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A Phase 2a Study of DP₂-antagonist GB001 for Asthma

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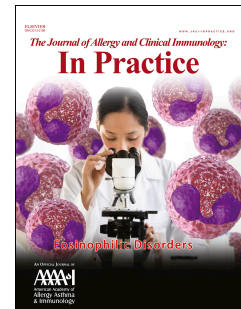
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Title: A Phase 2a Study of DP₂-antagonist GB001 for Asthma

Short Title: Effect of DP₂ antagonist GB001 on Asthma

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Abstract

Background

GB001, a DP₂ antagonist, may inhibit recruitment and activation of inflammatory cells in patients with asthma, consequently reducing airway inflammation.

Objective

Explore the efficacy and safety of GB001 in adults with mild-moderate asthma.

Methods

During a 4-week run-in period, adult asthma 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 worsening/exacerbation. Patients were tapered to and then discontinued from low-dose ICS at randomization and 4 weeks post-randomization, respectively. Primary endpoint was change in morning peak expiratory flow (AM PEF); secondary endpoints included measures of asthma control. Safety was also assessed.

Results

Baseline characteristics were similar among GB001 5 mg, 20 mg and placebo groups. Changes in AM PEF in 5 mg and 20 mg groups versus placebo showed mean differences (95% CI) of 15.2 (3.1, 27.4) L/min, $p=0.02$ and 13.7 (1.5, 25.8) L/min, $p=0.03$, respectively. The changes in FEV₁ of 55 ml and 32 ml, respectively were not significant. There was a significant difference between GB001 20mg and placebo for the secondary endpoints of time to asthma worsening/exacerbation (hazard ratio 0.29), ACQ-5 (-0.60 points), the percent of days without asthma symptoms (26%) and the percent of rescue-free days (22%). Patients with baseline eosinophils $\geq 300/\mu\text{L}$ had larger differences between GB001 20mg and placebo for changes in AM PEF. Similar effects were seen in a post-hoc analysis for time to worsening/exacerbations

and ACQ-5. The most common non-serious adverse event in the GB001 groups compared to the placebo group was nasopharyngitis.

Conclusion

GB001 was well tolerated and while not associated with clinically meaningful changes in lung function, improvements in asthma worsening/exacerbations and markers of asthma control were demonstrated. In addition, greater treatment effects were observed in patients with high baseline blood eosinophils. Further studies are needed to confirm these findings in the context of standard of care treatment.

Highlights

1) What is already known about this topic?

Lung function in patients treated with DP₂ antagonists generally has resulted in modest improvements and large variability.

2) What does this article add to our knowledge?

This is the first study with a DP₂ antagonist demonstrating clinical efficacy in asthma worsening and exacerbations in patients with asthma and enhanced response in patients with Type 2 inflammation.

3) How does this study impact current management guidelines?

This study provides proof-of-concept demonstrating the effectiveness of a DP₂ antagonist.

A Phase 2b trial with GB001 is ongoing and may provide further evidence of the role of DP₂ inhibition in reducing asthma worsening/exacerbations.

84

85 **Key Words**86 DP₂ antagonist, asthma, eosinophilic asthma, peak expiratory flow, Type 2 inflammation.

87

88 **List of Abbreviations**

89 ACQ, Asthma Control Questionnaire; AE, adverse event; ALT, alanine aminotransferase;

90 AM PEF, morning peak expiratory flow; ANCOVA, analysis of covariance; AST, aspartate

91 aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease;

92 CRTh2, chemoattractant receptor-homologous molecule expressed on Th2 cells; DP₂,93 prostaglandin D₂ receptor; FAS, full analysis set; FeNO, fractional exhaled nitric oxide; FEV₁,

94 forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid;

95 ILC2, group 2 innate lymphoid cells; K-M, Kaplan-Meier; LABA, long-acting β_2 -agonist; LS,96 least-squares; PGD₂, prostaglandin D₂; PM PEF, evening peak expiratory flow; SABA,97 short-acting β_2 -agonist; SE, standard error; SD, standard deviation; Th2, Type 2 T helper.

Introduction

The prostaglandin D₂ receptor (DP₂, also known as CRTh2), is expressed on a variety of cells implicated in the allergic process, including Type 2 T helper (Th2)-lymphocytes, eosinophils, basophils, and ILC2 (group 2 innate lymphoid cells)¹. The endogenous agonist, prostaglandin D₂ (PGD₂), is mainly elevated in patients with moderate and severe asthma^{2,3}. PGD₂ induces cell mobility, degranulation, and cytokine release of human Th2 cells, ILC2, eosinophils, and basophils⁴⁻⁶. Thus, DP₂ antagonists such as PTR-36 (Teijin Pharma Ltd, Japan) currently known as GB001 (Gossamer Bio, San Diego, USA) outside Japan may inhibit recruitment and activation of inflammatory cells in patients with asthma, with consequent reduction in airway inflammation.

Previous studies with various DP₂ antagonists have resulted in modest improvements in lung function and large variability⁷. A study evaluating the DP₂ antagonist fevipiprant in moderate to severe eosinophilic asthma using sputum eosinophil percentage as the primary endpoint, demonstrated a significant reduction in sputum eosinophils compared with placebo⁸, suggesting a role of the DP₂-PGD₂ axis in patients with Type 2 phenotype.

A phase 2 study with dupilumab⁹ (anti-IL-4R α monoclonal antibody) provided the basis for the current study design. In the dupilumab study, patients were instructed to discontinue use of the long-acting β_2 -agonist (LABA) and then taper and discontinue the use of inhaled corticosteroids (ICS). This approach allowed for observation of the effects of study treatment in combination with these agents and as monotherapy. This design led to the selection of endpoints of asthma exacerbations or worsening of asthma, and subsequently demonstrated a statistically significant

121 reduction in asthma exacerbations⁹. This model of background treatment taper and withdrawal
122 was used in the current study to assess a change in morning peak expiratory flow (AM PEF) as
123 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 at 27 centers in Japan from May 2015 through April 2016. This phase 2 study included 2 active doses of GB001 (5 and 20 mg) and placebo. The protocol was developed by Teijin Pharma Ltd. Japan and approved by appropriate ethics and regulatory agencies and conducted in accordance with the Japan Pharmaceutical and Medical Device Act, the Ministerial Ordinance on Good Clinical Practice for Drugs, and the Declaration of Helsinki. Each patient received detailed written and verbal information about the study and possible risks associated with participation. Written informed consent was obtained before any screening procedures were performed. The study was registered on JapicCTI (JapicCTI-152857).

Patients

Adult patients with a confirmed diagnosis of asthma based on the Japan Asthma Prevention and Management Guideline (JGL) 2012¹⁰ and demonstrated airway reversibility or enhanced airway hyperresponsiveness were enrolled to evaluate the efficacy and safety of once-daily oral administration of GB001 5 mg and 20 mg. Participants included male or female 20 to 75 years of age, with a body mass index (BMI) $<30 \text{ mg/kg}^2$ who had been receiving medium-dose ICS alone or LABA/ICS combination for ≥ 4 weeks preceding study start. Eligible patients were switched to ICS medium-dose monotherapy for 4 weeks. Afterwards, only those with a forced expiratory volume in 1 second (FEV_1) between 60-90% and not requiring use of any inhaled short-acting β_2 -agonist (SABA) at doses ≥ 5 puffs/day for ≥ 2 consecutive days were eligible to continue in the study.

Patients were excluded if they had abnormal liver function or positive hepatitis B or C serology; a diagnosis of COPD, eosinophilic granulomatosis with polyangiitis, eosinophilic pneumonia, idiopathic hyper-eosinophilic syndrome, allergic bronchopulmonary mycosis, or other disorders that affect respiratory function; an acute respiratory infection or asthma exacerbation requiring treatment with antibacterial agents, oral/intravenous steroids, an unscheduled visit to a clinic, or modification to asthma treatment within the prior 8 weeks of randomization. Patients with smoking history of a >10 pack-year or smoking within the prior 6 months also were excluded.

Treatments

The study schematic is shown in Figure 1A. Patients meeting the provisional eligibility criteria underwent assessment before receiving 4 weeks (Period I) of medium-dose ICS and matching placebo for the study drug. Patients who met all eligibility criteria were randomized (1:1:1) and concomitantly received 1 of 3 treatments (GB001 5 mg, GB001 20 mg or placebo) once-daily. During the subsequent 4 weeks (Period II) the ICS was dose tapered (reduced to low dose). Afterwards, during the final 12 weeks of dosing (Period III) ICS was discontinued and patients received only the double-blind study drug.

A composite criteria 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) $\geq 25\%$ decrease of AM PEF for 2 consecutive days compared to the mean value during the last 7 days of Period I, (2) $\geq 20\%$ decrease of FEV₁ compared to the value at randomization, (3) use of inhaled SABA at doses ≥ 5 puffs/day for 2 consecutive days, (4) a ≥ 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. After completing 16 weeks of dosing (or early discontinuation), there was a 2-week post-treatment washout (Period IV) prior to the follow-up examination.

Efficacy and Safety assessments

During the double-blind treatment period, evaluation of lung function, exacerbation, and symptoms were assessed via a patient asthma diary that included daily AM PEF, asthma symptoms, SABA use, and spirometry tests (FEV₁ and forced vital capacity [FVC] after 0, 4, 8, and 16 weeks of double-blind dosing, and early discontinuation). The ACQ was measured after 0, 4, 8, and 16 weeks of double-blind dosing, and early discontinuation (if applicable).

Biomarkers including IgE, blood eosinophil counts and fractional exhaled nitric oxide (FeNO using Niox Mino, Aerocrine, Sweden) were measured.

The primary endpoint was change from randomization in AM PEF to last assessment (i.e., after 16 weeks of double-blind dosing or the date of early discontinuation). The average AM PEF measurements for the 7 days before randomization and the average AM PEF of the last 7 days of the treatment period were used for the analysis. A minimal clinically important difference (MCID) in PEF has not been fully established, but in asthma clinical trials a change in AM PEF between 19 and 25 L/min from baseline is considered clinically significant^{11,12}. Secondary efficacy outcomes included evening (PM) PEF, FEV₁, FVC, time to the first asthma worsening/exacerbation, proportion of patients with asthma worsening/exacerbation, ACQ, daily symptoms, proportion of days without SABA use, proportion of days without asthma symptoms.

Safety assessments included ECG, and laboratory analysis. Adverse events (AEs) were recorded beginning in Period I.

Statistical analyses

For the primary endpoint, a sample size of 50 patients in each group had a 69% or 87% power to detect a difference in means of 20 L/min or 25 L/min, respectively (assuming a standard deviation [SD] of 40 L/min using a two-sample t-test with a 5% two-sided significance level).

The full analysis set (FAS), used for primary evaluation of all endpoints, encompassed all patients who received ≥ 1 dose of study treatment and had efficacy data available. The safety analysis set included all patients who received ≥ 1 dose of randomized study treatment and had a safety evaluation.

The AM PEF change from randomization to last assessment was compared between treatment groups using analysis of covariance (ANCOVA) with treatment group as a factor and % baseline AM PEF as a covariate. The comparison of the treatment groups for each of the secondary spirometry efficacy endpoints was also conducted using ANCOVA model with treatment group as a factor and 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. All other secondary efficacy endpoints and safety endpoints were summarized by descriptive statistics. The subgroups were defined by baseline blood eosinophil counts. The subgroup analyses for the secondary endpoints were exploratory and hypothesis-generating and conducted post-hoc with Wilcoxon rank sum tests or log-rank test to compare between treatment groups. All statistical tests employed a 2-sided significance level of 5%, with no adjustments for

216 multiplicity. All analyses were performed using SAS version 9.3. GraphPad Prism version 7.05
217 for Windows was used for graphical illustrations.

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Results

Patient disposition, demographics, and baseline characteristics

Of the 228 patients who provided informed consent, 224 satisfied the provisional enrollment criteria and received medium-dose ICS and matched placebo study drug in Period I (Figure 1 B); 158 of those were randomized to double-blind treatment (placebo n = 53, GB001 5 mg n = 52, GB001 20 mg n = 53). Demographic and baseline characteristics (Table 1) were generally similar across the treatment groups.

Change in morning peak expiratory flow (AM PEF)

AM PEF change was the primary endpoint. There was a statistically significant difference in AM PEF change (least-squares [LS] mean $\pm$ standard error [SE]) from randomization to last assessment (Figure 2) in both GB001 groups compared to placebo: -17.1 $\pm$ 4.4 L/min (GB001 5 mg group, point estimate [95% CI] for the difference 15.2 [3.1, 27.4], p = 0.02) and -18.6 $\pm$ 4.3 L/min (GB001 20 mg group, point estimate [95% CI] for the difference 13.7 [1.5, 25.8], p = 0.03) compared to -32.3 $\pm$ 4.4 L/min in the placebo group.

An analysis by baseline blood eosinophil count subgroups (Figure 2) demonstrated a statistically significant difference (mean $\pm$ SD) in AM PEF in patients with baseline eosinophils $\geq$ 300/ μ L for both GB001 groups versus placebo: -18.2 $\pm$ 28.5 L/min (GB001 5 mg group, p = 0.005) and -15.4 $\pm$ 30.1 L/min (GB001 20 mg group, p = 0.001) compared to -48.3 $\pm$ 33.2 L/min in the placebo group. The difference in AM PEF was not significant in the subgroups with baseline eosinophils <150/ μ L, or $\geq$ 150 to <300/ μ L.

Time to first asthma worsening/exacerbation

In the time to first asthma worsening/exacerbation (Figure 3), the GB001 20 mg group showed a statistically significant increase (hazard ratio: 0.29 [95% CI: 0.14, 0.58], $p < 0.001$.) versus the placebo group or 60% relative reduction. The proportion of patients with asthma worsening/exacerbations was 53% in the placebo group, and 33% and 21% in the GB001 5 and 20 mg, respectively. In a post-hoc analysis by baseline eosinophil count, the GB001 20 mg group also showed a significant increase from placebo group in eosinophil subgroups ≥ 150 to $< 300/\mu\text{L}$, and $\geq 300/\mu\text{L}$ ($p = 0.048$ and $p < 0.001$, respectively). Furthermore, time to asthma worsening/exacerbation for patients in the placebo group with baseline eosinophil counts $\geq 300/\mu\text{L}$ occurred earlier than those in the other eosinophil count subgroups (Figure 3).

Spirometry

The changes from baseline to the last assessment for FEV₁ of the GB001 groups (5 and 20 mg) were not statistically significant (0.055 [95% CI, -0.065, 0.175], $p = 0.370$ and 0.032 [95% CI, -0.086, 0.150], $p = 0.594$, respectively; Table 2). In the eosinophil $\geq 300/\mu\text{L}$ subgroup, there was a statistically significant difference between GB001 20 mg and placebo (0.152 [95% CI, -0.032, 0.336], $p = 0.02$) but the improvement (0.013 ± 0.216 L) was not clinically relevant.

Markers of Asthma Control

At baseline most patients were well controlled. Mean ($\pm$ SD) baseline ACQ-5 was 0.55 ± 0.66 , 0.50 ± 0.62 , and 0.53 ± 0.63 points for the placebo, GB001 5 mg, and GB001 20 mg groups, respectively. ACQ-5 changed by 0.80 ± 1.33 from baseline in the placebo group; in contrast the GB001 5 mg group changed by 0.38 ± 0.85 ; a -0.41 difference from placebo (95%CI, -0.85, 0.03,

p = 0.116) and the 20 mg group changed by 0.19 ± 0.70 ; a -0.60 difference from placebo (95% CI, -1.01, -0.19, p = 0.019) (Table 2 and Figure 4).

The changes in percentage of days without asthma symptoms (mean $\pm$ SD) were significantly different in both the GB001 5 mg and 20 mg groups compared to placebo: $-8.8 \pm 25.1\%$ (GB001 5 mg group, p = 0.003) and $-6.2 \pm 32.0\%$ (GB001 20 mg group, p < 0.001) versus $-31.8 \pm 43.8\%$ in the placebo group (Table 2). The changes in percentage of days without asthma symptoms by blood eosinophil thresholds were also evaluated in a post-hoc analysis, demonstrating consistent benefits in low and high eosinophil subgroups in the GB001 20 mg group (Table E1, supplemental material) In addition, there was a significant increase in the change in percentage of SABA free days (mean $\pm$ SD) with the GB001 20 mg treatment group compared to placebo: $-4.1 \pm 21.7\%$ versus $-26.4 \pm 37.0\%$, respectively (p < 0.001), (Table 2).

Asthma biomarkers

Mean blood eosinophil counts increased following ICS withdrawal from baseline to the last assessment for all treatment groups (GB001 5 mg (41.3%), 20 mg (18.7%), and placebo (33.1%) (Supplemental material, Table E1). Similarly, median FeNO increased from baseline to the last assessment for all treatment groups (GB001 5 mg (12.0 ppb), 20 mg (8.3 ppb), and placebo (19.0 ppb); Table E2, supplemental material). FeNO increases in the placebo group were larger than the GB001 treatment groups. In a post-hoc analysis baseline IgE and blood eosinophils had no impact on the primary endpoint (unadjusted and adjusted analyses) across treatment groups.

Safety

Adverse events (AEs) were reported by half of all patients who received placebo or GB001 5 mg, and by 67.9% of those receiving GB001 20 mg, and were generally mild or moderate in severity (Table 3). A single serious adverse event of cerebellar hemorrhage occurred in a patient receiving placebo. Two patients discontinued study drug due to an AE: the patient with the cerebellar hemorrhage, and one patient in the GB001 5 mg group with hepatic function disorder (assessed by the investigator as unrelated to study drug and attributed to excessive alcohol consumption and intake of a high-fat diet). No deaths occurred. Among the most common AEs (occurring in $\geq 5\%$ of patients in any treatment group), nasopharyngitis occurred twice as frequently in both GB001 treatment groups than in the placebo group, with no causal relationship to study drug for any of the events. There were no noteworthy differences between treatment groups for ECG, laboratory values and vital signs.

Discussion

GB001 treatment (5 and 20 mg) resulted in a statistically significant difference in AM PEF change versus placebo in the 16-week treatment period with less worsening of their lung function in patients receiving GB001. These changes were accompanied with improvements in asthma worsening/exacerbations, asthma control, and reduced rescue medication use.

Most adult patients with asthma are treated with medium-dose ICS for control of asthma symptoms, with discontinuation of ICS therapy often resulting in uncontrolled disease. To evaluate the efficacy of the DP₂ antagonist GB001, a treatment withdrawal design was implemented by gradually tapering ICS treatment. This approach of tapering and subsequent withdrawal of background treatment enable the assessment of the endpoints of asthma exacerbations or asthma worsening, similar to a previous study with dupilumab reported by Wenzel et al.⁹ Although the current study design is similar to the dupilumab trial, a key difference is the study population. The current study enrolled patients with mild to moderate asthma, whereas the dupilumab study enrolled patients with moderate to severe asthma. The difference between dupilumab versus placebo in AM PEF was 34.6 L/min, whereas in the current study the difference with GB001 20 mg was 13.7 L/min. The GB001 treatment changes reflect a protection from worsening of lung function, while dupilumab provided clear improvements on this endpoint. In contrast, the percent of asthma exacerbations with dupilumab was 6% versus 44% in the placebo group, corresponding to an 87% reduction with dupilumab. In the current study, the reduction in asthma worsening/exacerbations with GB001 20 mg versus placebo was 60%. In addition, the difference between dupilumab versus placebo in ACQ-5 was -

0.73 points, whereas GB001 20 mg versus placebo was -0.60 points. These similarities and differences in outcomes might be related to study population and the unique mechanism of action of these therapies.

Daily PEF measurement offers the ability to capture fluctuations in lung function, including periods during and after an exacerbation. In contrast, FEV₁ measured at the clinic (e.g., every 4 weeks in clinical trials) provides only a cross-sectional view of the patient's status at the time of the visit, which could be influenced by an ongoing exacerbation or increased uncontrolled asthma^{13,14}, particularly in this type of study design where treatment was removed. Notably, in this study PEF changes with GB001 were statistically significant different from placebo, but generally the changes did not translate in PEF improvement but rather in less worsening. These changes were less than a change considered as clinically significant (between 19 and 25 L/min) in asthma trials^{11,12}.

In the analysis by baseline eosinophil counts, patients with eosinophil counts $\geq 300/\mu\text{L}$ showed a significant increase in time to asthma worsening/exacerbation compared to placebo. Previous studies have reported a relationship between blood or sputum eosinophil counts and asthma-related outcomes¹⁵⁻¹⁷. In the current study, the percent of patients who experienced asthma worsening/exacerbation with 5 mg, 20 mg of GB001 and placebo was 32.7%, 20.8% and 52.8%, respectively (Figure 1B). These findings suggest that GB001 may prevent asthma worsening/exacerbations. Placebo-treated patients with baseline counts $\geq 300/\mu\text{L}$, resulted in 70.8% discontinuation due to asthma worsening/exacerbation, resulting in a median time to asthma exacerbation of 62 days (approximately 50% earlier than the 112 or 120 days in patients

344 treated with GB001 5 mg or 20 mg, respectively). Greater treatment effects were observed in
345 patients with high baseline blood eosinophils, consistent with observations from previous
346 studies^{1,18-20}. The findings from the post-hoc analysis, however, should be interpreted with
347 caution considering the small sample size (n = 63 [40%]) with eosinophil counts $\geq 300/\mu\text{L}$,
348 relative to the overall study population. Notably, several of the secondary endpoints displayed
349 the same pattern, further supporting the observation that the treatment effect is driven by those
350 with Type 2 inflammatory phenotype mainly characterized by elevated baseline eosinophil
351 counts.

352
353 While previous studies have used eosinophil counts as biomarkers for the evaluation of Type 2
354 antagonists²¹, a dose-dependent treatment effect was not seen in the blood eosinophil counts in
355 this study, consistent with previous results using dupilumab⁹. This may have been related to the
356 imbalance among treatment groups at baseline in mean eosinophil counts (i.e., the GB001 5 mg
357 group was lower than either the GB001 20 mg or placebo groups).

358
359 As expected with a study design that includes ICS withdrawal, increases in FeNO values were
360 observed ($\geq 40\%$ in FeNO) and consistent with a shift from well to poorly controlled asthma^{22,23}.
361 The increase in FeNO in the active treatment groups was numerically lower than that observed in
362 the placebo group, with a greater effect in the GB001 20 mg (8 ppb, 12 ppb, and 19 ppb in the
363 GB001 20 mg, 5 mg, and placebo, respectively) (Table E1). Based on ATS guidelines a change
364 greater than 10 ppb indicate a relevant increase in airway inflammation²³. In the current study
365 the GB001 20 mg dose prevented an increase greater than 10 ppb. This observation may be
366 important for understanding the mechanisms of action of DP₂ antagonists in the context of Type

2 inflammation. In a recent study by Ortega and colleagues²⁴, GB001 demonstrated a modest reduction relative to placebo in FeNO (-4.47 ppb [95% CI: -13.70, 4.77]) in the overall population. However, larger reductions were seen in patients stratified by high FeNO at baseline (defined as ≥ 35 ppb), with a reduction of 13.42 ppb (95% CI: -29.55, 2.72) compared to the low FeNO (<35 ppb) subgroup, 1.26 ppb (95% CI: -9.08, 6.56). These changes were also associated with improvements in FEV₁²⁴. These changes in FeNO are consistent with the changes observed with dupilumab.⁹

As demonstrated in the fevipiprant study, this class of drugs suppresses the recruitment of eosinophils into the airways⁸ with reduction of sputum eosinophils (3.5-fold), improvement in quality of life, and improvement in post bronchodilator FEV₁ compared with placebo. These findings support the role of DP₂ antagonists in reducing airway inflammation. It is likely that the activity on eosinophil recruitment could be mediated by the interruption of PGD₂-dependent eosinophil chemotaxis, in concert with suppression of Th2 cytokine release from Th2/ILC2.

In another study with the DP₂ antagonist AZD1981, responders for FEV₁ and ACQ endpoints occurred in the atopic asthma cohort²⁵. In the current study, 81.6% of patients had atopic asthma (i.e., tested positive to at least 1 specific IgE antigen). While atopic status might be important, it is unlikely to be responsible for the treatment effect and has likewise not been predictive of efficacy in several other studies of agents targeting the Type 2 phenotype²⁶.

In this study of 16 weeks of treatment in patients with mild-to-moderate asthma, GB001 was well tolerated and associated with less worsening of lung function, longer time to asthma

worsening/exacerbation, less rescue inhaler use, more asymptomatic days, and fewer asthma symptoms. Most of the adverse events were of mild or moderate severity. The most common adverse event in the GB001 groups was nasopharyngitis. When data was analyzed by baseline blood eosinophil counts, in those patients with baseline blood eosinophil counts $\geq 300/\mu\text{L}$ greater treatment effects were observed. Additional studies, including an ongoing Phase 2b study with GB001 in moderate-to-severe eosinophilic asthma (NCT03683576, clinicaltrials.gov), are needed to confirm these results, and to further elucidate the specific target population that could benefit from DP₂ antagonism.

398 **Declaration of interest**

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Figure legends**Figure 1.** A. Study schema; B. Patient disposition

*did not meet the criteria for early termination or physician decision

Figure 2. Change in morning peak expiratory flow (L/min) in all patients and by baseline eosinophil count.

*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)

Figure 3. Time to first asthma worsening/exacerbation in A. the overall population and by blood eosinophil count: B. <150 μ L, C. 150 to <300/ μ L, and D. $\geq$ 300/ μ L. NR, not reached.

*Hazard ratio 0.29 (95% CI 0.14, 0.58) and [†]Hazard ratio 0.163 (95% CI 0.05, 0.49), using the Cox proportional hazard model

Figure 4. Change in mean Asthma Control Questionnaire-5 (ACQ-5) score in all patients and by baseline eosinophil count.

*The point estimate (95% CI) for the difference was -0.604 (-1.013, -0.194); [†]the point estimate (95% CI) for the difference was -0.880 (-1.622, -0.139)

Table 1. Demographic and Other Baseline Characteristics

	Placebo (N = 53)	GB001 5 mg (N = 52)	GB001 20 mg (N = 53)	Total (N = 158)
Age, years (mean $\pm$ SD)	50.2 $\pm$ 12.2	49.9 $\pm$ 12.4	48.8 $\pm$ 13.3	49.7 $\pm$ 12.6
Sex, 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 $\pm$ SD)	23.2 $\pm$ 2.8	23.4 $\pm$ 2.8	23.1 $\pm$ 3.2	23.2 $\pm$ 2.9
Duration of Bronchial Asthma, years (mean $\pm$ SD)	24.6 $\pm$ 17.3	20.6 $\pm$ 15.2	20.1 $\pm$ 14.4	21.8 $\pm$ 15.7
Emergency Department Visit within 2 years (n [%])	3 (5.7)	2 (3.8)	2 (3.8)	7 (4.4)
Prior Medication (n [%])				
ICS	19 (35.8)	17 (32.7)	15 (28.3)	51 (32.3)
ICS/LABA	34 (64.2)	35 (67.3)	38 (71.7)	107 (67.7)
AM PEF at Randomization, L/min				
Mean $\pm$ SD	346 $\pm$ 110	343 $\pm$ 103	344 $\pm$ 83	345 $\pm$ 99
<80% predicted (n [%])	39 (73.6)	39 (75.0)	39 (73.6)	117 (74.1)
FEV ₁ , L				
Mean $\pm$ SD	2.15 $\pm$ 0.61	2.22 $\pm$ 0.62	2.19 $\pm$ 0.49	2.19 $\pm$ 0.57
<80% predicted (n [%])	31 (58.5)	30 (57.7)	25 (47.2)	86 (54.4)
Atopic asthma (n [%])	47 (88.7)	41 (78.8)	41 (77.4)	129 (81.6)
ACQ5, score (mean $\pm$ SD)	0.55 $\pm$ 0.66	0.50 $\pm$ 0.62	0.53 $\pm$ 0.63	0.53 $\pm$ 0.63

Table 2. Change from Baseline in Primary and Secondary Endpoints

	Placebo (N = 53)	GB001 5 mg (N = 52)	GB001 20 mg (N = 53)
Primary Endpoint: Change in AM PEF^{*1}			
Change in LS mean (SE) from baseline	-32.32 (4.36)	-17.08 (4.37)	-18.63 (4.33)
Difference of treatment groups (95% CI)		15.24 (3.05, 27.42)	13.69 (1.54, 25.83)
p-value (GB001 vs placebo)		0.015	0.027
Secondary Endpoints: Asthma worsening/exacerbations^{*2}			
Proportion with asthma worsening	53%	33%	21%
HR (95%CI)		0.59 (0.32, 1.07)	0.29 (0.14, 0.58)
p-value (GB001 vs placebo)		0.088	<0.001
Change in Pre-bronchodilator FEV₁^{*3}			
Change in LS mean (SE) from baseline	-0.060 (0.043)	-0.005 (0.043)	-0.028 (0.042)
Difference of treatment groups (95% CI)		0.055 (-0.065, 0.175)	0.032(-0.086, 0.150)
p-value (GB001 vs placebo)		0.370	0.594
Change in ACQ-5^{*4}			
Change in mean (SD) from baseline	0.80 (1.33)	0.38 (0.85)	0.19 (0.70)
Difference of treatment groups (95% CI)		-0.41 (-0.85, 0.03)	-0.60 (-1.01, -0.19)
p-value (GB001 vs placebo)		0.116	0.019
Change in percentage of days without asthma symptoms^{*4}			
Change in mean (SD) from baseline	-31.8 (43.8)	-8.8 (25.1)	-6.2 (32.0)
Difference of treatment groups (95% CI)		23.0 (9.0, 36.9)	25.6 (10.8, 40.4)
p-value (GB001 vs placebo)		0.003	<0.001
Change in percentage of SABA free days^{*4}			
Change in mean (SD) from baseline	-26.4 (37.0)	-13.7 (29.0)	-4.1 (21.7)
Difference of treatment groups (95% CI)		12.7 (-0.20, 25.6)	22.3 (10.6, 34.0)
p-value (GB001 vs placebo)		0.044	<0.001

Abbreviations: LS mean = least square mean; HR= hazard ratio; CI = confidence interval; SABA = short-acting β_2 -agonist; SE = standard error; SD = standard deviation.

Note: *1: ANCOVA with treatment group as a factor and % baseline AM PEF as a covariate. *2: HR are based on Cox proportional hazard model with treatment group as a factor. P value are based on Log-rank test. *3: ANCOVA model with treatment group as a factor and baseline value as a covariate. *4: 95% CIs are based on two-sample T-test. p-values are based on Wilcoxon rank sum test (post-hoc analyses).

Table 3. Adverse Events

	Placebo (N = 53)	GB001 5 mg (N = 52)	GB001 20 mg (N = 53)
Any adverse event	27 (50.9)	26 (50.0)	36 (67.9)
Any serious adverse event	1 (1.9)	0	0
Study drug withdrawal due to adverse event	1 (1.9)	1 (1.9)	0
Severity of adverse event			
Mild	5 (9.4)	3 (5.8)	7 (13.2)
Moderate	21 (39.6)	22 (42.3)	29 (54.7)
Severe	1 (1.9)	1 (1.9)	0
Most common adverse events *			
Nasopharyngitis	6 (11.3)	12 (23.1)	12 (22.6)
Pharyngitis	3 (5.7)	4 (7.7)	4 (7.5)
Urticaria	1 (1.9)	0	3 (5.7)
Bronchitis	3 (5.7)	3 (5.8)	2 (3.8)
Upper respiratory tract inflammation	1 (1.9)	3 (5.8)	1 (1.9)

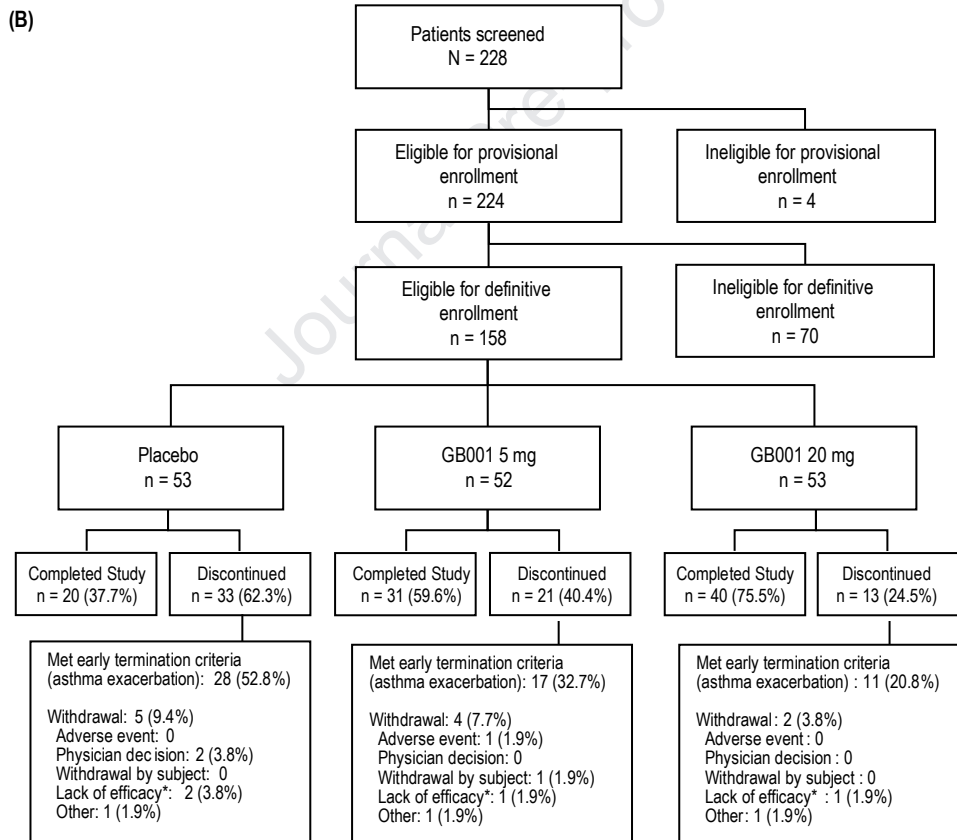
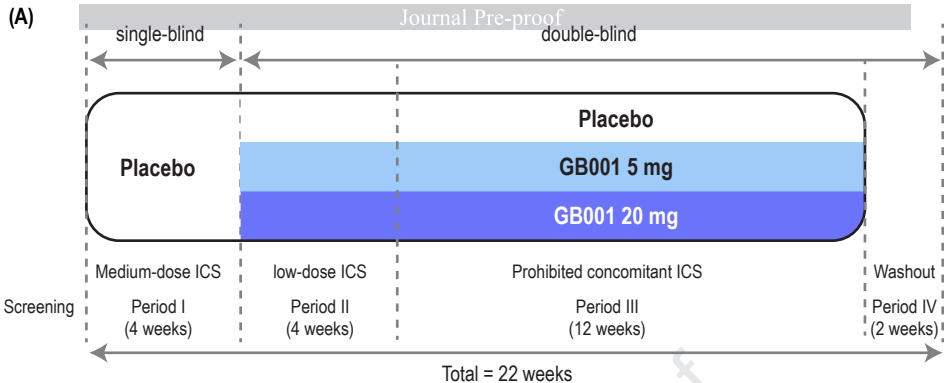
Table E-1. Change from Baseline in Asthma Symptoms in the Overall Population and by Blood Eosinophil Thresholds

	Placebo (N = 53)	GB001 5 mg (N = 52)	GB001 20 mg (N = 53)
Change in percentage of days without asthma symptoms – All Patients			
Mean $\pm$ SD at last assessment	50.7 $\pm$ 43.6	72.5 $\pm$ 38.3	73.9 $\pm$ 38.1
Change in Mean $\pm$ SD from baseline	-31.8 $\pm$ 43.8	-8.8 $\pm$ 25.1	-6.2 $\pm$ 32.0
Difference of treatment groups (95% CI)		23.0 (9.0, 37.0)	25.6 (10.8, 40.4)
p-value (GB001 vs placebo)		0.003	0.001
Change in percentage of days without asthma symptoms – baseline EOS <150/ μ L			
N	16	14	19
Mean $\pm$ SD at last assessment	63.4 $\pm$ 43.3	70.4 $\pm$ 44.3	75.9 $\pm$ 36.3
Change in Mean $\pm$ SD from baseline	-23.2 $\pm$ 36.1	-13.8 $\pm$ 26.1	3.0 $\pm$ 39.2
Difference of treatment groups (95% CI)		9.4 (-14.4, 33.3)	26.2 (0.1, 52.3)
p-value (GB001 vs placebo)		0.51	0.03
Change in percentage of days without asthma symptoms – baseline EOS $\geq$ 150 to <300/ μ L			
N	13	20	11
Mean $\pm$ SD at last assessment	67.0 $\pm$ 44.9	87.8 $\pm$ 15.8	83.1 $\pm$ 31.2
Change in Mean $\pm$ SD from baseline	-25.3 $\pm$ 40.9	-1.4 $\pm$ 21.7	-1.3 $\pm$ 17.4
Difference of treatment groups (95% CI)		23.9 (1.6, 46.1)	24.0 (-3.6, 51.5)
p-value (GB001 vs placebo)		0.18	0.10
Change in percentage of days without asthma symptoms – baseline EOS $\geq$ 300/ μ L			
N	24	17	22
Mean $\pm$ SD at last assessment	33.3 $\pm$ 38.1	55.5 $\pm$ 46.3	66.9 $\pm$ 43.5
Change in Mean $\pm$ SD from baseline	-41.1 $\pm$ 49.5	-13.5 $\pm$ 27.4	-16.2 $\pm$ 29.7
Difference of treatment groups (95% CI)		27.6 (0.8, 54.5)	24.8 (0.3, 49.4)
p-value (GB001 vs placebo)		0.02	0.02

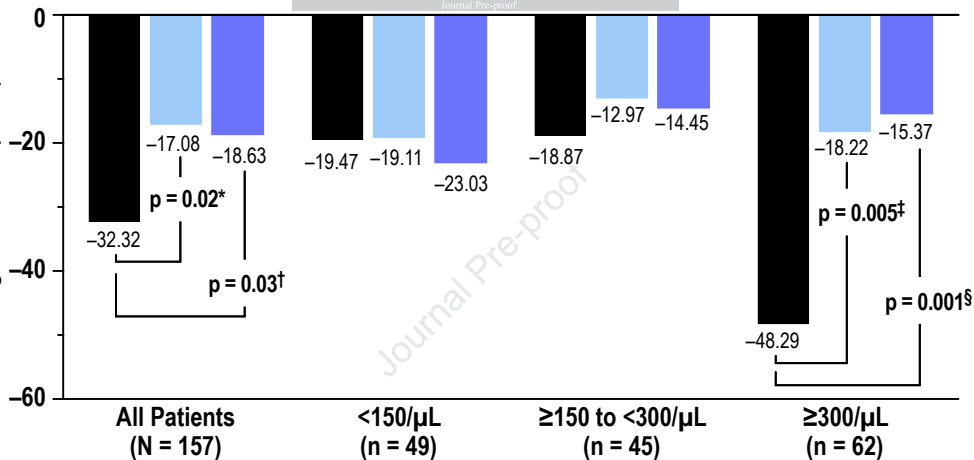
Abbreviations: CI = confidence interval; EOS = eosinophils; SABA = short-acting β 2-agonist; SD = standard deviation.
 Note: 95% CIs are based on two-sample T-test. p-values are based on Wilcoxon rank sum test (post-hoc analysis).

Table E2 –Change in Biomarkers from Baseline to Last Assessment

	Placebo (N = 53)	GB001 5 mg (N = 52)	GB001 20 mg (N = 53)
Eosinophils, cells/μL			
Mean $\pm$ SD at baseline	350 $\pm$ 322	266 $\pm$ 180	341 $\pm$ 290
Mean $\pm$ SD at last assessment	466 $\pm$ 402	376 $\pm$ 361	414 $\pm$ 362
Mean change $\pm$ SD from baseline	116 $\pm$ 291	110 $\pm$ 231	65 $\pm$ 236
Percent Mean change from baseline	33.1	41.3	18.7
Total IgE, IU/mL			
Median (IQR) at baseline	310 (98, 550)	155 (72, 435)	180 (100, 450)
Median (IQR) at last assessment	300 (105, 610)	155 (70, 420)	160 (97, 450)
Median change (IQR) from baseline	0 (-30, 35)	0 (-21, 20)	0 (-20, 17)
Fractional Exhaled Nitric Oxide (FeNO), ppb			
Median (IQR) at baseline	20.3 (13.5, 37.8)	21.8 (14.5, 31.0)	20.0 (12.3, 37.5)
Median (IQR) at last assessment	48.5 (21.3, 88.5)	34.5 (25.0, 59.0)	37.0 (22.5, 56.5)
Median change (IQR) from baseline	19.0 (1.0, 44.0)	12.0 (3.5, 33.0)	8.3 (0.3, 30.0)



Change in AM PEF (L/min)



Baseline Eosinophil Count

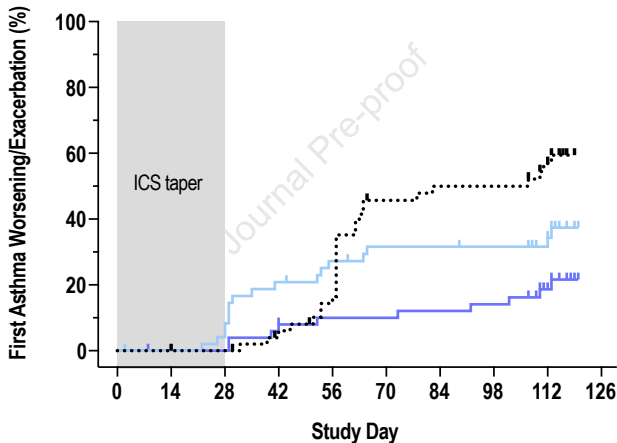
Placebo

GB001 5 mg

GB001 20 mg

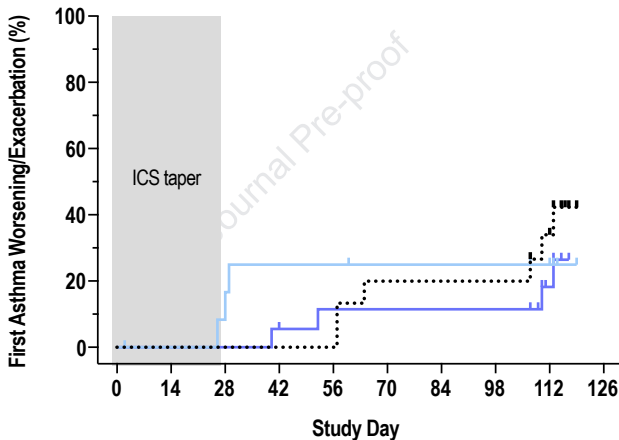
(A)

- ... Placebo (n = 53); median = 107 days
- GB001 5 mg (n = 52); median = NR; p = 0.09
- GB001 20 mg (n = 53); median = NR; p < 0.001*



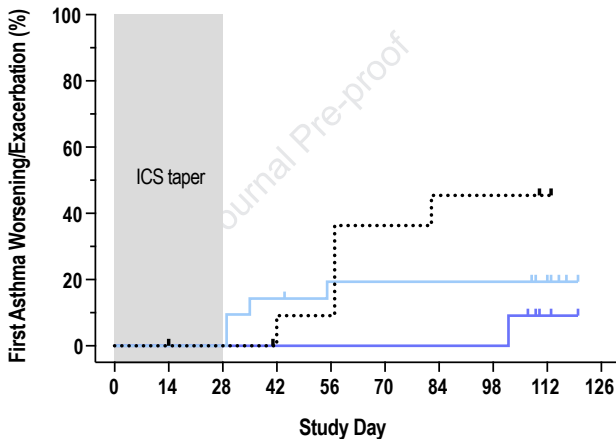
(B)

- ... Placebo (n = 16); median = NR
- GB001 5 mg (n = 14); median = NR; p = 0.67
- GB001 20 mg (n = 19); median = NR; p = 0.38



(C)

- ... Placebo (n = 13); median = NR
- GB001 5 mg (n = 21); median = NR; p = 0.24
- GB001 20 mg (n = 11); median = NR; p = 0.048



(D)

- ... Placebo (n = 24); median = 62 days
- GB001 5 mg (n = 17); median = 112 days; p = 0.30
- GB001 20 mg (n = 22); median = 120 days; p < 0.001†

