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Pharmacokinetics, Pharmacodynamics, and Safety of GB001 in Healthy Non-Asian, Non-Japanese Asian and Japanese Subjects

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INTRODUCTION

- GB001 is a potent and highly selective oral DP2 receptor antagonist in development as a once daily, oral add-on maintenance treatment for moderate to severe eosinophilic asthma (NCT03683576) and chronic rhinosinusitis (NCT03956862)
- DP_2 is expressed on cells implicated in the allergic process, including T helper cell type 2 lymphocytes, eosinophils, basophils, mast cells, and innate lymphoid type cells; its endogenous antagonist, PGD2 is elevated in patients with moderate to severe asthma[1-4]

OBJECTIVES

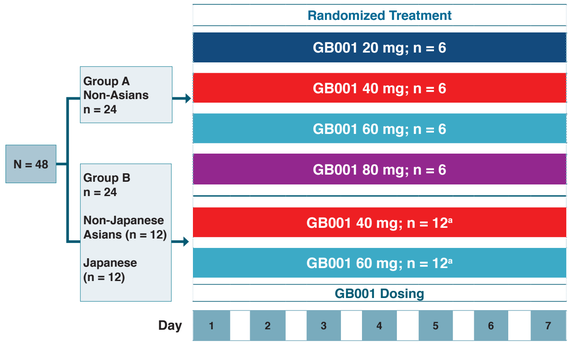
- **Primary:** Explore the pharmacokinetic parameters of GB001 in healthy non-Asian (NA), non-Japanese Asian (NJA) and Japanese (JA) subjects
- **Secondary:** Explore the safety/tolerability of GB001 in healthy NA, NJA, and JA subjects
- **Exploratory:** Explore the effects of GB001 on PD biomarkers

METHODS

- This was a Phase 1, randomized, parallel, investigator- and subject-blinded, multiple-dose study
- Healthy adult subjects were randomized to receive GB001 20, 40, 60 and 80 mg QD for 7 days as described in Figure 1; randomization was stratified by race category (NA, NJA, or JA) and weight group (45 to <55 kg or ≥55 kg)
- Subjects were followed for an additional 28 days following 7 days of GB001 dosing
- Serial plasma samples were collected pre- and post-dose on Days 1 and 7 to estimate the following PK parameters:
  - Maximum observed plasma concentration during a dosing interval (C_{max})
  - Area under the plasma concentration-time curve during a dosing interval ($AUC_{(0\text{-}t)}$)
- Plasma samples for PD exploration were collected in parallel at assigned PK timepoints; PD assessments of target engagement included inhibition of DP_2 receptor internalization, eosinophil shape change, and CD11b expression in whole blood samples stimulated with and without prostaglandin D_2 prior to flow cytometry analysis
- Safety and tolerability assessments were performed throughout the dosing and follow-up periods via standard clinical monitoring (physical exam, vital signs, laboratory tests, ECG) and recording of adverse events (AEs)
- Statistical analyses
  - General linear models were used to compare race categories for log-transformed Day 7 PK parameters for the GB001 40 mg and 60 mg dose levels
  - Dose proportionality for C_{maxss} and $AUC_{(0\text{-}t)ss}$ on Day 7 was assessed by estimating slope and associated 95% CI using a power model.

METHODS

Figure 1: Study schema



[a]Two additional subjects beyond the planned sample size of 48 were randomized. Both were Japanese subjects, with 1 subject randomized to GB001 40 mg and the other to GB001 60 mg.

RESULTS

- Fifty subjects were randomized and treated, with all 50 subjects completing study treatment. Baseline demographic characteristics are summarized below (**Table 1**).

Table 1. Baseline characteristics

	GB001 20 mg (n = 6)	GB001 40 mg (n = 19)	GB001 60 mg (n = 19)	GB001 80 mg (n = 6)	GB001 Total (N = 50)
Age, years, Median (range)	28.0 (19-45)	36.0 (27-52)	40.0 (27-54)	35.0 (25-46)	36.5 (19-54)
Sex, Male, n (%)	4 (66.7)	7 (36.8)	10 (52.6)	3 (50.0)	24 (48.0)
Race category, n (%)					
Non-Asian	6 (100.0)	6 (31.6)	6 (31.6)	6 (100.0)	24 (48.0)
Non-Japanese Asian	0	6 (31.6)	6 (31.6)	0	12 (24.0)
Japanese	0	7 (36.8)	7 (36.8)	0	14 (28.0)
Weight group, n (%)					
45 to < 55 kg	2 (33.3)	6 (31.6)	6 (31.6)	2 (33.3)	16 (32.0)
≥ 55 kg	4 (66.7)	13 (68.4)	13 (68.4)	4 (66.7)	34 (68.0)

RESULTS

Pharmacokinetics

- GB001 was rapidly absorbed following oral administration in all dose groups (median T_{max} 2-3 hr) and reached steady state on Day 4. Minimal GB001 accumulation was observed following doses of 20 mg to 80 mg administered daily for 7 days.
- PK of GB001 were generally similar between NA, NJA, and JA subjects receiving GB001 doses of 40 mg or 60 mg (**Table 2**)
- GB001 exposure increased in a dose-proportional manner (**Table 3**)

Table 2. Statistical comparisons of Day 7 GB001 C_{maxss} and $AUC_{(0\text{-}t)ss}$ by Race Category

PK Parameter	GB001 Dose	Test Race Category	Reference Race Category	Geometric Mean Ratio (95% CI) for Test vs Reference
C_{maxss}	40 mg	Japanese	Non-Asian	1.5 (1.00, 2.33)
		Non-Japanese Asian	Japanese	0.6 (0.41, 0.95)
			Non-Asian	1.0 (0.62, 1.48)
	60 mg	Japanese	Non-Asian	1.0 (0.66, 1.53)
		Non-Japanese Asian	Japanese	1.0 (0.68, 1.58)
			Non-Asian	1.0 (0.67, 1.62)
$AUC_{(0\text{-}t)ss}$	40 mg	Japanese	Non-Asian	1.4 (0.88, 2.16)
		Non-Japanese Asian	Japanese	0.6 (0.39, 0.96)
			Non-Asian	0.8 (0.53, 1.34)
	60 mg	Japanese	Non-Asian	0.8 (0.51, 1.26)
		Non-Japanese Asian	Japanese	1.2 (0.76, 1.87)
			Non-Asian	1.0 (0.60, 1.53)

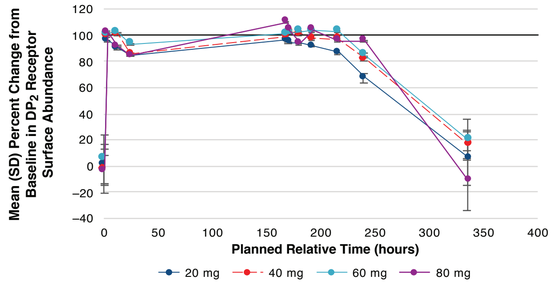
Table 3. Dose Proportionality Assessment at Day 7

Parameter	Slope (95% CI)
C_{maxss}	1.09 (0.74, 1.43)
$AUC_{(0\text{-}t)ss}$	1.02 (0.67, 1.36)

Note: Dose proportionality was assessed using the following power model: ln (PK parameter) = μ + β* ln (dose), where μ is the intercept and β is the slope.

Pharmacodynamics

Figure 2. Mean Percent Change from Baseline in DP_2 Receptor Surface Abundance



SD, Standard Deviation

- All doses of GB001 rapidly inhibited DP_2 receptor internalization; inhibition was maintained throughout the 7-day dosing period, approaching baseline levels by 7 days following the last dose of GB001 (**Figure 2**)
- Similar inhibition was observed in eosinophil shape change and CD11b expression

Safety

- GB001 was generally well tolerated after QD dosing for 7 days at 20 to 80 mg in NA subjects and at 40 to 60 mg in NJA and JA subjects
- There were no serious or severe adverse events reported
- The incidence of AEs was similar in NA (25%) and NJA (25%) subjects, with no AEs reported in JA subjects

CONCLUSIONS

- PK of GB001 were similar in healthy NA, NJA, and JA subjects, indicating no race-related differences
- Exposures of GB001 increased in a dose-proportional manner following oral doses of 20 to 80 mg QD
- GB001 resulted in rapid, profound and sustained target engagement and PD effects
- GB001 was well tolerated following doses of 20 to 80 mg once daily

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Prepared for presentation at the American Thoracic Society International Conference, May 15-20, 2020 (canceled due to COVID-19). Virtual meeting, August 5-10, 2020. Abstract 3019.