Phase 1a Safety and Pharmacokinetic Effects of GB004, a Novel Prolyl Hydroxylase Inhibitor and Potential Therapy for Inflammatory Bowel Disease

P051

Barrett G. Levesque, MD, MS[1]; Michael Flynn, MS[2]; Kevin Peters, MD[2]; Akshay Buch, PhD[2]

[1]Gossamer Bio, Inc., San Diego, CA; [2]Aerpio Pharmaceuticals, Inc.; Cincinnati, OH

BACKGROUND

- Inflammatory Bowel Disease (IBD) is the result of an unrelenting, severe, inflammatory response mounted against an environmental trigger in a genetically susceptible host, which in turn, causes a breach in intestinal barrier integrity, allowing influx of luminal antigens, setting up a vicious cycle of inflammation and epithelial injury that perpetuates the disease process.[1]
- Despite the improved efficacy of IBD treatment with anti-tumor necrosis factor (anti-TNF) agents and anti-integrin agents (e.g. vedolizumab), there is still a large subset of patients who either do not respond adequately to conventional therapy or biologic therapy and do not achieve long-term remission.[2,3]
- GB004 is an oral, small molecule, prolyl hydroxylase inhibitor (PHDi) that stabilizes hypoxia inducible factors (HIF-α), key transcription factors involved in the adaptive and protective cellular responses at the intersection of hypoxia and inflammation.
- For diseases such as IBD, an ideal PHDi profile would encompass gut-targeted pharmacokinetics and preferential activation of tissue-specific protective mechanisms where HIF transcription factors have a role [e.g., erythropoietin (EPO) production].
- In animal models of colitis, orally administered GB004 demonstrated a significant reduction in disease activity, an improvement in histology, greater exposure in GI tissue relative to plasma, and no increase in systemic EPO or hematocrit.[4]

OBJECTIVES

- The primary objective was to assess the safety and tolerability of GB004 following single ascending doses administered to healthy male subjects.
- A secondary objective was to characterize the pharmacokinetic profile of GB004 in the same population.
- A potential pharmacodynamic relationship between drug exposure and changes in biomarker levels [plasma EPO and vascular endothelial growth factor (VEGF)] were explored.

METHODS

- Randomized, double-blind, placebo-controlled, single-ascending dose, Phase 1a study conducted at a single site in Canada.
- Single oral doses were investigated in 5 sequential cohorts, summarized in **Table 1.**
- PK and safety were evaluated through follow-up on day 8.
- EPO and VEGF levels were measured at baseline, 4, 8, and 12 hours post dose.

Table 1. Treatment Schema

Cohort	GB004 Dose n = 6/group	Volume of Dosing solution
1	20 mg	50 mL
2	60 mg	50 mL
3	120 mg	50 mL
4	240 mg	50 mL
5	240 mg	100 mL

RESULTS

Disposition and Baseline Characteristics

- 40 male subjects were randomized.
- Each dosing cohort comprised two placebo- and six GB004-treated subjects.
- All subjects completed the study (**Table 2**).

Table 2. Demographics and Baseline Characteristics

Baseline characteristic	N = 40
Age, years	
Median (range)	37 (20-48)
Race, n (%)	
White	19 (47.5)
Black or African American	11 (27.5)
Asian	8 (20.0)
Other	2 (5.0)
Body mass index, kg/m²	
Median (range)	25.75 (20.2-30.3)

Pharmacokinetic-Pharmacodynamic Profile

- GB004 was rapidly absorbed, with a median T_{max} of 0.5 hour observed for all doses (**Figure 1**).
- Peak GB004 concentration (C_{max}) increased in a dose-proportional manner while AUC of GB004 increased slightly larger than dose proportional.
- GB004 was rapidly eliminated from the systemic circulation.
- No dose-related changes were observed in plasma EPO or VEGF at any dose level (**Figure 2**).

Figure 1. Mean GB004 Pharmacokinetic Profiles for all Subjects (Linear Scale)

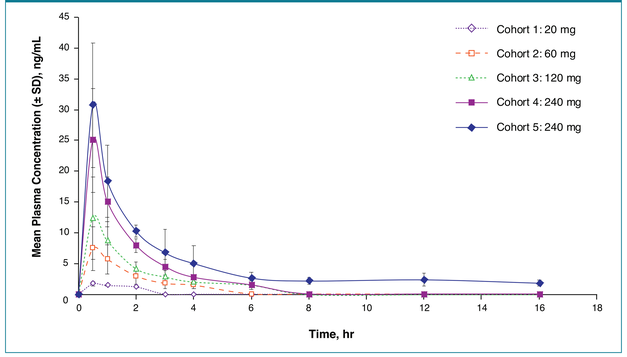
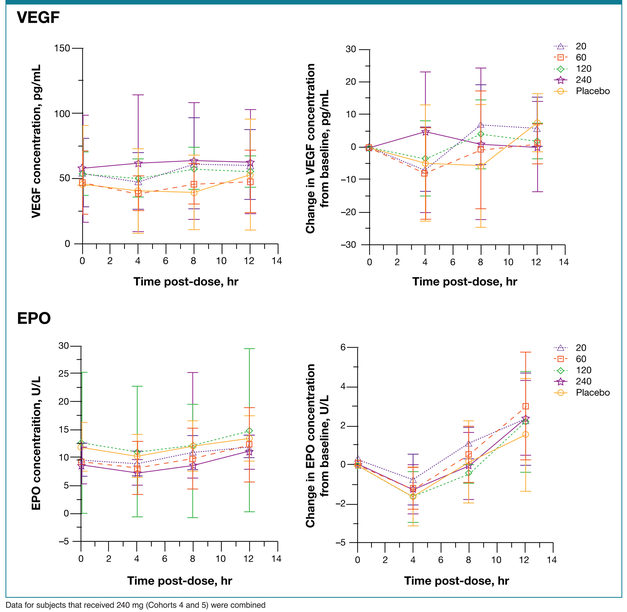


Figure 2. Mean ± SD Plasma Concentrations and Change from Baseline for VEGF and EPO Biomarkers by GB004 Dose



Data for subjects that received 240 mg (Cohorts 4 and 5) were combined

Safety

- No adverse events (AEs) leading to discontinuation were recorded
- No serious adverse events (SAEs) or deaths were recorded
- The incidence of treatment-emergent AEs was 47% and 50% in GB004- (n = 30) and placebo-treated (n = 10) subjects
- AEs with an incidence ≥10% in GB004-treated subjects and higher than in placebo were: nausea (20.0% GB004 vs 0% placebo), vomiting (13.3% vs 0%), feeling cold (13.3% vs 10.0%), and somnolence (10.0% vs 0%).
- All AEs reported in GB004-treated subjects were mild, and the incidence of AEs for GB004 240 mg in 100 ml was lower than 240 mg or 120 mg in 50 ml.

Table 3. Summary of Treatment-Emergent Adverse Events (TEAE) (N = 40)

n (%)	Placebo (n = 10)	Cohort 1 20 mg (n = 6)	Cohort 2 60 mg (n = 6)	Cohort 3 120 mg (n = 6)	Cohort 4 240 mg (n = 6)	Cohort 5 240 mg (n = 6)
Any TEAE	5 (50)	2 (33)	1 (17)	5 (83)	5 (83)	1 (17)
Serious TEAE	0	0	0	0	0	0
Severe TEAE	0	0	0	0	0	0
Related TEAE	5 (50)	1 (17)	1 (17)	5 (83)	5 (83)	1 (17)
Subjects D/C due to AE	0	0	0	0	0	0
TEAE occurring in ≥10% of GB004-treated subjects and more frequent vs placebo						
Nausea	0	0	0	2 (33)	3 (50)	1 (17)
Vomiting	0	0	0	0	4 (67)	0
Feeling cold	1 (10)	0	0	3 (50)	1 (17)	0
Somnolence	0	0	1 (17)	0	2 (33)	0

CONCLUSIONS

- **This single ascending dose (SAD) study is the first-in-human study to evaluate the safety, tolerability, and PK of GB004 in healthy subjects.**
- **This study demonstrated that single doses of GB004 solution were generally well tolerated, with no effects observed on serum EPO or VEGF levels, consistent with the intended PK profile and animal model data.**
- **Clinical studies of GB004 are ongoing in patients with ulcerative colitis to explore PK and PD both systemically and within colonic tissue (NCT03860896).**
- **A tablet formulation is being developed.**

REFERENCES

1. Danese S, Fiocchi C. *N Eng J Med.* 2011; 365:1713-1725.
2. Nielsen OH, Ainsworth MA. *N Eng J Med.* 2013; 369:754-762.
3. Petkau JM, Eksteen B. *Biologics.* 2016;10:33-52.
4. Marks E, Goggins BJ, Cardona J, et al. *Inflamm Bowel Dis.* 2015;21:267-275.

ACKNOWLEDGMENTS

Thank you to Ellen Zigmont, Jill Luer, and Karen Watson for their assistance in the preparation of this poster.

Presented at the Advances in Inflammatory Bowel Diseases conference, Orlando, FL, December 12-14, 2019.