P0589

Safety, Pharmacokinetic, Biomarker, Histologic, and Rectal Bleeding Activity Following Treatment with the Gut-Targeted, PHD-Inhibitor and HIF-1α Stabilizer GB004 in a Phase 1b Trial in Mild-to-Moderate Ulcerative Colitis

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INTRODUCTION

- GB004 is a small molecule gut-targeted oral inhibitor of the prolyl hydroxylase enzymes; it stabilizes HIF-1α, which promotes mucosal healing and resolves local inflammation in ulcerative colitis without systemic immunosuppression[1-3]
- GB004 restores local immune homeostasis in intestinal epithelial cells which may protect against further inflammatory insults[1-3]
- In a previous study of healthy subjects, GB004 showed a gut-targeted pharmacokinetic (PK) profile[4]

OBJECTIVES

- Primary: Evaluate the safety and tolerability of GB004 when administered daily for 28 days to adult subjects with active ulcerative colitis (UC)
- Secondary: Estimate PK parameters of GB004
- Exploratory: Assess the pharmacodynamic response in the context of target engagement and clinical and histologic activity

METHODS

- Phase 1b, double-blind, placebo-controlled study
- Eligible subjects
  - ✓ Age 18-74 years
  - ✓ Robarts Histopathology Index (RHI) ≥ 4 with neutrophils in the epithelium (subscore ≥ 1) in sigmoid or rectum
  - ✓ Mayo endoscopic subscore (MES) ≥ 1 in sigmoid or rectum
  - ✓ Blood in the stool
  - ✓ Currently receiving 5-ASA, prednisone, budesonide MMX, azathioprine, or 6-MP
- Subjects were randomized 2:1 to GB004 120 mg formulated as a solution or placebo once daily for 28 days
- Colonic biopsies of the sigmoid and rectum were obtained at screening and Day 28
- Mucosal healing was defined as MES improvement (0 or 1; 0 if baseline 1) and histologic remission (RHI ≤ 3 with lamina propria neutrophils and neutrophils in epithelium sub-scores of 0)
- Subjects with missing values for binary clinical or histologic endpoints were considered to have not met the endpoint

RESULTS

- Thirty-four subjects were randomized; 33 completed the study
- Baseline characteristics were generally similar between the two treatment groups; ongoing steroid treatment was greater in the GB004 group (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Placebo (n = 11)	GB004 120 mg (n = 23)
Age, years	45.5 (15.42)	45.4 (11.58)
Sex, male	8 (72.7)	15 (65.2)
Extent of Disease		
Left side of colon	3 (27.3)	12 (52.2)
Extensive	8 (72.7)	11 (47.8)
Prior UC treatment		
Aminosalicylates	11 (100.0)	23 (100.0)
Steroids	6 (54.5)	14 (60.9)
Immunomodulators	2 (18.2)	8 (34.8)
Anti-TNF	0	1 (4.3)
Ongoing UC treatment		
Aminosalicylates	11 (100.0)	23 (100.0)
Steroids	0	6 (26.1)
Immunomodulators	0	1 (4.3)
Mayo Score	7.6 (1.91)	7.4 (2.08)
MES, Sigmoid	2.4 (0.92)	2.1 (0.97)
RHI Score, Sigmoid	14.5 (8.97)	14.0 (8.66)

Mean (SD) for continuous data, n (%) for categorical data. Mayo Score utilizes MES, Sigmoid.

Table 2. Summary of Adverse Events (AE)

Number (%) of subjects with:	Placebo (n = 11)	GB004 120 mg (n = 23)
Any AE	3 (27.3)	9 (39.1)
Serious AE	0	1 (4.3)
Treatment-related AE	1 (9.1)	7 (30.4)
AE leading to study drug discontinuation	0	1 (4.3)

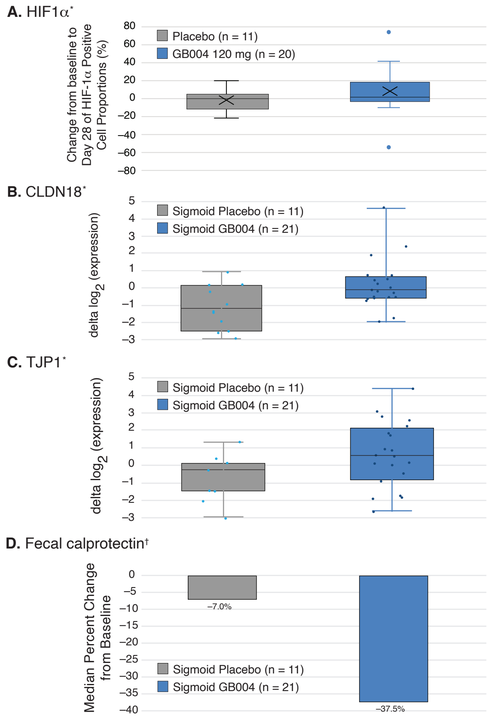
- Most frequent AEs in GB004-treated subjects were nausea and dysgeusia; all were grade 1 in severity, except for one grade 2 event of nausea
- No effect relative to placebo was observed on systemic EPO or VEGF levels
- One GB004-treated subject developed a serious AE of worsening UC leading to treatment/study withdrawal after 21 days of GB004 dosing; this was assessed as unrelated to GB004

Pharmacokinetics

- GB004 was rapidly absorbed, with low systemic exposure and rapid clearance; minimal accumulation was observed based on C_{max} and AUC after 28 days of dosing
- Colonic tissue levels of GB004 substantially exceeded plasma levels at time of biopsy, consistent with a gut targeting profile

Pharmacodynamics

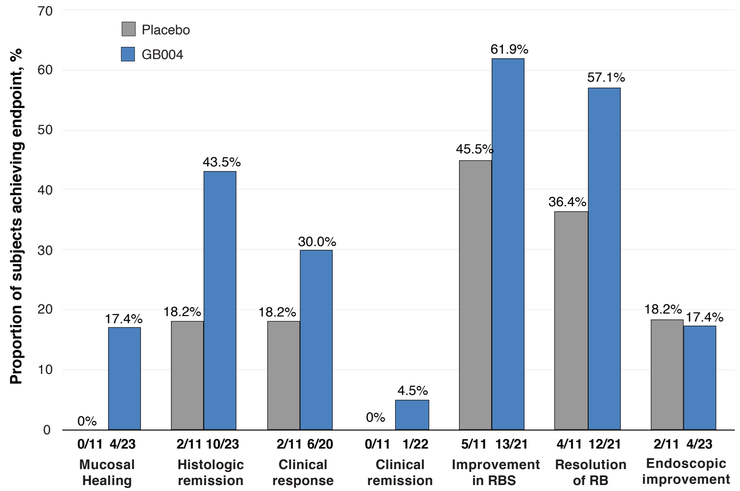
Figure 1. Change from baseline to Day 28 in A. HIF1α-positive cell level by IHC, B. Claudin gene expression, C. Tight junction protein gene expression, and D. Fecal calprotectin



*Horizontal line represents the median, the top and bottom of the box represent first and third quartiles, respectively, and the whiskers a range of maximally 1.5 times the distance between the first and third quartile, with outliers represented by circles. The mean is denoted by "x".

†Difference in median percent change from baseline between GB004 and placebo (95% distribution-free confidence interval based on the inverted rank-score test method) was –30.5% (–143.2, 68.1).

Figure 2. Positive trends in exploratory efficacy outcomes



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); clinical response & remission based on Mayo score.

CONCLUSIONS

- GB004 oral solution was generally well tolerated in subjects with UC treated for 28 days
- Oral administration of GB004 demonstrated a gut targeted profile consistent with low systemic exposure and preferential localization to gut tissue
- Evidence of target engagement and positive effect on barrier function genes was observed; lack of peripheral target engagement is supported by no effect on EPO or VEGF relative to placebo
- Trends in clinical efficacy were observed across multiple endpoints despite the limited 4 week treatment period and limited sample size
- A phase 2 study evaluating two doses of GB004 as a tablet formulation in mild to moderate UC is ongoing (NCT04556383)

REFERENCES

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DISCLOSURES

Funded by GB004, Inc., a wholly owned subsidiary of Gossamer Bio, Inc.

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