Target Engagement and Pharmacodynamic Biomarker Analysis Following Treatment with the Oral Gut-Targeted HIF-1α Stabilizer GB004 in a Phase 1b Trial in Active Ulcerative Colitis

William J. Sandborn
University of California San Diego, La Jolla, CA, USA

On behalf of co-authors: Zhaoqing Ding[1], Robin Osterhout[1], Brian Feagan[2], Silvio Danese[3], Alina Jucov[4], B.R. Bhandari[5], Kartik Raghupathi[1], Allan Olson[1], Courtney Van Biene[1], Julia Ford[1], Richard Aranda[1], Barrett G. Levesque[1], Jean-Marie Bruey[1]

[1]Gossamer Bio, Inc., San Diego, CA, USA; [2]Western University, Alimentiv, Inc., London, Ontario, Canada; [3]Humanitas Research and Teaching Hospital, Milano, Italy; [4]ARENSIA Exploratory Medicine GmbH, Düsseldorf, Germany and Nicolae Testemițanu State University of Medicine and Pharmacy, Chișinău, Moldova; [5]Delta Research Partners, Bastrop, LA, USA

Video recorded on: June 4, 2021

Disclosures of potential conflicts of interest

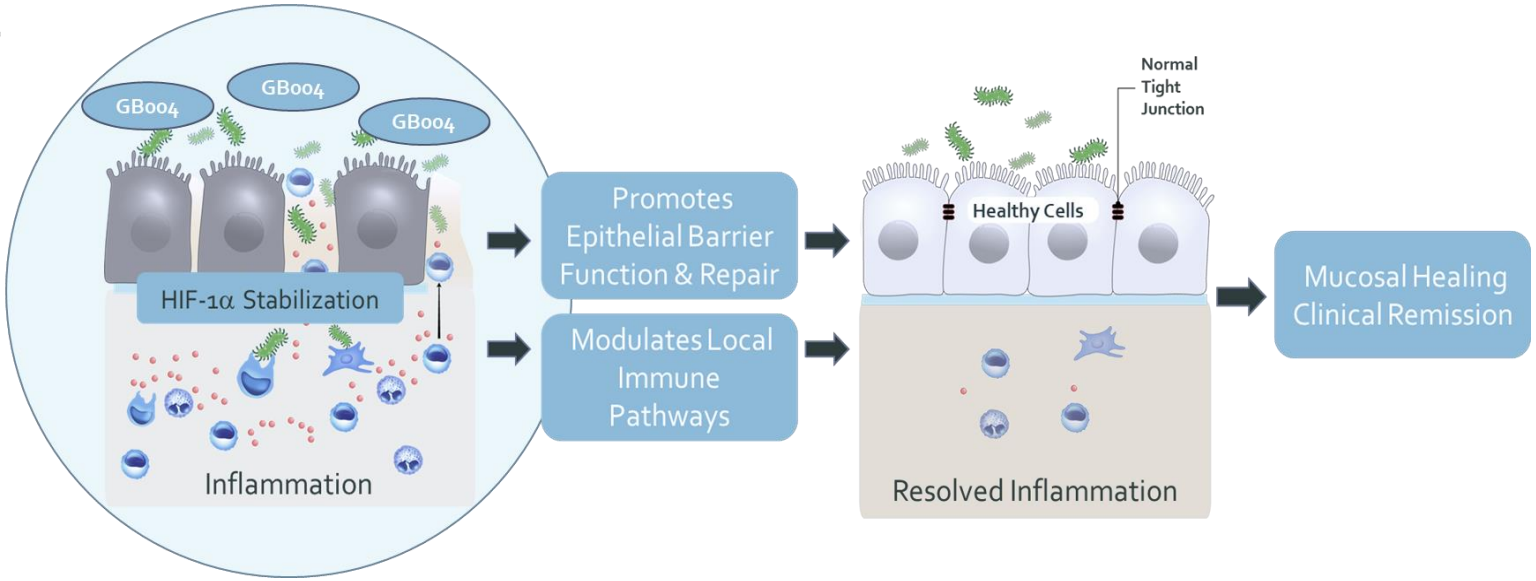
Sandborn, William:|:|WJS reports: research grants from Abbvie, Abivax, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Biosciences, Seres Therapeutics, Shire, Takeda, Theravance Biopharma; consulting fees from Abbvie, Abivax, Admirx, Alfasigma, Alimentiv (previously Robarts Clinical Trials, owned by Alimentiv Health Trust), Alivio Therapeutics, Allakos, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Bausch Health (Salix), Beigene, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Meyers Squibb, Celgene, Celltrion, Cellularity, Cosmo Pharmaceuticals, Escalier Biosciences, Equillium, Forbion, Genentech/Roche, Gilead Sciences, Glenmark Pharmaceuticals, Gossamer Bio, Immunic (Vital Therapies), Index Pharmaceuticals, Intact Therapeutics, Janssen, Kyverna Therapeutics, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pandion Therapeutics, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Provention Bio, Reistone Biopharma, Seres Therapeutics, Shanghai Pharma Biotherapeutics, Shire, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Thetis Pharmaceuticals, Tillotts Pharma, UCB, Vendata Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals, Vivreon Biosciences, Zealand Pharma; and stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences, Prometheus Laboratories Progenity, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Oppilan Pharma - consultant, stock options; Prometheus Biosciences - employee, stock, stock options; Prometheus Laboratories – stock, stock options, consultant; Ventyx Biosciences – stock, stock options; Vimalan Biosciences – stock, stock options.||Dr. Ding, Zhaoqing:|:|Employee, shareholder: Gossamer Bio, Inc.||Osterhout, Robin:|:|Employee, shareholder: Gossamer Bio, Inc.||Dr. Feagan, Brian:|:|Grant/Research Support: AbbVie Inc., Amgen Inc., AstraZeneca/MedImmune Ltd., Atlantic Pharmaceuticals Ltd., Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech Inc/Hoffmann-La Roche Ltd., Gilead Sciences Inc., GlaxoSmithKline (GSK), Janssen Research & Development LLC., Pfizer Inc., Receptos Inc. / Celgene International, Sanofi, Santarus Inc., Takeda Development Center Americas Inc., Tillotts Pharma AG, UCB. Consultant: Abbott/AbbVie, AgomAB Therapeutics, Allakos, Allergan, Amgen, Applied Molecular Transport Inc, Aptevo Therapeutics, Astra Zeneca, Atlantic Pharma, BioMx Israel, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Connect BioPharma, Disc Medicine Inc., Everest Clinical Research Corp., Galapagos, Galen Atlantica, Genentech/Roche, Gilead, Gossamer Pharma, GSK, Hoffmann-LaRoche, Index Pharma, Janssen, Kyowa Kakko Kirin Co Ltd., Leadiant, Lilly, Lument AB, Merck, Millenium, Mylan, Nestles, Nextbiotix, Origo BioPharma, Pandion Therapeutics, ParImmune, Parvus Therapeutics Inc., Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Qu Biologics, Rebiotix, Receptos, Salix Pharma, Sandoz, Sanofi, Shire, Surrozen Inc., Takeda, Tillotts, UCB Pharma, VHsquared Ltd., Viatris, Ysios, Zealand Pharma. Speakers Bureau: AbbVie, Janssen, Takeda, Tillotts. Scientific advisory board: AbbVie, Allergan, Amgen, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Genentech/Roche, Janssen, Novartis, Origo BioPharma, Pfizer, Prometheus, Protagonist, Takeda, Tillotts Pharma. Board of Directors: Senior Scientific Director – Alimentiv Inc, London. Shareholder: Gossamer Bio, Inc.||Dr. Danese, Silvio: No conflict of interest||Dr. Jucov, Alina: No conflict of interest||Dr. Bhandari, Bal Raj: No conflict of interest||Dr. Raghupathi, Kartik:|:|Employee, shareholder: Gossamer Bio, Inc.||Dr. Olson, Allan:|:|Employee, shareholder: Gossamer Bio, Inc.||Van Biene, Courtney:|:|Employee, shareholder: Gossamer Bio, Inc.||Ford, Julia:|:|Employee, shareholder: Gossamer Bio, Inc.||Dr. Aranda, Richard:|:|Employee, shareholder: Gossamer Bio, Inc.||Dr. Levesque, Barrett G.:|:|Employee, shareholder: Gossamer Bio, Inc.||Dr. Bruey, Jean-Marie:|:|Employee, shareholder: Gossamer Bio, Inc.

GB004 Phase 1b Study in Ulcerative Colitis

Background

- UC is associated with a breakdown of the epithelial barrier[1]
- GB004 is an oral small molecule stabilizer of hypoxia inducible factor (HIF-1α) that targets epithelial repair and function[2-5]
- GB004 showed preliminary evidence for histologic improvement and clinical activity compared to placebo in a Phase 1b study of UC[6] and as expected, had a gut-targeted PK profile

GB004 Mechanism of Action



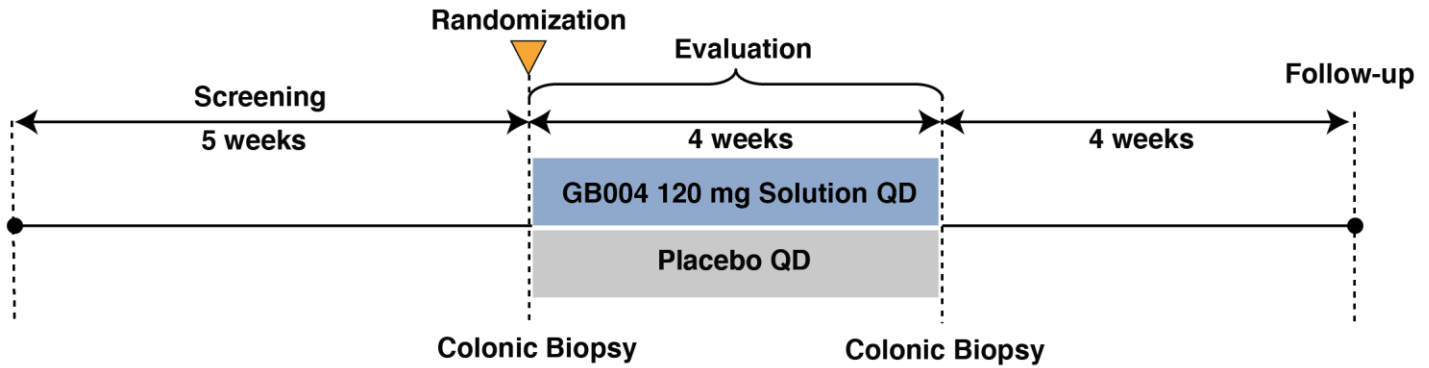
Exploratory Biomarkers Measured

- Proportion of HIF-1α positive and MPO positive cells by IHC
- Levels of fecal calprotectin and fecal secretory IgA
- mRNA expression levels of *ITGA6* and *TJP1*

1. Ungaro R, et al. Lancet. 2017;389:1756-70; 2. Keely S, et al. Mucosal Immunol. 2014;7(1):114-23; 3. Marks E, et al. Inflamm Bowel Dis. 2015;21(2):267-75; 4. Okumura CY, et al. J Mol Med (Berl) 2012;90(9):1079-89; 5. Levesque BG, et al. J Crohns Colitis. 2020; 14 (Suppl 1):S461–2; 6. Sandborn W, et al. UEG Journal 2020; 8(8S):462

Preliminary Evidence for Histologic Improvement and Clinical Activity in Mild-to-Moderate UC Following Treatment with GB004

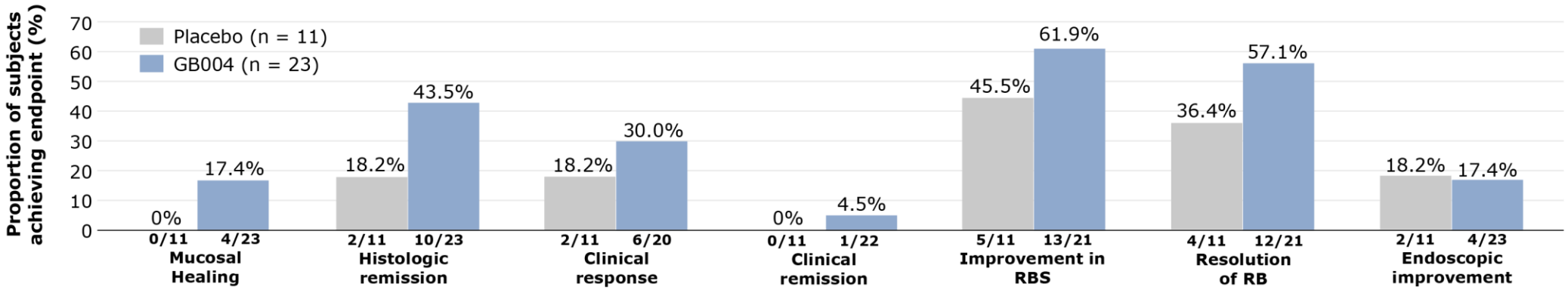
Phase 1b Study Design



Entry Criteria:
Mayo Score 3-12 with evidence of active inflammation on baseline colonic biopsy

(RHI ≥ 4 with neutrophils in the epithelium)

Exploratory Efficacy Endpoints at Day 28



Note: Mucosal healing, histologic remission, and endoscopic improvement analyzed as achieving endpoint in either sigmoid or rectum; (a) baseline RBS > 0 and/or (b) baseline MES > 0 required to be evaluable for clinical response (a & b), clinical remission (b), and RB endpoints (a).

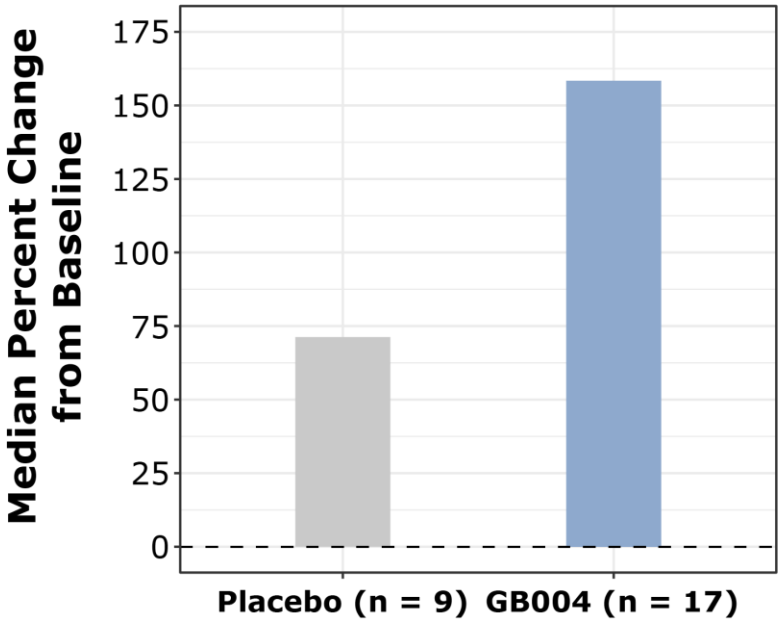
MES, Mayo Endoscopic Subscore; RBS, Rectal Bleeding Score; RB, Rectal Bleeding; RHI, Robarts Histopathology Index

Modulation of Fecal Secretory IgA and Calprotectin Levels Following Treatment with GB004

Increase in secretory IgA, consistent with **improved gut epithelium and local immune defense**

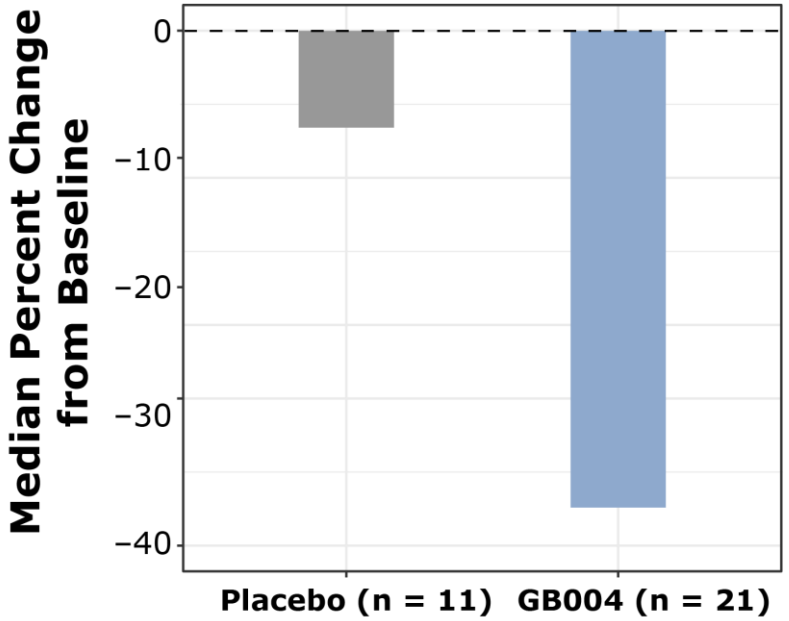
Decrease in fecal calprotectin, consistent with **reduction in mucosal inflammation**

Secretory IgA



Increase in Median (95% CI) Percent Change from Baseline to Day 28 in Fecal Secretory IgA Levels, GB004 vs Placebo: 87.16% (-215.28%,389.60%)

Fecal Calprotectin



Decrease in Median (95% CI) Percent Change from Baseline to Day 28 in Fecal Calprotectin Levels, GB004 vs Placebo: -30.4% (-131.6%,70.7%)

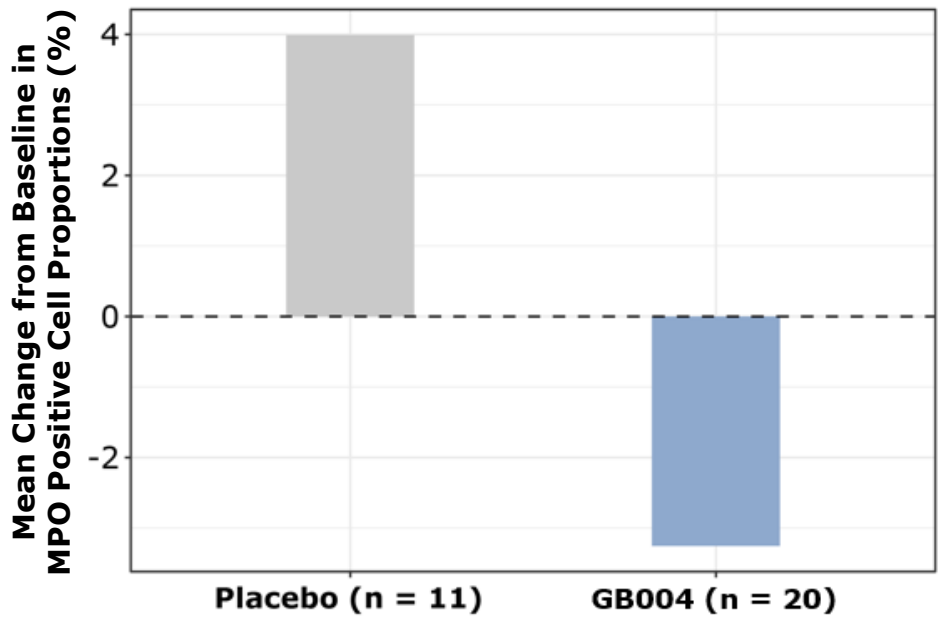
Difference in medians estimated based on quantile regression employing an optimization algorithm. 95% CIs for difference in median change from baseline based on inverted rank-score method.

Reduction of MPO and Increase of HIF-1α Immunostaining in Biopsies from Sigmoid Colon Following Treatment with GB004

Reduction of MPO positive cells in sigmoid colon, consistent with **reduction in local mucosal (neutrophilic) inflammation**

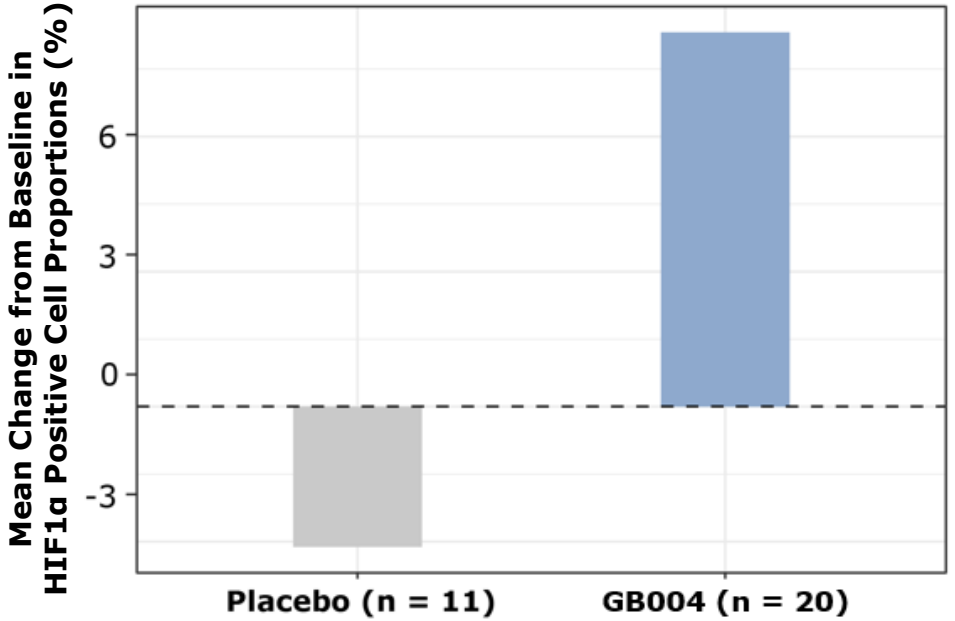
Increase in HIF-1α positive cells in sigmoid colon, consistent with **target engagement**

Proportion of MPO Positive Cells



Decrease (95% CI) in Mean Change from Baseline to Day 28 in Proportion of MPO Positive Cells in Sigmoid Colon, GB004 vs Placebo: -7.25% (–20.05, 5.56%)

Proportion of HIF-1α Positive Cells



Increase in Mean Change from Baseline to Day 28 in Proportion of HIF-1α Positive Cells in Sigmoid Colon, GB004 vs Placebo: +11.43% (–5.04%,27.91%)

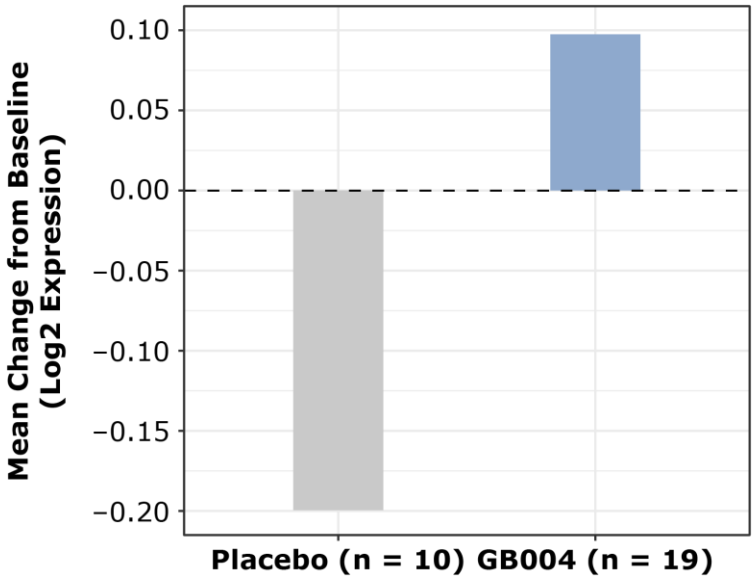
95% CIs for difference in mean change from baseline based on analysis of variance

Modulation in *ITGA6* and *TJP1* Gene Expression in Biopsies from Sigmoid Colon Following Treatment with GB004

Increase in TJP1 expression, consistent with **restoring the integrity** of the gut mucosal barrier

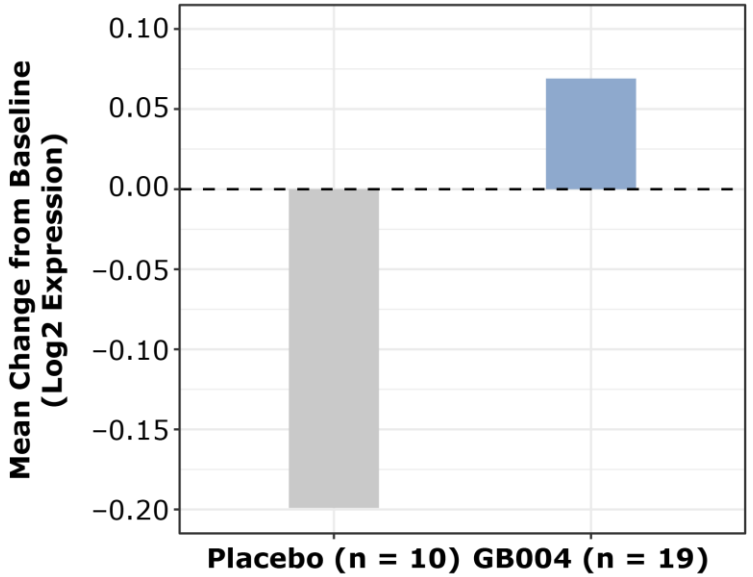
Increase in ITGA6 expression, consistent with **increased barrier restitution** and migration

Tight Junction Protein-1 (*TJP1*)



Increase (95% CI) in Mean log_2-fold change in *TJP1* mRNA expression from Baseline to Day 28 in Sigmoid Colon, GB004 vs Placebo: 0.30 (-0.03, 0.62)

Integrin-α6 (*ITGA6*)



Increase in Mean (95% CI) log_2-fold change in *ITGA6* mRNA expression from Baseline to Day 28 in Sigmoid Colon, GB004 vs Placebo: 0.26 (-0.06, 0.60)

95% CIs for difference in mean change from baseline based on analysis of variance

Conclusion

- In this exploratory study GB004, an oral, gut-targeted, HIF-1α stabilizer, demonstrated numeric
  - Increase in HIF-1α positive cells
  - Increases in gene expression (*TJP1, ITGA6)* and fecal secretory IgA
  - Decreases in MPO positive cells and fecal calprotectin
- These biomarker results, along with trends in clinical activity, suggest that GB004 could improve mucosal healing and reduce inflammation in UC patients
- A Phase 2 study of GB004 in patients with mild-to-moderate UC (SHIFT-UC, NCT04556383, EudraCT 2020-002306-12) is ongoing