Pharmacokinetics, Pharmacodynamics, Immunogenicity, and Safety of AVX-470, an Oral, Bovine-Derived Anti-TNF Antibody, in Patients with Active Ulcerative Colitis (UC): Initial Human Experience

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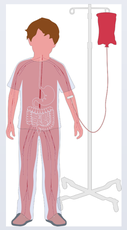
BACKGROUND & AIMS

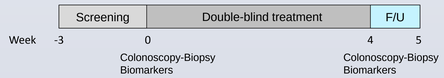
AVX-470 is an oral, enteric-coated, bovine-derived, polyclonal antibody designed to target TNF in the gastrointestinal (GI) tract without significant systemic exposure. AVX-470 was evaluated in a double-blind, placebo-controlled, first-in-human trial undertaken to explore the pharmacodynamics (bio-markers, clinical, endoscopic response), pharmacokinetics (tissue, stool, systemic bioavailability), immunogenicity & safety of 4 weeks of AVX-470 administration in patients with active ulcerative colitis (UC).

Advantages of Oral Gut-Targeted Anti-TNF Antibodies



PARENTERAL ANTI-TNF Abs	ORAL Anti-TNF Abs
Parenterally administered Infusion reactions common	**Orally administered**
Distribute throughout the body	**Locally active** Works at site of disease
Cause systemic immunosuppression Black box warning	**No systemic immunosuppression** Overcomes major drawback of anti-TNFs
May develop anti-drug antibodies Drugs lose effectiveness	**Anti-drug antibodies not induced** Potential for better long-term efficacy

METHODS



- 36 patients with active UC
- 13 centers in US, Canada, Belgium and Hungary
- 4 weeks treatment, 3 ascending-dose cohorts
  - 0.2 g/d BID, 1.6 g/d BID, and 3.5 g/d TID in divided doses
  - Within each cohort, patients randomized 3:1 to AVX-470 or placebo
- Colonoscopy with central reading at Baseline and Week 4
  - biopsy from cecum/ascending, transverse, descending, sigmoid, & rectum

Demographics

Parameter	Overall (n = 36)
Months since diagnosis, mean (SD)	87.5 (86.0)
Site of disease	
Rectum	2.8%
Left colon	50.0%
Entire colon	47.2%
Prior and Concomitant Meds	
5-ASA	77.8%
Corticosteroids	55.6%[A]
AZA/ 6-MP	41.7%[B]
Prior anti-TNF use (secondary failures only)	33.3%

[A] concurrent use 36.1%; [B] concurrent use 30.6%

Study Enrollment and Disposition

Parameter	Placebo	0.2 g/d	1.6 g/d	3.5 g/d	Pooled Active	Overall
Enrolled	9	8	12	8	28	37
Treated	9	8	12	7	27	36
Completed study	8	8	11	6	25	33
Reason for Early Termination (ET):						
Withdrew consent	1[a]		1[a]	1[b]	2	3
Investigator opinion				1[c]	1	1

[a] uncontrolled UC activity during Week 1 of treatment; [b] Patient withdrew before first dosing; [c] recurrence of nausea and dysphagia for medications, established pre-study, precluded continued study participation

RESULTS

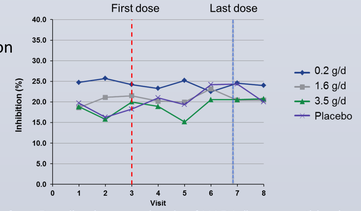
Treatment-Emergent AEs (TEAEs)

Parameter	Placebo (n = 9)	0.2 g/d (n = 8)	1.6 g/d (n = 12)	3.5 g/d (n = 7)	Pooled Active (n = 27)	Overall (n = 36)
All, n (%) [A]	7 (77.8)	3 (37.5)	6 (50.0)	5 (71.4)	14 (51.9)	26 (72.2)
AEs (Total) [B]	13 (100.0)	8 (100.0)	13 (100.0)	13 (100.0)	34 (100.0)	47 (100.0)
Mild	9 (69.2)	7 (87.5)	10 (77.0)	9 (69.2)	26 (76.5)	35 (74.5)
Moderate	4 (30.8)	1 (12.5)	2 (15.9)	4 (30.8)	7 (20.6)	12 (23.4)
Severe	0 (0.0)	0 (0.0)	1 (7.7)†	0 (0.0)	1 (2.9)	1 (2.1)
SAEs, n (%) [A]	0 (0.0)	0 (0.0)	1 (8.3)†	0 (0.0)	1 (3.7)	1 (2.8)
AEs of Special Interest [C]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[A] no. of patients experiencing AEs, n (%); [B] no. of AEs, n (%); [C] allergic reaction or opportunistic infection; † worsening UC on Day 3 of study drug

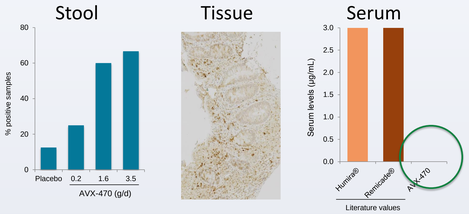
Lack of Immunogenicity

Competition ELISA



No change from Baseline in serum levels of HABA (human anti-bovine antibody) in AVX-470 or placebo treatment arms.

Pharmacokinetics



Bovine immunoglobulin (Ig) in stool by ELISA analysis

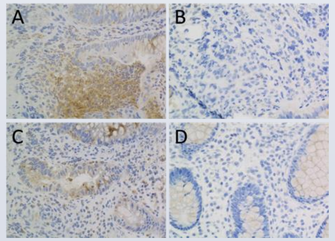
Bovine Ig in colon tissue by IHC staining

Calculated levels of TNF binding antibodies

Stool, tissue, and serum samples collected at Week 4

SUMMARY: AVX-470 is confined to the GI tract

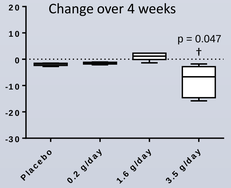
AVX-470 Reduces TNF in Colon: Direct Effect on Therapeutic Target



TNF immunohistochemistry (IHC) staining in sigmoid colon (A, B) and rectum (C, D) at baseline (A, C) and Week 4 (B, D) in AVX-470 3.5 g/d group. Brown staining indicates TNF protein. Magnification 400x.

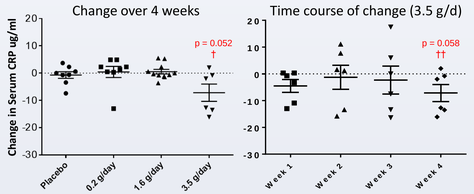
Changes in TNF Levels in Colon Tissue Across Treatment Arms

Fold Change IHC staining index



†3.5 g/day vs placebo; two-tailed, unpaired t-test of geometric means of changes across five colon segments

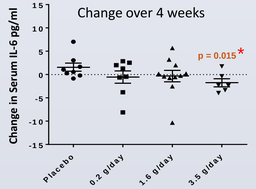
Changes in Serum CRP Levels Across Treatment Arms & Duration



† 3.5 g/day vs placebo – two-sided, two-sample paired t-tests

†† Week 4 vs baseline CRP, paired analysis

Changes in Serum IL-6 Levels Across Treatment Arms



*Change in IL-6 compared by ANCOVA as a function of treatment adjusting for baseline: AVX-470 3.5 g vs. placebo (p = 0.015).

Clinical & Endoscopic Remission†

Parameter	Placebo (n = 9)	0.2 g/d (n = 8)	1.6 g/d (n = 12)	3.5 g/d (n = 7)	Pooled Active (n = 27)
Clinical Response	1/9 (11.1)	3/8 (37.5)	2/12 (16.7)	2/7 (28.6)	7/25 (25.9)
Clinical Remission	0	0	0	1/7 (14.3)	1/27 (3.7)
Endoscopic Response	0	0	1/12 (8.3)	1/7 (14.3)	2/27 (7.4)
Endoscopic Remission	0	0	1/12 (8.3)	1/7 (14.3)	2/27 (7.4)

† expressed as n/N (%)

Clinical Response
Reduction of ≥ 3 points on the total Mayo score and an overall decrease of at least 30%, plus a decrease in the rectal bleeding subscore of at least 1-point or an absolute rectal bleeding score of 1 or less

Clinical Remission: Total Mayo score of 2 or lower and no subscores higher than 1

Endoscopic Response: 1-point decrease in Mayo endoscopic subscore

Endoscopic Remission: Mayo endoscopic subscore of 0-1

CONCLUSIONS

- AVX-470 was well-tolerated with no drug-related SAEs, opportunistic infections or allergic reactions.
- AVX-470 was stable in passage through the GI tract and was not associated with significant systemic exposures. No immunogenicity was observed.
- Bovine Ig was shown to penetrate the colonic mucosa, even in areas of normal endoscopic activity. However, prior dietary exposures interfered with detection of changes in tissue levels.
- Efficacy trends were observed across multiple parameters (clinical, endoscopic, biomarker) of disease activity, most favoring the 3.5g/d dose group.
- This is the first study to suggest the benefit of an orally delivered, locally-active agent in a moderate-severe UC population. Future studies will examine the effects of higher doses and longer dose duration.

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