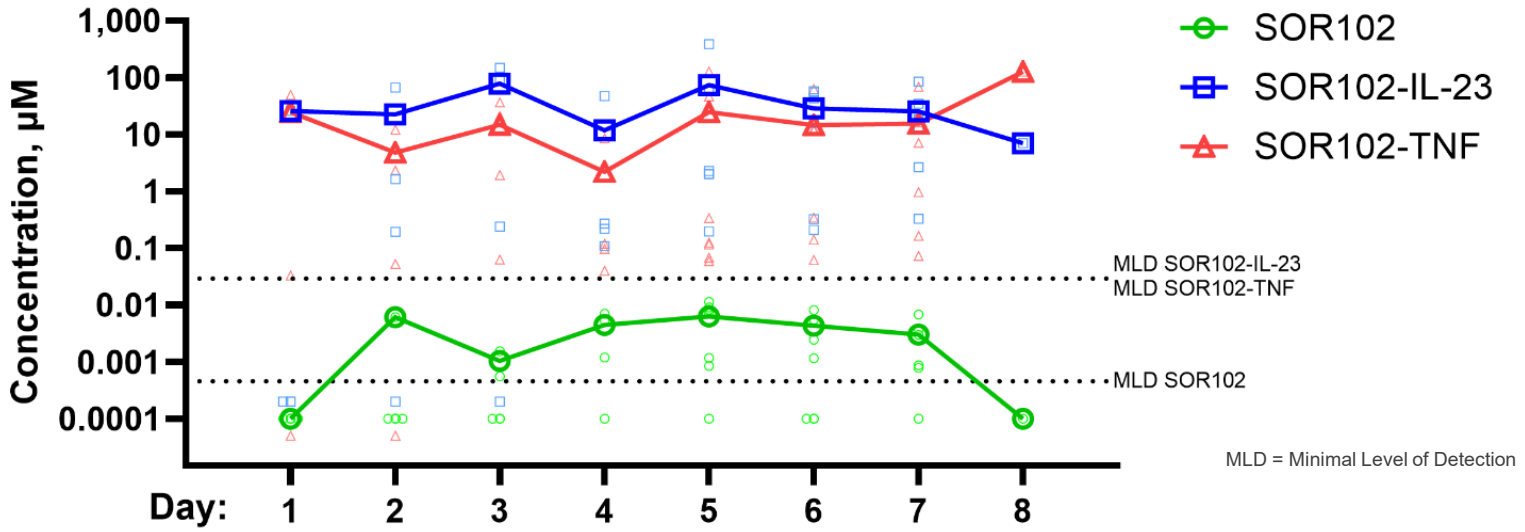


Means of positive samples only, all collected samples are shown

High, Sustained Concentrations of Active Monomers Observed in Stool During Repeat Dosing of SOR102

Stool: Part 2 - Multiple dose (1215mg BID for 7 days)

- Similar to Part 1, low levels of intact SOR102 and high levels of SOR102 monomers confirm SOR102 is efficiently cleaved after oral dosing
- Mean concentrations rapidly increase after initiation of dosing, and remain high and stable through Day 7
- After Day 3, all stool samples tested in subjects receiving SOR102 demonstrated detectable levels of monomers



Means of positive samples only, all collected samples are shown

Conclusions

- SOR102 was well tolerated at all tested doses.
- Systemic exposure of SOR102 and its monomers was not observed, supporting its gut selectivity.
- Low levels of intact SOR102 and high levels of active SOR102 monomers in faeces confirm that SOR102 is efficiently cleaved and maintains activity after oral dosing, as designed.
- Monomer faecal concentrations were observed at all doses in Part 1 (SAD) and generally increased with each ascending dose, peaking between Day 2 and 3 after administration.
- In Part 2 (MD), monomer faecal concentrations peaked after Day 2 and were detected in all stool samples tested after Day 3.
- Low-level ADA positive signal observed in 2 subjects
- Part 3, a Phase 1b study in patients with mild to severe ulcerative colitis, is ongoing.

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