P540

GB004, a Novel Gut-Targeted Prolyl Hydroxylase Inhibitor for Inflammatory Bowel Disease: First In-Human Multiple Dose Study in Healthy Subjects With Gut Biopsies

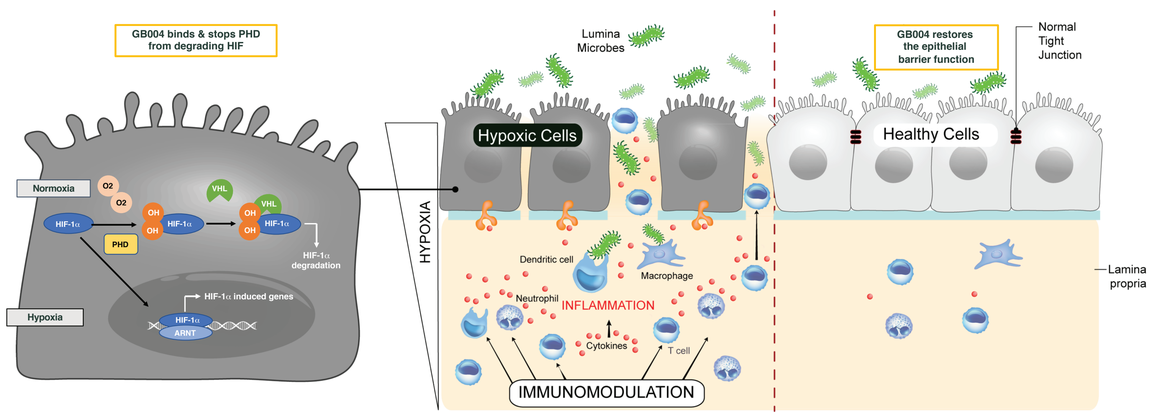
Barrett G. Levesque[1], Kristen Taylor Meadows[1], Akshay Buch[2], Michael Flynn[2], Kevin Peters[2], Allan Olson[1], Jinshan Shen[1], Masha Sergeeva[1], Debbie Slee[1], Courtney Van Biene[1], Richard Aranda[1], Gregory J. Opiteck[1]

[1]Gossamer Bio, Inc., [2]Aerpio Pharmaceuticals, Inc.

INTRODUCTION

- GB004 is a small molecule hypoxia inducible factor (HIF-1α) stabilizer, a key transcription factor involved in the protective cellular responses at the intersection of hypoxia and inflammation (**Figure 1**)[1]
- GB004 was selected based on its gut-targeted profile to limit systemic on-target effects associated with HIF-1α stabilization
- In animal models of colitis, GB004 demonstrated a significant reduction in disease activity, improvements in histologic measures, and greater exposure in GI tissue relative to plasma[2]
- GB004 is in clinical development for treatment of inflammatory bowel disease; in a single ascending dose study in normal healthy subjects, GB004 was well tolerated, without serious adverse events (AEs) or discontinuations related to AEs[3]
- This study aimed to explore the safety and pharmacokinetic profile with multiple doses of GB004 administered in healthy subjects

Figure 1. GB004 mechanism of action



OBJECTIVES

- Primary: Assess the safety and tolerability of GB004 following administration of multiple daily doses in healthy male and female subjects
- Secondary: Determine the pharmacokinetics (PK) of GB004 and the associated pharmacodynamic response
- Exploratory: Assess the relationship between target engagement (biomarkers in plasma and colonic tissue) and GB004 treatment

METHODS

- Phase 1a, randomized, double-blind, placebo-controlled, multiple dose study conducted in healthy subjects at a single site in Canada
- Healthy male and female subjects, 18-55 years in age, were randomized sequentially to
  - Ascending doses of GB004 (60 mg, 120 mg, 240 mg) formulated as a solution (GB004 + 10 g cyclodextrin) or placebo solution (10 g cyclodextrin) orally once daily for 8 days
  - Two additional cohorts evaluated GB004 in descending doses (120 mg, 60 mg) to gather further information on safety and PK in female subjects
- Primary endpoints of safety and tolerability (adverse events; clinically significant changes in vital signs, ECG, and laboratory parameters) were assessed throughout the study and on Day 15 of follow-up
- Secondary endpoint: GB004 PK parameters
- Exploratory endpoints: Plasma levels of EPO and VEGF, and HIF-1α expression levels determined by IHC staining in colonic biopsies

Table 1. GB004 dose cohorts

GB004 dose, mg	Placebo, n	GB004, n	Total n
60	4	12	16
120	4	12	16
240	2	6	8

RESULTS

Disposition and Baseline Characteristics

- 42 subjects received study treatment; most subjects were White and non-Hispanic, ranging in age from 27 to 55 years; the number of males and females was similar overall and within treatment groups (**Table 2**)

Table 2. Demographics and baseline characteristics by treatment group

Characteristic	Placebo (n = 10)	GB004 60 mg (n = 12)	GB004 120 mg (n = 12)	GB004 240 mg (n = 8)	All (N = 42)
Age, years					
Mean (SD)	49.6 (6.4)	47.4 (8.7)	46.3 (9.9)	47.5 (8.4)	47.6 (8.3)
Sex, male, n (%)	5 (50)	6 (50)	6 (50)	3 (38)	20 (48)
Race, White, n (%)	7 (70)	8 (67)	8 (67)	7 (88)	30 (71)
Ethnicity, n (%)					
Non-Hispanic or Latino	9 (90)	11 (92)	10 (83)	7 (88)	37 (88)

Safety

- Overall, AEs were reported in 69% and 60% of GB004- and placebo- treated subjects, respectively
- All planned doses were administered in 100%, 100%, 100%, and 63% of subjects receiving placebo, GB004 60 mg, 120 mg, and 240 mg, respectively
- The most common AEs in GB004-treated subjects were dizziness (31%), headache (28%), diarrhea (28%), and nausea (25%); most AEs were classified as mild
- Two subjects receiving GB004 240 mg discontinued treatment due to AEs of vomiting and non-cardiac chest pain, respectively
- No clinically significant, treatment-related changes were observed in physical exam, ECG, or laboratory parameters
- No serious AEs or deaths were reported

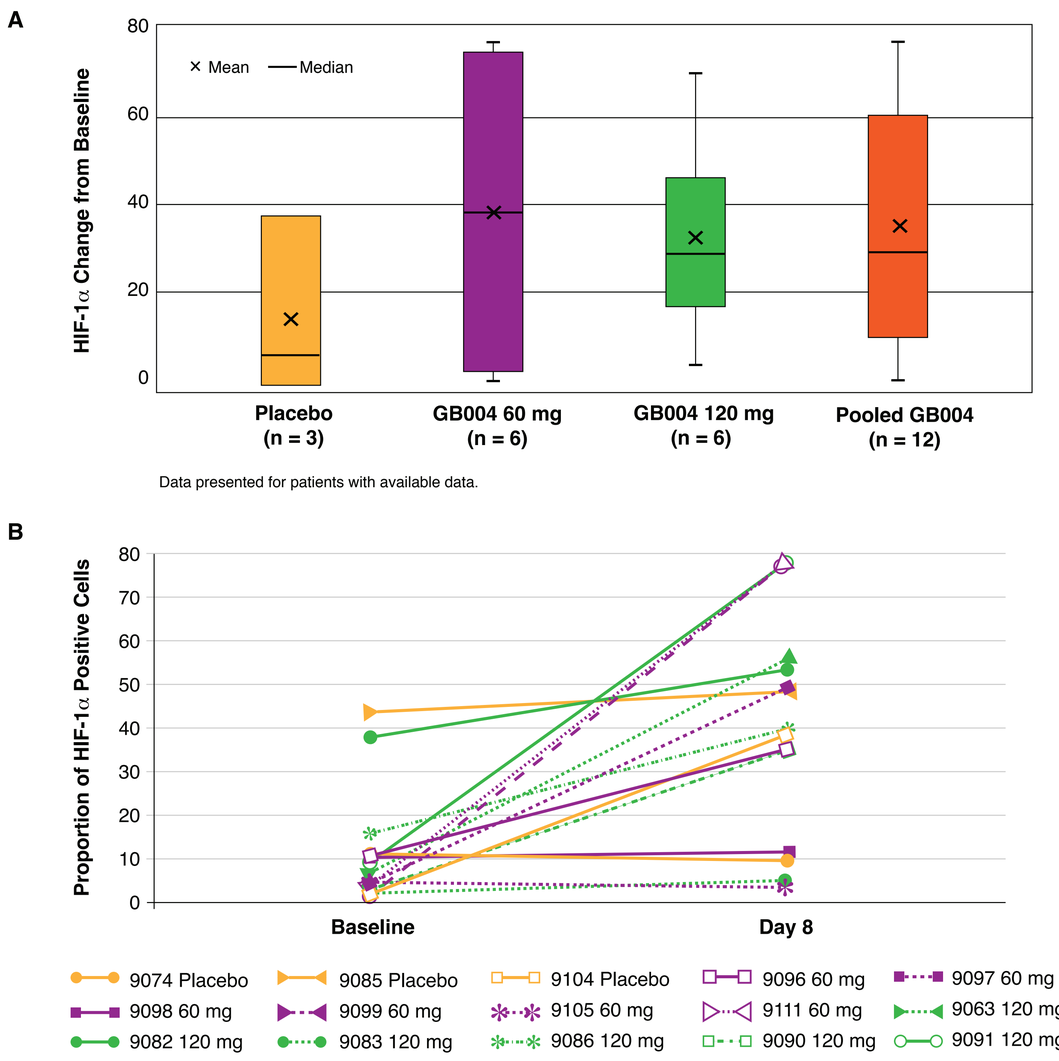
Pharmacokinetics

- GB004 was rapidly absorbed (mean T_{max} 0.5 hour) and rapidly eliminated from the systemic circulation
- Colonic tissue concentrations of GB004, though variable, were greater than plasma concentrations at the time of biopsy (~8 hours post dose). Median colonic tissue-to-plasma concentration ratios were ~4-fold or greater in all dose groups.

Pharmacodynamics

- No dose-related changes were observed in plasma EPO or VEGF levels
- Increases from baseline in HIF-1α expression were observed with GB004 treatment (**Figure 2**)

Figure 2. HIF-1α expression in colon biopsy following 8 days of oral dosing



CONCLUSIONS

- This study demonstrated that multiple daily doses of a GB004 solution formulation were tolerable. A tablet formulation of GB004, without cyclodextrin, is also being developed.
- The PK profile for GB004 was consistent with its intended preferential exposure in the gut. In support of the gut-targeted exposure, HIF2 target genes EPO and VEGF were not modulated in plasma relative to placebo.
- GB004 engaged the target and stabilized HIF-1α, as demonstrated by upregulated gene expression in the gut
- A clinical study of GB004 is ongoing in patients with ulcerative colitis to explore safety, PK and PD systemically and within colonic tissue (NCT03860896)

REFERENCES

1. Robinson A, Keely S, Karhausen J, et al. *Gastroenterology* 2008; 134:145-155.
2. Marks E, Goggins BJ, Cardona J, et al. *Inflamm Bowel Dis* 2015; 21(2):267-275.
3. Levesque, BG, Flynn M, Peters K, et al. Presented at the Advances in Inflammatory Bowel Diseases Conference, Orlando, FL, December 12-14, 2019. P051.

ACKNOWLEDGEMENTS

Angela Pietrofeso, Gossamer Bio, Inc.; Harry Southworth, Data Clarity Consulting; Matthew Rueffer, Niels Vande Casteele, and Pavine Lefevre, Robarts Clinical Trials for data analysis and trial support, respectively.

DISCLOSURES

BGL, KTM, AO, JS, MS, DS, CVB, RA, and GJO are employed by Gossamer Bio, Inc.; AB, MF, and KP are employed by Aerpio Pharmaceuticals, Inc.

Presented at the 15th European Crohn's and Colitis Organisation Congress (ECCO 2020), Vienna, Austria, February 12-15, 2020.