AVX-470, an Orally Delivered Anti-TNF Antibody for Treatment of Acute Ulcerative Colitis: Results of a First-in-Human Trial

M Scott Harris[1], Deborah Hartman[1], Sharon Spence[1], Sally Kennedy[1], Theodore Ptak[2], Ronald Pruitt[3], Severine Vermeire[4], Barbara Fox[1]

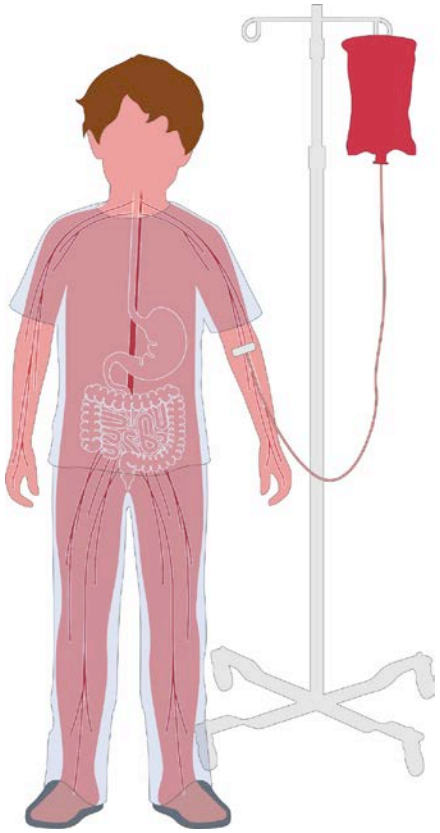
[1] Avaxia Biologics, Lexington, United States; [2] Toronto Digestive Disease Associates, Toronto, Canada; [3] Nashville Medical Research Institute, Nashville, United States; [4] University Hospital Gasthuisberg, Leuven, Belgium

Disclosures

I am currently consult for Avaxia Biologics, the sponsor of this study. I also disclose that I have consulted for or have had financial interests in the following companies or organizations in the past two years:

Ardelyx
Bill and Melinda Gates Foundation
Biomedical Systems
CIPAC
CymaBay
Drais Pharmaceuticals
Kala Pharmaceuticals
Lyric Pharmaceuticals
Neurogastrx
Ocera Therapeutics
Orchid Pharmaceuticals
PATH-One World Health
Rhythm Pharmaceuticals
Symbiomix
Theravance
White Sands Pharmaceuticals
ZS Pharma

Disadvantages of Parenteral Anti-TNF Antibodies



PARENTERAL ANTI-TNF Abs

Parenterally administered

Infusion reactions common

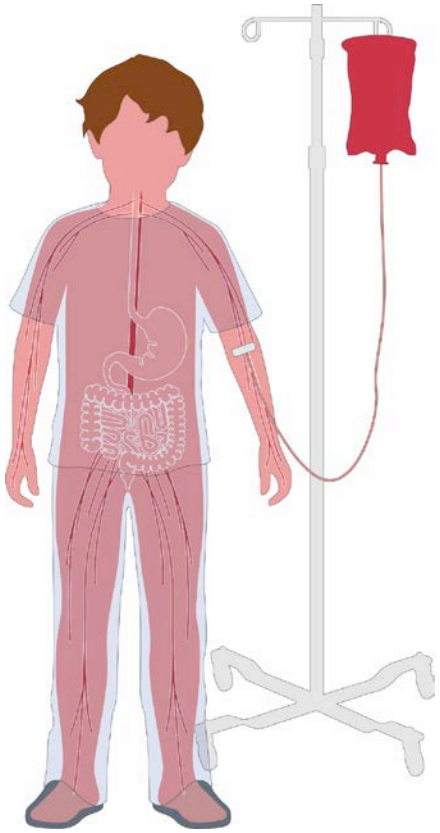
Distribute throughout the body

Cause systemic immunosuppression

May develop anti-drug antibodies

Drugs lose effectiveness

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	**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

AVX-470

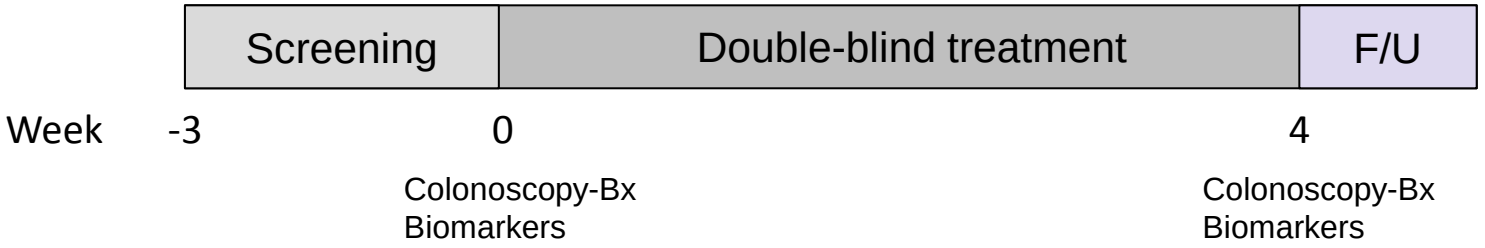
Milk-based polyclonal anti-TNF antibodies for oral delivery

- Pregnant dairy cows immunized with recombinant human TNF
- Antibody is purified from colostrum (early milk)
  - Approximately 0.3-0.9% by weight is TNF-specific
- Antibody retains activity in GI tract
  - Bovine milk antibodies are inherently stable to intestinal digestion
  - Enteric coating designed to release drug at pH 6.0
- Long history of safe oral exposure to bovine immunoglobulin
  - Dairy products, meat, whey-based food additives
  - Lactose free, no risk of BSE in dairy products

First-in-Human Trial of AVX-470
Study Endpoints and Objectives

Endpoint		Objective
Primary	Safety	Assess safety in adult UC patients
Secondary	Pharmacokinetics	Assess systemic exposure
		Confirm stability of AVX-470 in human GI tract
		Assess ability of AVX-470 to penetrate colonic mucosa of UC patients
	Immunogenicity	Assess induction of anti-drug antibodies
Exploratory	Pharmacodynamics	Measure TNF levels in tissues
		Assess systemic markers of disease activity (CRP, IL-6)
	Clinical efficacy	Assess clinical and endoscopic remission and response

Overview



- 37 patients with active UC
- 13 centers in US, Canada, Belgium and Hungary
- Placebo-controlled, double-blind
- 4 weeks treatment, 3 ascending-dose cohorts
  - 0.2 g/d, 1.6 g/d, and 3.5 g/d in divided dose 2x or 3x daily
  - Within each cohort, patient randomized 3:1 to AVX-470 or placebo
- Colonoscopy and biopsy by central reading at baseline and Week 4

Inclusion and Exclusion Criteria

- Men and women ages 18-75
- Total Mayo score 5-12, inclusive
- Mayo endoscopic subscore ≥ 2 at or above 15 cm from anus
- Permitted medications:
  - Concomitant use of 5-ASA, corticosteroids (up to prednisone 20mg equivalent), immunosuppressives
  - Prior use of TNF agents (secondary failure only)

Definitions

- 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

Colonoscopy

- UCEIS (Ulcerative Colitis Index of Severity) scored in 3 segments
  - Proximal colon (ascending and transverse colons)
  - Descending colon and sigmoid (above 15 cm)
  - Rectum (below 15 cm)`
- Biopsies obtained from worst area of inflammation in each segment.
- Mucosal bovine Ig and TNF assessed by immunohistochemistry

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

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%
Total Mayo score, mean (SD)	8.1 (1.2)

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

Treatment-Emergent Adverse Events (AEs)

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;

Pharmacokinetics

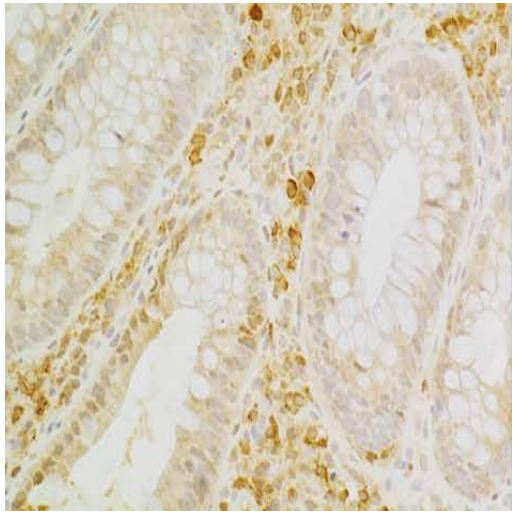
Minimal Levels of Bovine Ig in Serum

Treatment Group	Pre-dose (Visit 3)		Post-dose (Visit 7A)		
	Bovine Ig		Bovine Ig		Anti-TNF†
	# positive (%)	range (µg/mL)	# positive (%)	range (µg/mL)	range (µg/mL)
Placebo	0/8 (0)	-	1/8 (13%)	0.424	--
0.2 g/d	2/8 (25%)	0.418 - 0.653	1/8 (13%)	0.430	0.0013
1.6 g/d	0/11 (0)	-	2/11 (18%)	0.551 – 0.589	0.0017-0.0018
3.5 g/d	1/6 (17%)	0.481	4/6 (67%)	0.412 – 0.990	0.0012-0.0030

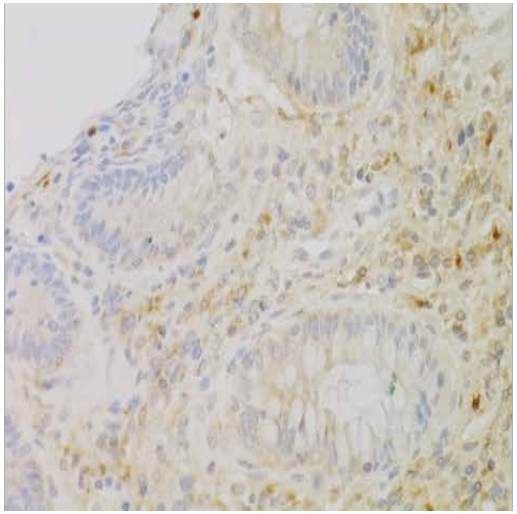
- Bovine Ig detectable before dosing, presumably of dietary origin
- Concentrations not significantly different from baseline levels and remained 1000x lower than levels associated with clinical activity

Bovine Ig in Colon Tissue

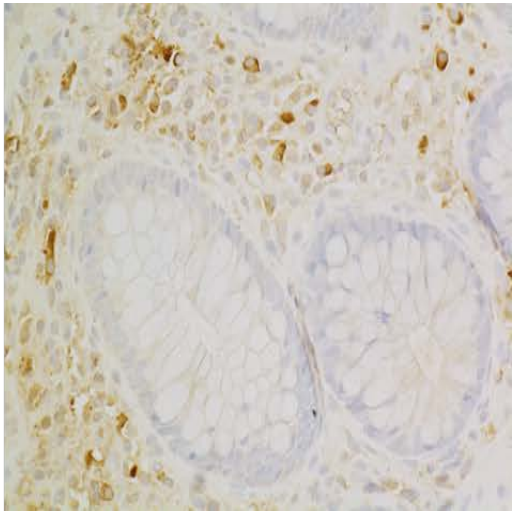
Bovine Ig Detected by IHC in Colon Lamina Propria



Placebo (105004)



Pre-Dosing (502003)



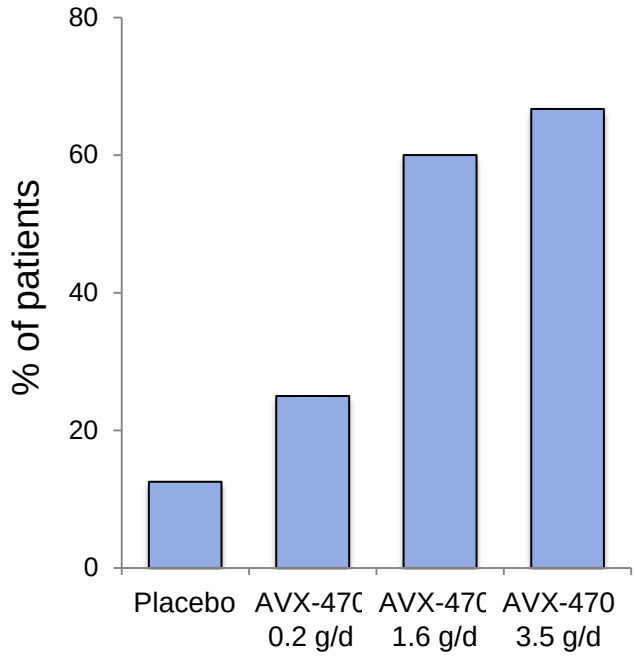
Post-Dosing (502003)

Bovine Ig staining observed in baseline samples and after 4 weeks dosing

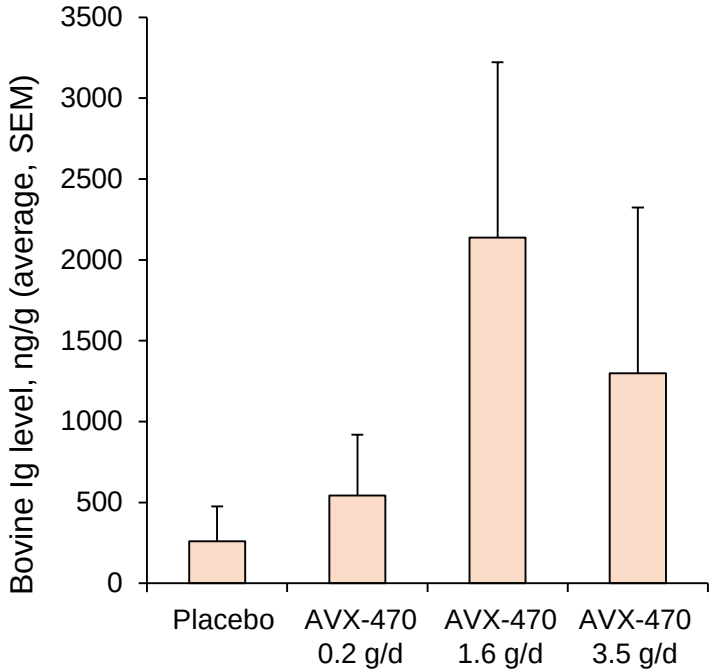
- All colon regions
- Every patient
- With or without AVX-470 dosing
- With or without endoscopic disease activity
- Submucosa stained when present

Bovine Ig in Stool

Patients with Bovine Ig in stool



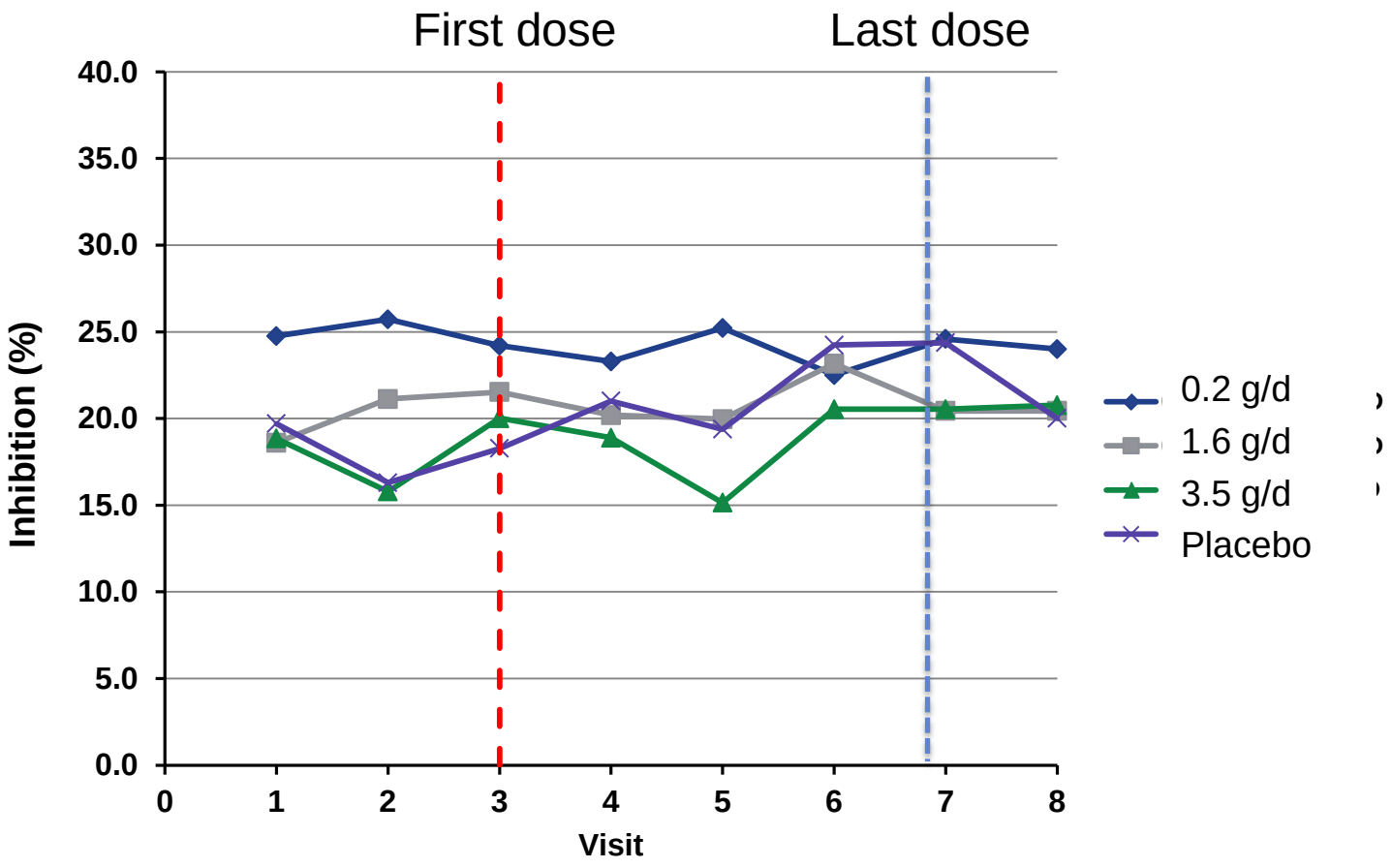
Levels of Bovine Ig in stool (ng/g)



- All pre-dose samples were negative.
- Post-dosing stool samples with highest levels of bovine Ig contained anti-TNF activity.

Immunogenicity

HABA Concentrations by Treatment Arm



Clinical and 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 (%)

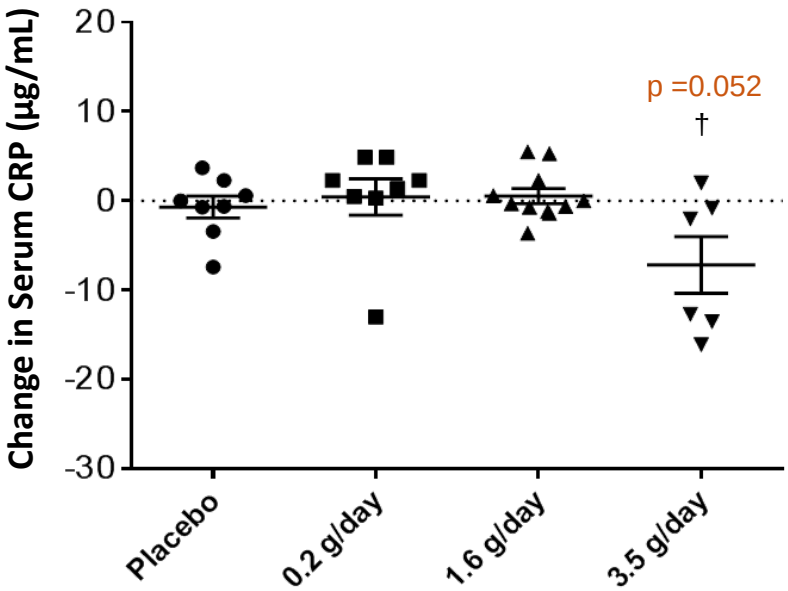
UC Endoscopic Index of Severity (UCEIS) (0-8)

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)
Proximal Colon					
Baseline	2.8	0.6	1.0	3.3	1.5
Week 4	3.5	1.5	1.4	2.5	1.7
Δ from Baseline[A]	+0.7	+0.9	+0.4	-0.8*	+0.3
* p = 0.14, student t-test					
Descending Colon and Sigmoid (above 15 cm)					
Baseline	4.3	3.8	3.4	4.3	3.8
Week 4	4.3	3.6	3.8	4.0	3.8
Δ from Baseline [A]	0.0	-0.1	+0.4	-0.3	0.0

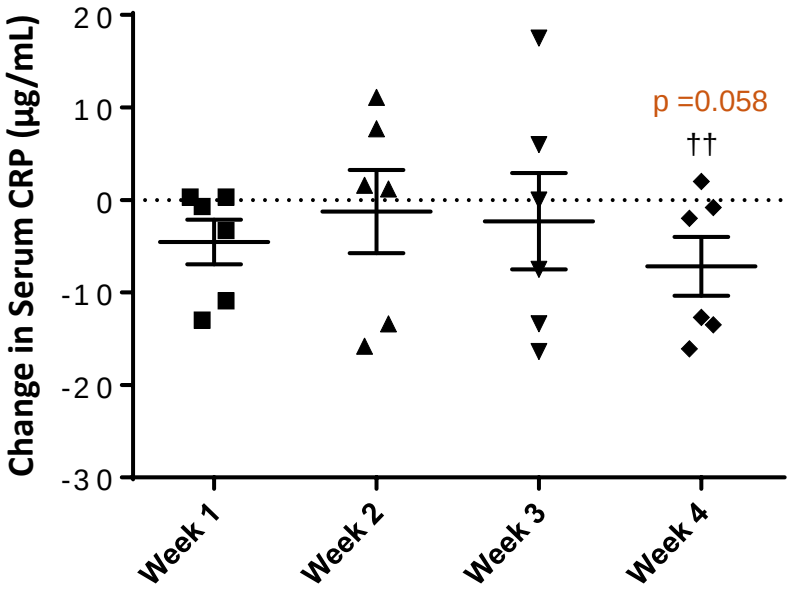
[A] mean of individual patient changes

Changes in Serum CRP Across Treatment Arms and Treatment Duration

Change over 4 weeks

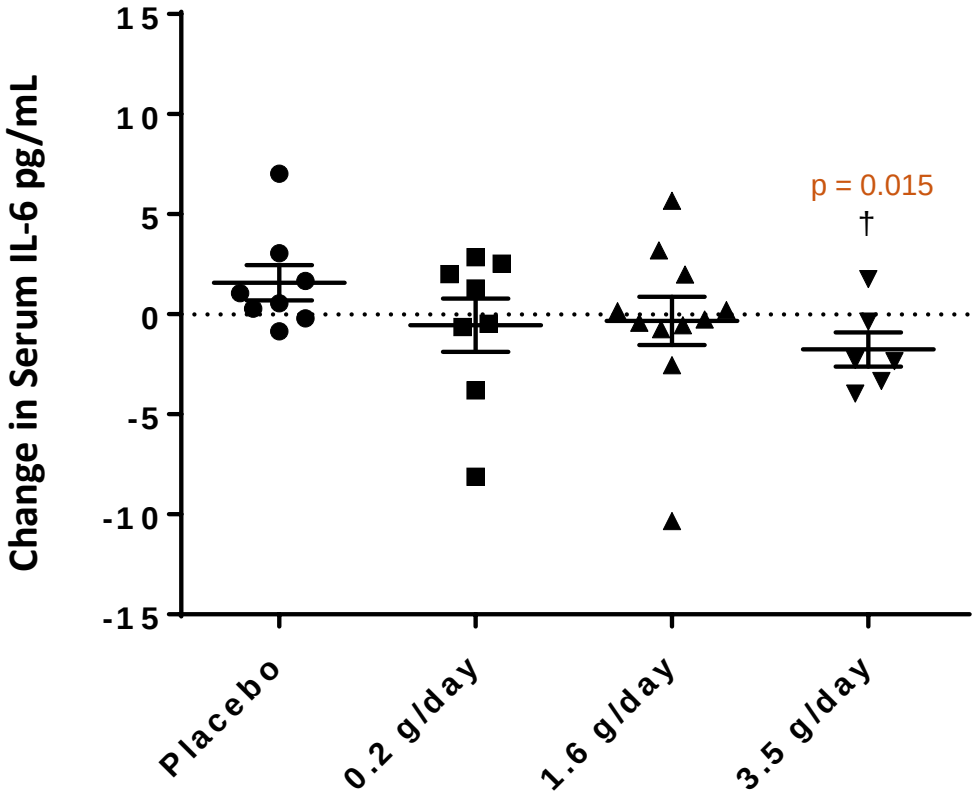


Time course of change (3.5 g/d)



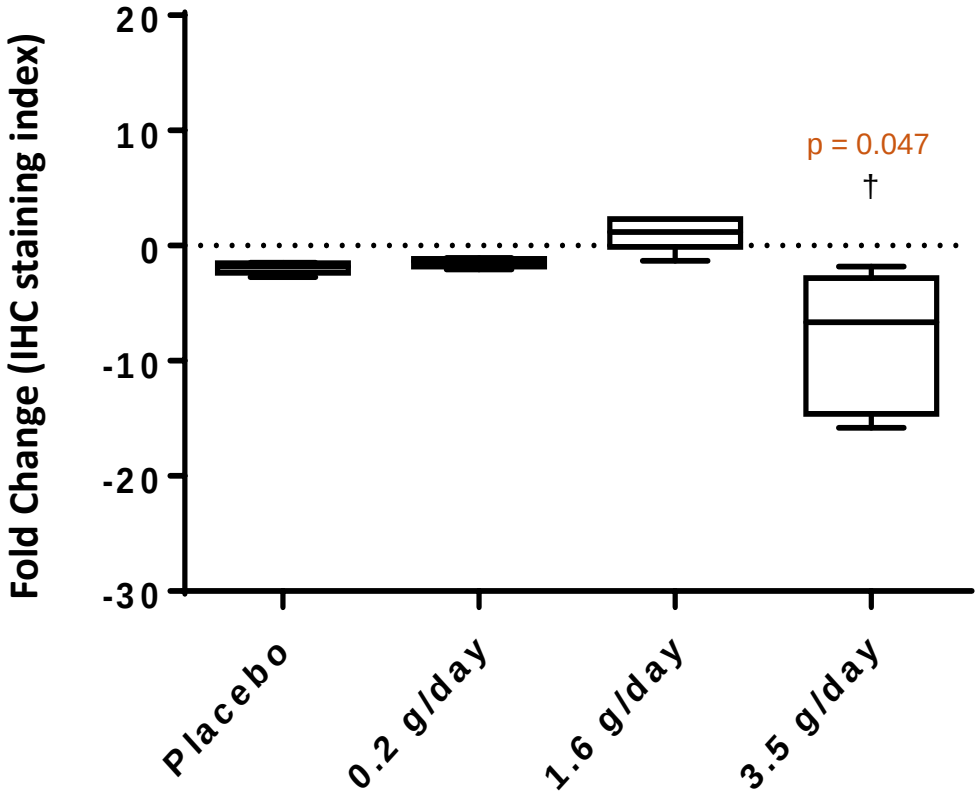
† 3.5 g/day vs placebo, paired analysis
†† Week 4 vs baseline CRP,paired analysis

Changes in Serum IL-6 Across Treatment Arms



† 3.5 g/day vs placebo, paired analysis

Changes in Tissue TNF Across Treatment Arms



† 3.5 g/day vs placebo, un-paired group analysis of all colon segments

Conclusions

1. AVX-470 was well-tolerated with no drug-related SAEs, opportunistic infections or allergic reactions.
2. AVX-470 was stable in passage through the GI tract and was not associated with significant systemic exposures. No immunogenicity was observed.
3. Prior dietary exposures interfered with detection of changes in tissue levels. However, bovine Ig was shown to penetrate the colonic mucosa, even in areas of normal endoscopic activity.
4. Efficacy trends were observed across multiple parameters (clinical, endoscopic, biomarker) of disease activity, most favoring the 3.5g/d dose group, with a proximal to distal gradient of response.
5. Future studies will examine the effects of higher doses and longer dose treatment duration.