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 to moderate to severe eosinophilic asthma (NCT03888576) and chronic rhinosinusitis (NCT03595692).
- DP2 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

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 post-dose on Days 1 and 7 to estimate the following PK parameters:
  - Maximum observed plasma concentration during a dosing interval (Cmax).
  - Area under the plasma concentration-time curve during a dosing interval (AUC(t)).
- Plasma samples for PD exploration were collected in parallel at assigned PK timepoints. PD assessments of target engagement included inhibition of DP2 receptor internalization, eosinophil shape change, and CD11b expression in whole blood samples stimulated with and without prostaglandin D2 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, flow cytometry analysis).
- 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 Cmaxss and AUC(t)ss on Day 7 was assessed by estimating slope and associated 95% CI using a power model.

RESULTS

- GB001 was rapidly absorbed following oral administration in all dose groups (median tmax = 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).
- AUC(t)ss of GB001 was rapidly inhibited in eosinophil shape change and CD11b expression.

CONCLUSIONS

- GB001 was well tolerated following 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.

REFERENCES