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Effect of the DP_2 Antagonist GB001 on Asthma Worsening in Patients With Mild-Moderate Asthma

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BACKGROUND

- Asthma is a heterogeneous condition characterized by phenotypes related to specific biomarkers that may predict therapeutic response in selected patient populations.[1] Asthmatic patients with increased Type 2 biomarkers [eosinophils (Eos), fractional exhaled nitric oxide (FeNO)] may exhibit increased PGD_2 levels.[1]
- DP_2 is a G-protein-coupled receptor selectively expressed by T lymphocytes (Th2), Eos, basophils and Type 2 innate lymphoid cells (ILC2s). DP_2 binds to PGD_2, promoting recruitment and activation of Eos and basophils and stimulating Th2 and ILC2 cells to release Type 2 cytokines IL-4, IL-5 and IL-13, leading to persistent Type 2 inflammation.[3]
- GB001 is a potent and highly selective oral DP_2 antagonist in development as a once-daily, oral, add-on maintenance treatment for moderate to severe eosinophilic asthma and chronic rhinosinusitis

OBJECTIVE

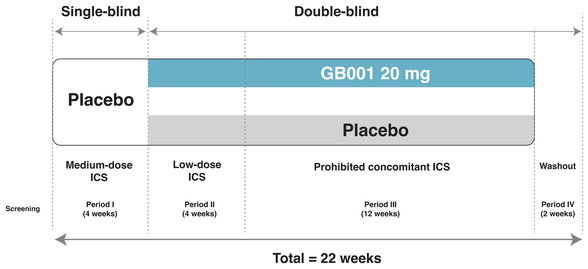
- This post-hoc analysis aimed to assess the effect of GB001 on time to asthma worsening in the overall population and by low and high baseline FeNO (< 25 & ≥ 25 ppb) and Eos (< 250 & ≥ 250 cells/μL) subgroups. Other FeNO & Eos thresholds were also explored.

METHODS

- Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in Japan from May 2015 through April 2016[4]
- During a 4-week run-in period, patients received medium-dose inhaled corticosteroids (ICS) and oral placebo and were then randomized 1:1:1 to once-daily GB001 5 mg, 20 mg, or placebo for 16 weeks or until asthma worsening. ICS were tapered to and then discontinued from low-dose levels at randomization and 4 weeks post-randomization, respectively. (**Figure 1**)
- A composite endpoint was used to determine asthma worsening; if any of the criteria were met, the study drug was discontinued and patients were restarted on standard of care therapy: (1) ≥ 25% decrease from baseline in morning peak expiratory flow (AM PEF) for 2 days, (2) ≥ 20% decrease from baseline in FEV_1, (3) use of inhaled short-acting β-agonists at doses ≥ 5 puffs/day for 2 days, (4) a ≥ 0.5 point increase from baseline in the ACQ-5 score, or (5) asthma exacerbation requiring administration of oral corticosteroids or an unscheduled visit to the clinic
- Results are presented for placebo- and GB001 20 mg-treated patients; results for the GB001 5 mg group were generally consistent with the 20 mg dose group (data not shown)
- Biomarkers included blood Eos and FeNO (Niox MINO®, Aerocrine AB, Solna, Sweden)

METHODS

Figure 1. Study Design*



*Study design also included a GB001 5 mg arm. See Methods.

RESULTS

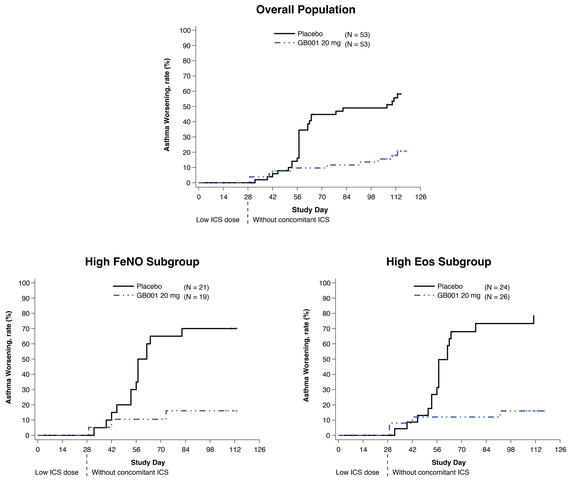
Table 1. Baseline Demographic and Clinical Characteristics

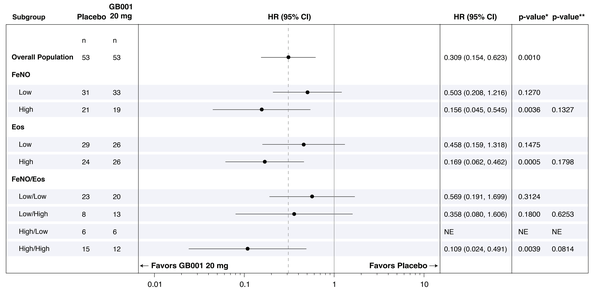
Parameter	Low FeNO < 25 ppb (n = 64)	High FeNO ≥ 25 ppb (n = 40)	Low Eos < 250 cells/μL (n = 55)	High Eos ≥ 250 cells/μL (n = 50)	Overall (n = 106)
Age, years	47.9 (13.6)	52.3 (11.1)	48.8 (14.0)	49.9 (11.1)	49.5 (12.7)
Female	44 (68.8)	20 (50.0)	35 (63.6)	30 (60.0)	65 (61.3)
Race, Asian	64 (100.0)	40 (100.0)	55 (100.0)	50 (100.0)	106 (100.0)
BMI, kg/m^2	22.8 (3.2)	23.7 (2.7)	23.1 (3.1)	23.2 (2.9)	23.2 (3.0)
Allergic rhinitis	53 (82.8)	28 (70.0)	41 (74.5)	41.0 (82.0)	82 (77.4)
ACQ-5	0.5 (0.7)	0.6 (0.6)	0.5 (0.7)	0.6 (0.6)	0.5 (0.6)
Eos, cells/μL	267.8 (246.2)	446.7 (345.4)	129.1 (59.8)	583.4 (289.1)	345.4 (305.3)
FeNO, ppb	15.0 (5.0)	51.8 (26.9)	20.9 (13.2)	38.7 (31.2)	29.1 (24.8)
IgE, IU/mL	387.1 (524.3)	405.2 (436.0)	294.1 (436.8)	862.3 (2528.1)	565.8 (1778.0)
ICS	16 (25.0)	16 (40.0)	17 (30.9)	17 (34.0)	34 (32.1)
ICS/LABA	48 (75.0)	24 (60.0)	38 (69.1)	33 (66.0)	72 (67.9)
FEV_1, L*	2.1 (0.6)	2.2 (0.5)	2.2 (0.6)	2.1 (0.5)	2.2 (0.5)
Percent predicted FEV_1	78.3 (8.2)	78.0 (8.0)	79.2 (8.0)	77.2 (8.1)	78.3 (8.1)

Data presented as mean (SD) for continuous parameters and n (%) for categorical parameters. Baseline data not available for FeNO (n = 2) and Eos (n = 1).
*Pre-bronchodilator FEV_1; ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting β-agonist; ppb, parts per billion.

RESULTS

Figure 2. Time to Asthma Worsening





CI, confidence interval; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; HR, hazard ratio; NE, not estimable due to no events in the GB001 20 mg group.
Subgroup analyses based on a Cox proportional hazards model with covariates for treatment group, subgroup, and treatment group by subgroup interaction.
**P*-value for the treatment contrast within the subgroup.
***P*-value for the treatment by subgroup interaction, which evaluates heterogeneity of treatment effect across different levels of the subgroup.

- In the overall population, GB001 20 mg significantly delayed time to asthma worsening versus placebo (hazard ratio [HR] 0.31, 95% CI 0.15, 0.62, $P = 0.0010$)
- GB001 had a substantially greater effect in delaying time to asthma worsening in the high baseline FeNO subgroup compared to the low baseline FeNO subgroup (HR 0.16, high FeNO vs 0.50, low FeNO)
- A similar finding was observed when asthma worsening was analyzed by baseline Eos subgroups (HR 0.17, high Eos vs 0.46, low Eos)
- Patients with both high baseline FeNO and Eos experienced a greater delay in time to asthma worsening compared to patients with both low baseline FeNO and Eos (HR 0.11, high FeNO & high Eos vs 0.57, low FeNO & low Eos)
- Similar findings were observed using a baseline FeNO ≥ 35 ppb threshold
- No safety signals were identified

CONCLUSIONS

- GB001 was associated with a longer time to asthma worsening
- Greater treatment effects were observed in patients with high baseline FeNO and/or high baseline Eos
- In addition to being markers of airway inflammation, these biomarkers may be useful predictors for treatment response to GB001
- Given the post-hoc nature of this analysis and the small subgroup sample sizes, further studies are needed to confirm these findings in moderate-to-severe asthma patients treated with standard of care

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DISCLOSURES

KA received consultancy from Teijin Pharma Ltd, expert testimony from Novartis Pharma and Sanofi, and lecture fees from Astellas Pharma, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Kyorin Pharma, MSD, and Novartis Pharma. **MH** is employee of Teijin Pharma Ltd, Tokyo, Japan. **CT**, **GO**, **KD** and **HO** are employed by Gossamer Bio, Inc.

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