# Phase 2 study results of DP2-antagonist GB001 on asthma worsening and other asthma control markers

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## BACKGROUND

- Asthma is a heterogeneous condition characterized by different phenotypes related to specific biomarkers that may predict therapeutic response in selected patient populations.[1] Asthmatic patients with increased Type 2 biomarkers (eosinophils and exhaled nitric oxide [FeNO]) have been reported to have increased PGD2 levels.[2]
- DP2 is a G-protein-coupled receptor selectively expressed by Type 2 T lymphocytes (Th2), eosinophils (Eos), basophils and Type 2 innate lymphoid cells (ILC2s). DP2 binds to PGD2 and promotes recruitment and activation of eosinophils and basophils and stimulates Th2 cells and ILC2 cells to release Type 2 cytokines including IL-4, IL-5 and IL-13, leading to persistence of Type 2 inflammation.[3]
- GB001 is a potent and highly selective oral DP2 antagonist being developed as a once daily oral add-on maintenance treatment for moderate to severe eosinophilic asthma.

## OBJECTIVE

- The objective of this study was to assess the efficacy and safety of GB001, including change in morning peak expiratory flow (AM PEF) as the primary efficacy outcome and the evaluation of other key markers of asthma control.

## METHODS

- This phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japan from May 2015 through April 2016 (submitted for publication).
- During a 4-week run-in period, patients (N = 158) received medium-dose ICS and placebo and were then randomized to treatment once daily with GB001 5 mg, 20 mg, or placebo for 16 weeks or until asthma exacerbation. Patients were tapered and then discontinued from low-dose ICS at randomization and 4 weeks post-randomization, respectively. After completing 16 weeks of dosing (or early discontinuation), there was a 2-week post-treatment washout prior to follow-up examination (**Figure 1**).
- The following composite criteria was used to determine asthma worsening:
  - (1) ≥ 25% decrease of AM PEF for 2 consecutive days compared to the mean value during the last 7 days of Period I
  - (2) ≥ 20% decrease of $FEV_1$ compared to the value at randomization
  - (3) use of inhaled SABA at doses ≥ 5 puffs/day for 2 consecutive days
  - (4) ≥ 0.5 point increase in the Asthma Control Questionnaire (ACQ) score compared to the value at randomization, or
  - (5) asthma exacerbation requiring administration of oral corticosteroids or an unscheduled visit to the clinic
- Assessments included lung function, exacerbations, and symptoms (assessed via a patient asthma diary). The ACQ was also measured throughout the study. Biomarkers included blood eosinophil counts and FeNO (Niox Mino, Aerocrine, Sweden).
- The comparison of treatment groups for the primary and the secondary endpoints was conducted using ANCOVA model with baseline value as a covariate. A log-rank test and Cox proportional hazard model were used for the time to first asthma worsening/exacerbation, and Kaplan-Meier plots were generated.

## RESULTS

**Table 1. Baseline Demographic and Clinical Characteristics**

| | Placebo (n = 53) | GB001 5 mg (n = 52) | GB001 20 mg (n = 53) | Total (N = 158) |
|---|---|---|---|---|
| Age, years (mean ± SD) | 50.2 ± 12.2 | 49.9 ± 12.4 | 48.8 ± 13.3 | 49.7 ± 12.6 |
| Female (n [%]) | 31 (58.5) | 30 (57.7) | 34 (64.2) | 95 (60.1) |
| Race, Asian (n [%]) | 53 (100.0) | 52 (100.0) | 53 (100.0) | 158 (100.0) |
| BMI, kg/m$^2$ (mean ± SD) | 23.2 ± 2.8 | 23.4 ± 2.8 | 23.1 ± 3.2 | 23.2 ± 2.9 |
| Asthma duration, years (mean ± SD) | 24.6 ± 17.3 | 20.6 ± 15.2 | 20.1 ± 14.4 | 21.8 ± 15.7 |
| ED visit within 2 years, Yes (n [%]) | 3 (5.7) | 2 (3.8) | 2 (3.8) | 7 (4.4) |
| Atopic asthma (n [%]) | 47 (88.7) | 41 (78.8) | 41 (77.4) | 129 (81.6) |
| Total IgE, IU/mL, (mean ± SD) | 432 ± 468 | 526 ± 916 | 699 ± 2476 | 553 ± 1545 |
| Blood eosinophils/μL, (mean ± SD) | 350 ± 322 | 266 ± 180 | 341 ± 290) | 319 ± 272 |
| FeNO ppb, (mean ± SD) | 30.57 ± 25.51 | 26.48 ± 21.03 | 27.71 ± 24.20 | 28.28 ± 23.60 |
| ICS, n (%) | 19 (35.8) | 17 (32.7) | 15 (28.3) | 51 (32.3) |
| ICS/LABA, n (%) | 34 (64.2) | 35 (67.3) | 38 (71.7) | 107 (67.7) |
| AM PEF, L/min (mean ± SD) | 346 ± 110 | 343 ± 103 | 344 ± 83 | 345 ± 99 |
| $FEV_1$, L (mean ± SD) | 2.15 ± 0.61 | 2.22 ± 0.62 | 2.19 ± 0.49 | 2.19 ± 0.57 |
| ACQ-5, score (mean ± SD) | 0.55 ± 0.66 | 0.50 ± 0.62 | 0.53 ± 0.63 | 0.53 ± 0.63 |

ACQ5 = Asthma Control Questionnaire (questions 1–5); AM PEF = Morning peak expiratory flow; ED = Emergency department; FeNO = fractional exhaled nitric oxide; $FEV_1$ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting β2 agonist; ppb = parts per billion; SD = standard deviation. Atopic asthma was defined as having tested positive to at least 1 specific IgE antigen

- Baseline characteristics were generally similar across treatment groups (**Table 1**).
- A total of 228 patients were screened and 158 were eligible for enrollment. The study included 4 periods (**Figure 1**). Per protocol, patients who met the asthma worsening or exacerbation endpoint were required to discontinue the study. A total of 28 (52.8%) patients in the placebo group discontinued due to asthma worsening, 17 (32.7%) in the GB001 5 mg group, and 11 (20.8%) in the GB001 20 mg group.
- The differential discontinuation rates directly mirror the differential asthma worsening rates in a dose-response fashion and were a function of a study design that required discontinuation upon asthma worsening.

**Figure 1. Study Design**

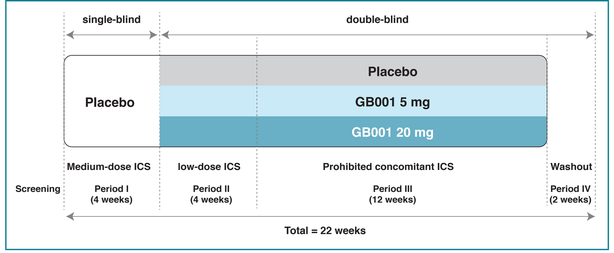
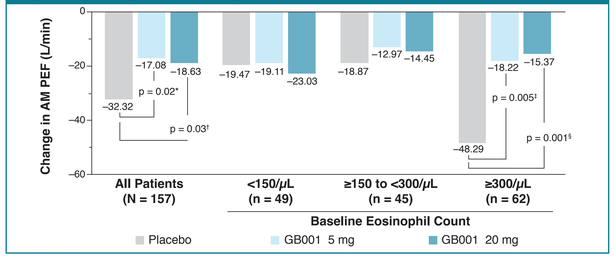



**Figure 2. Change in AM PEF From Baseline to Last Assessment in the Overall Population and by Blood Eosinophil Counts.**

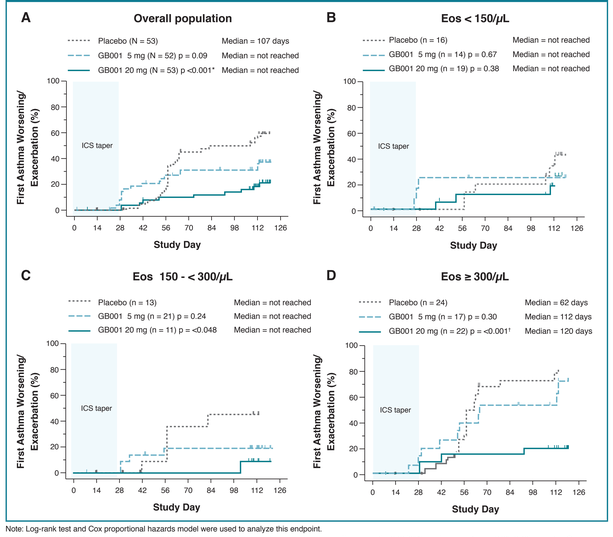



Note: One missing value at the end of the study in the ≥300/μL subgroup.

*The point estimate (95% CI) for the difference was 15.24 (3.05, 27.42); †The point estimate (95% CI) for the difference was 13.69 (1.54, 25.83); ‡The point estimate (95% CI) for the difference was 30.06 (9.78, 50.34); §The point estimate (95% CI) for the difference was 32.92 (13.84, 52.00)

- AM PEF: Difference in AM PEF changes (least squares [LS] mean ± standard error [SE]) from randomization to last assessment in both GB001 treatment groups compared to placebo were observed: –17.1 ± 4.4 L/min (GB001 5 mg) and –18.6 ± 4.3 L/min (GB001 20 mg) vs. –32.3 ± 4.4 L/min in the placebo group (**Figure 2**).

**Figure 3. Time to First Asthma Worsening/Exacerbation in the Overall Population and by Blood Eosinophil Counts (N = 158).**




Note: Log-rank test and Cox proportional hazards model were used to analyze this endpoint.

*Hazard ratio: 0.29 [95% confidence interval: 0.14, 0.58] using the Cox proportional hazard model; †Hazard ratio: 0.16 [95% confidence interval: 0.05, 0.49] using the Cox proportional hazard model.

- Exacerbations: GB001 20 mg group showed (all patients) a statistically significant reduction ($p < 0.001$, hazard ratio: 0.29 [95% CI: 0.14, 0.58]) vs. the placebo group. In a post-hoc analysis by baseline Eos count, the GB001 20 mg group also showed a significant reduction from placebo in the Eos subgroups ≥ 150 to < 300/μL, and ≥ 300/μL ($p = 0.048$ and $p < 0.001$, respectively) (**Figure 3, C & D**).
- ACQ-5: A benefit in asthma control was observed in patients receiving GB001 5 mg and 20 mg, as evidenced by ACQ-5 changes of 0.38 ± 0.85 and 0.19 ± 0.70, respectively, vs placebo (0.80 ±1.33). These observed ACQ-5 changes reflect corresponding differences of –0.41 (95% CI, –0.85, 0.03, p = 0.12) and -0.60 (95% CI, –1.01, –0.19, p = 0.02) vs placebo.
- The increase in FeNO in the active treatment groups was numerically lower than that observed in the placebo group, with a greater effect in the GB001 20 mg group: 8 ppb, 12 ppb and 19 ppb in the 20 mg, 5 mg and placebo groups, respectively.
- Overall, AE were reported in 51%, 50%, and 68% of patients treated with placebo, GB001 5 mg, and GB001 20 mg, respectively, and were classified as primarily mild to moderate in severity.
  - Most common AE were nasopharyngitis: GB001, 23% (both doses) vs. placebo, 11%; pharyngitis: GB001, 8% (both doses) vs. 6%, placebo; and urticaria: GB001 20 mg, 6% vs. placebo, 2%
  - One patient treated with GB001 5 mg discontinued treatment due to hepatic dysfunction, considered unrelated to study drug
- One serious AE of cerebellar hemorrhage was reported in a placebo-treated patient and led to discontinuation.

## CONCLUSIONS

- **GB001 was well tolerated and associated with less worsening of lung function, longer time to asthma worsening/exacerbation, and better asthma control as compared to placebo.**
- **Greater treatment effects were observed in patients with high baseline blood eosinophils. Blood eosinophils, in addition to being a marker of airway inflammation, may be a useful marker for treatment response to GB001.**
- **Further studies are needed to confirm these findings in moderate-severe asthma patients treated with standard of care.**

## REFERENCES

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