CHEST

Results of a Phase 2b Trial With GB001, a Prostaglandin D_2 Receptor 2 Antagonist, in Moderate to Severe Eosinophilic Asthma

*Mark H. Moss, MD; Njira L. Lugogo, MD; Mario Castro, MD; Nicola A. Hanania, MD; Andrea Ludwig-Sengpiel, MD; Dinesh Saralaya, MD; Rafal Dobek, MD; Iñigo Ojanguren, MD; Ivan Vyshnyvetskyy, MD; Jean-Marie Bruey, PhD; Robin Osterhout, PhD; Cindy-ann Tompkins, MS; Karen Dittrich, PhD; Kartik Raghupathi, MS; and Hector Ortega, MD, ScD; on behalf of the LEDA Investigators**

BACKGROUND: Prostaglandin D_2 receptor 2 (DP_2) antagonists inhibit prostaglandin D_2-induced effects, including recruitment and activation of cells driving asthma pathogenesis. However, challenges identifying target population and end points persist.

RESEARCH QUESTION: What is the effect of the DP_2 antagonist GB001 on asthma worsening in patients with moderate to severe eosinophilic asthma?

STUDY DESIGN AND METHODS: In this phase IIb, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter study, GB001 or placebo was added to standard-of-care treatment in patients with moderate to severe asthma with a blood eosinophil count $\geq$ 250 cells/μL. Patients aged $\geq$ 18 years to $<$ 75 years received one of four once-daily treatments (GB001 20 mg, 40 mg, or 60 mg or placebo). The primary end point was the proportion of patients who experienced asthma worsening by 24 weeks. Efficacy analyses were performed for the intention-to-treat population and safety analyses for patients who received at least one dose of study treatment.

RESULTS: A total of 480 patients were treated. The ORs for asthma worsening for GB001 20 mg, 40 mg, and 60 mg vs placebo were 0.674 (95% CI, 0.398-1.142), 0.677 (95% CI, 0.399-1.149), and 0.651 (95% CI, 0.385-1.100), respectively. Analysis according to baseline blood eosinophil levels and/or fractional exhaled nitric oxide did not show greater treatment effects with higher values. Elevated liver aminotransferase levels and adverse events leading to discontinuation were more frequent for GB001 60 mg than with placebo, GB001 20 mg, and GB001 40 mg.

INTERPRETATION: Although GB001 did not significantly reduce the odds of asthma worsening, reductions favoring GB001 were observed. Treatment effects were consistent regardless of high/low type 2 phenotype. The overall safety profile was acceptable, although GB001 60 mg was associated with risk of liver injury.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT03683576; URL: www.clinicaltrials.gov

CHEST 2022; 162(2):297-308

KEY WORDS: asthma; asthma exacerbation; asthma worsening; DP_2 antagonist; eosinophilic asthma

ABBREVIATIONS: ACQ-5 = Asthma Control Questionnaire-5; AE = adverse event; AEI = adverse event of interest; ALT = alanine aminotransferase; AM PEF = morning peak expiratory flow; AST = aspartate aminotransferase; DP_2 = prostaglandin D_2 receptor 2; FENO = fractional exhaled nitric oxide; PGD_2 = prostaglandin D_2; RR = rate ratio; ULN = upper limit of normal

AFFILIATIONS: From the Division of Allergy, Pulmonary and Critical Care Medicine (M. H. Moss), University of Wisconsin School of Medicine and Public Health, Madison, WI; Division of Pulmonary & Critical Care Medicine (N. L. Lugogo), University of Michigan, Ann Arbor, MI; Division of Pulmonary, Critical Care & Sleep Medicine (M. Castro), University of Kansas, Kansas City, KS; Section of Pulmonary

Take-home Points

Study Question: What is the effect of the DP_2 antagonist GB001 on asthma worsening in patients with moderate to severe eosinophilic asthma?

Results: GB001 showed numeric reductions in the odds of and significant delays in time to asthma worsening. The overall safety profile was acceptable, as shown by similar rates of AEs across treatment groups; however, the highest dose of GB001 60 mg was associated with risk for liver injury.

Interpretation: Several DP_2 receptor antagonists have been investigated in clinical trials. Challenges persist in identifying the appropriate asthma target population and adequate end points. The current findings suggest that irrespective of markers of type 2 inflammation, patients may benefit from a nonbiologic oral therapy to control asthma worsening and exacerbations. Nonbiologic oral therapies are needed for patients with moderate to severe asthma who continue to experience exacerbations despite treatment.

Despite available therapies for moderate to severe asthma, the disease in many patients remains uncontrolled.[1] Asthma is a heterogeneous disease that includes clinical phenotypes differing in severity, natural history, biomarker profile, and response to therapy. In patients with more severe disease, increased prostaglandin D_2 (PGD_2) levels have been associated with poor asthma control.[2,3] The prostaglandin D_2 receptor 2 (DP_2) is selectively expressed on many cells involved in the inflammatory response.[4] Binding of the endogenous agonist of DP_2, PGD_2, induces a cascade of proinflammatory downstream effects, contributing to recruitment, activation, and/or migration of T-helper type 2 cells, group 2 innate lymphoid cells, basophils, and eosinophils leading to release of IL-4, IL-5, and IL-13 and persistence of type 2 inflammation. Asthma associated with eosinophilic inflammation, as measured by elevated blood eosinophils, has been associated with greater clinical severity, including increased risk of asthma exacerbations.[5-7]

GB001 is a potent and highly selective oral antagonist of DP_2 that binds reversibly to the PGD_2 receptor with a slow dissociation rate. In pharmacokinetic studies, absorption of GB001 was reasonably rapid, reaching a maximum plasma exposure within 3 h of dosing.[8] Systemic exposure increased with increasing dose in a greater than dose-proportional manner. Steady state was reached on day 4 of treatment, with little evidence of accumulation. Overall, data indicate that GB001 is suitable for once-daily dosing.

In a phase IIa study in Japanese patients, GB001 20 mg significantly delayed time to asthma worsening irrespective of baseline blood eosinophil levels in an inhaled corticosteroid treatment-withdrawal design.[9] GB001 20 mg showed greater effects in patients with baseline blood eosinophil levels $\geq$ 300 cells/μL compared with the overall population on improvement in morning peak expiratory flow (AM PEF) and time to asthma worsening. Greater effects were also observed in patients with high baseline fractional exhaled nitric oxide (FENO) and/or blood eosinophil levels.[10] These findings provided the foundation to further assess dose response in LEDA, a larger phase IIb study in patients with moderate to severe eosinophilic asthma treated with standard-of-care therapy, to evaluate whether GB001 at doses of 20 mg, 40 mg, and 60 mg once daily could reduce asthma worsening relative to placebo.

Study Design and Methods

Study Design

LEDA was a phase IIb, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter study. Patients were randomized at 95 sites in 11 countries. GB001 or placebo was added to standard-of-care treatment in patients with moderate to severe asthma with a blood eosinophil count $\geq$ 250 cells/μL (Fig 1). The study consisted of a 2- to 6-week run-in period, a 24-week treatment period, and a 4-week follow-up period. The study protocol,

& Critical Care Medicine (N. A. Hanania), Baylor College of Medicine, Houston, TX; KLB Gesundheitsforschung Lübeck (A. Ludwig-Sengpiel), Lübeck, Germany; NIHR PRC (D. Saralaya), Bradford Institute for Health Research, Bradford, England; 2nd Department of Respiratory Medicine (R. Dobek), Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; NZOZ Research Clinic (R. Dobek), Wroclaw, Poland; Pulmonary Department (I. Ojanguren), University Hospital Vall d'Hebron, Barcelona, Spain; Departament de Medicina (I. Ojanguren), Universitat Autònoma de Barcelona, Catalonia, Spain; CIBER de Enfermedades Respiratorias (I. Ojanguren), Barcelona, Catalonia, Spain; Research & Development (I. Vyshnyvetskyy), Evidence-Based Medicine and Good Clinical Practice Research Institute, LLC, Kyiv, Ukraine; and Gossamer Bio Inc. (J.-M. Bruey, R. Osterhout, C. Tompkins, K. Dittrich, K. Raghupathi, and H. Ortega), San Diego, CA.

*A list of LEDA Investigators is available in the e-Appendix 1.

CORRESPONDENCE TO: Hector Ortega, MD, ScD; email: hector.ortega@nexstone.bio

DOI: https://doi.org/10.1016/j.chest.2022.02.038

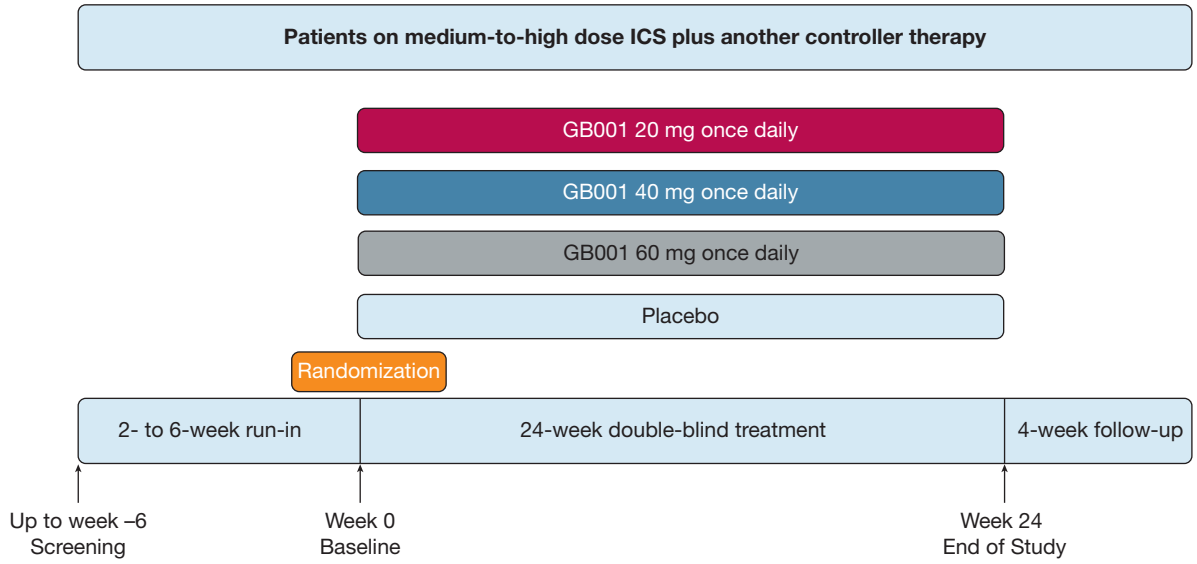

Figure 1 – *Study design. ICS = inhaled corticosteroids.*

amendments, informed consent forms, and other relevant documents were reviewed by the independent ethics committee or institutional review board for each site. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice guidelines. An independent data monitoring committee periodically reviewed study data to oversee benefit/risk considerations to ensure the continuing protection of patients.

Patients were required to have a qualifying peripheral blood eosinophil count ≥ 250 cells/μL between screening and prior to the day of randomization. Eligible patients were 18 to < 75 years of age, on medium- or high-dose inhaled corticosteroids in combination with at least one other controller without maintenance oral corticosteroids, and had a diagnosis of asthma for ≥ 12 months, with a history of ≥ 2 asthma exacerbations within the previous 12 months or 1 exacerbation within the previous 12 months with an Asthma Control Questionnaire-5 (ACQ-5) score ≥ 1.5. Patients were required to have a pre-bronchodilator FEV_1 ≤ 85% of predicted normal and airway reversibility or hyperresponsiveness. Patients with a known, preexisting, clinically important condition other than asthma, such as liver, metabolic, or autoimmune disease, were excluded. Patients provided written informed consent before participating in the study.

Patients were randomized (1:1:1:1) to one of four treatment groups: GB001 20 mg, 40 mg, or 60 mg or placebo once daily. Randomization was stratified according to baseline inhaled corticosteroid dose (medium or high) and country.

Patients remained on stable current standard-of-care therapy throughout the study. Patients who permanently discontinued study treatment were encouraged to complete any remaining study visits as per the study protocol.

Efficacy was assessed by recording the components of asthma worsening (AM PEF via an electronic diary [eDiary, eResearch Technology GmbH], pre-bronchodilator FEV_1 via pulmonary function testing at visits, rescue medication use via eDiary, ACQ-5 at visits, and severe asthma exacerbation). Other assessments included blood eosinophil counts, FENO [Niox Mino, Aerocrine], exploratory biomarkers, and safety.

Study Outcomes

The primary end point was the proportion of patients who experienced worsening of asthma by 24 weeks as defined by at least one of the following: (1) on two consecutive days, AM PEF ≤ 75% of mean AM PEF measured over the last 7 days of the run-in period; (2) FEV_1 < 80% of baseline; (3) increase in rescue medication use of ≥ 6 puffs per day on two consecutive days compared with mean use over the last 7 days of the run-in period; (4) increase in ACQ-5 score of ≥ 0.5 compared with baseline; or (5) the occurrence of a severe asthma exacerbation, defined as deterioration of asthma that led to the use of systemic corticosteroids for at least 3 days, hospitalization, or an ED visit. Secondary end points included time to first asthma worsening, annualized rate of severe asthma exacerbations, and changes from baseline to 24 weeks in pre-bronchodilator FEV_1, AM PEF, and ACQ-5 score. Safety end points included the incidence of adverse events (AEs), including AEs of interest (AEIs), and changes from baseline in laboratory parameters. AEIs were protocol-defined liver chemistry AEs that resulted in temporary or permanent discontinuation of study treatment and were closely monitored.

Statistical Analysis

A sample size of 480 patients (120 per treatment group) was expected to provide 80% power to detect a reduction in odds of 66% between each GB001 group and placebo at a .050 two-sided level of significance for the primary end point, with an assumed placebo proportion of 25%. This was based on results for asthma worsening by 16 weeks from a previous phase II inhaled corticosteroid withdrawal study of GB001[8] and the presumption that asthma worsening would occur approximately one-half as frequently in an add-on to standard-of-care design.

Evaluation of efficacy end points was performed without multiplicity adjustment, and statistical significance was based on excluding a null effect by using two-sided 95% CIs. Efficacy analyses used the intention-to-treat population, which included all randomized patients who received at least one dose of study treatment, grouped according to randomized treatment. Safety analyses used the safety population, which included all patients who received at least one dose of study treatment, grouped according to treatment actually received.

The primary end point was analyzed by using a logistic regression model adjusted for treatment group, inhaled corticosteroid dose (medium or high) per randomization, region, baseline pre-bronchodilator FEV_1, and baseline ACQ-5 score. ORs and corresponding two-sided, asymptotic 95% CIs were calculated.

Time to first asthma worsening was analyzed by using a Cox proportional hazards model, with the same covariate adjustment as for the primary end point and was also presented by using a Kaplan-Meier plot. A post hoc analysis of the annualized rate of asthma worsening was performed by using a negative binomial regression model, with the total number of asthma worsening events as the outcome and the logarithmic transformation of follow-up time as the offset parameter, with the same covariate adjustment as for the primary end point. The annualized rate of severe asthma exacerbations was also analyzed in a similar manner, with covariate adjustment for treatment group, inhaled corticosteroid dose per randomization, region, age, and number of exacerbations in the previous 12 months. Secondary efficacy end points of changes from baseline to 24 weeks were analyzed by using analysis of covariance models with a multiple imputation approach.

Statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc.) and R version 4.0.3 (R Foundation for Statistical Computing).

Results

Baseline and Demographic Characteristics

Between October 22, 2018, and February 4, 2020, a total of 480 patients were randomized to treatment and were administered GB001 20 mg (n = 120), GB001 40 mg (n = 118), GB001 60 mg (n = 122), or placebo (n = 120) (Fig 2). Baseline characteristics were generally similar across treatment groups (Table 1). Mean ± SD baseline blood eosinophil count was 464 ± 372 cells/μL. Although nearly all patients (476 of 480 [99.2%]) had a qualifying eosinophil count ≥ 250 cells/μL, 107 (22.3%) had a count < 250 cells/μL when measured at baseline due to a decrease from their qualifying value. Fifty-six of 480 patients (11.7%) discontinued study treatment, with a higher percentage discontinuing GB001 60 mg (n = 23 [18.9%]) and GB001 40 mg (n = 18 [15.3%]) than discontinuing placebo (n = 7 [5.8%]) or GB001 20 mg (n = 8 [6.7%]).

Efficacy

All GB001 groups (20 mg, 40 mg, and 60 mg) showed numeric reductions in the odds of asthma worsening relative to placebo that were not statistically significant (OR, 0.674 [95% CI, 0.398-1.142]; OR, 0.677 [95% CI, 0.399-1.149]; and OR, 0.651 [95% CI,

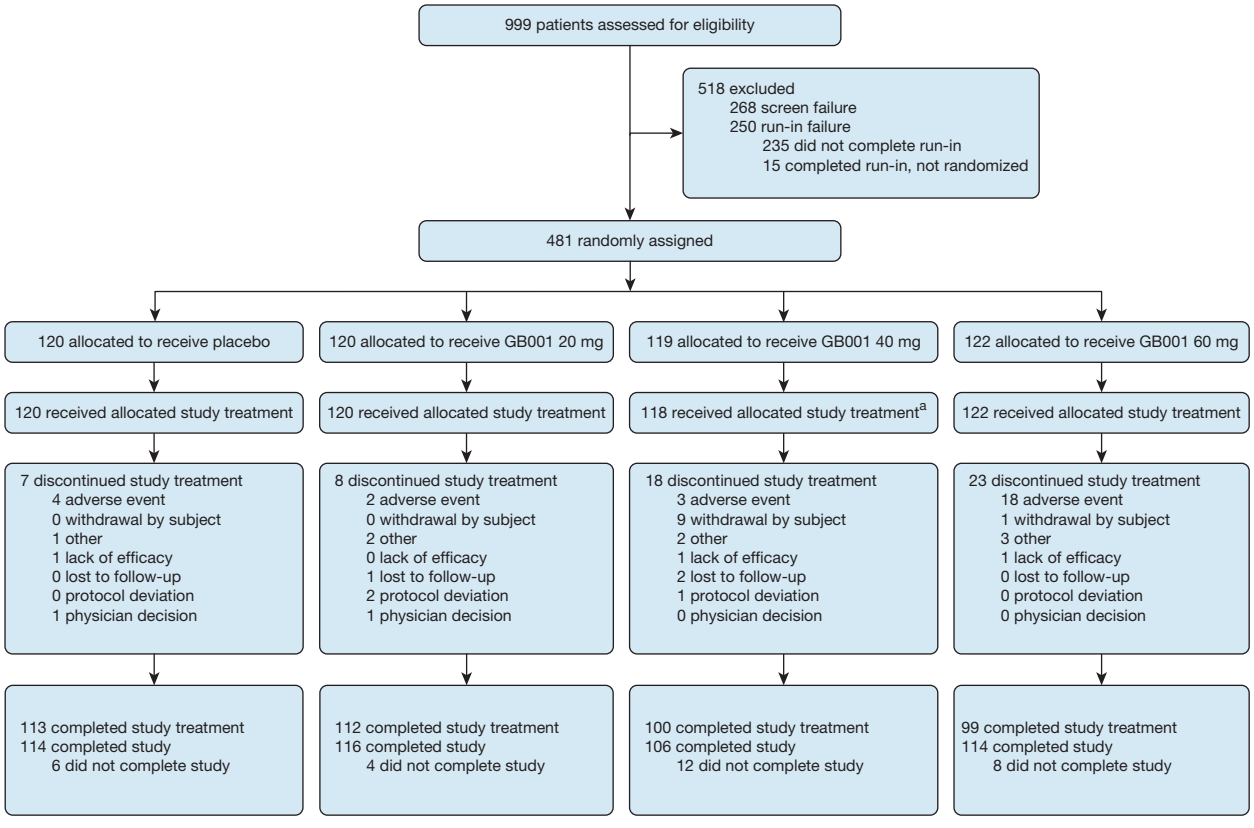

Figure 2 – *Patient disposition.* [a]*One patient withdrew following randomization and did not receive study treatment.*

TABLE 1] Baseline Demographic and Clinical Characteristics (Intention-to-Treat Population)

Characteristic	Placebo (n = 120)	GB001 20 mg (n = 120)	GB001 40 mg (n = 118)	GB001 60 mg (n = 122)
Age, y	51.5 ± 11.91	52.8 ± 11.81	52.9 ± 13.32	49.9 ± 14.37
Sex				
Female	76 (63.3)	86 (71.7)	74 (62.7)	72 (59.0)
Male	44 (36.7)	34 (28.3)	44 (37.3)	50 (41.0)
BMI, kg/m^2	27.98 ± 5.088	29.05 ± 5.233	29.27 ± 5.407	28.18 ± 5.534
Duration of asthma, y	19.986 ± 13.481	21.581 ± 15.542	19.920 ± 13.627	20.761 ± 14.602
Race				
White	108 (90.0)	109 (90.8)	109 (92.4)	112 (91.8)
Black or African American	6 (5.0)	7 (5.8)	8 (6.8)	6 (4.9)
Other[a]	6 (5.0)	4 (3.3)	1 (0.8)	4 (3.3)
Ethnicity				
Not Hispanic or Latino	107 (89.2)	113 (94.2)	112 (94.9)	116 (95.1)
Hispanic or Latino	11 (9.2)	2 (1.7)	5 (4.2)	5 (4.1)
Not reported	2 (1.7)	5 (4.2)	1 (0.8)	1 (0.8)
Allergic/atopic conditions[b]				
Allergic rhinitis	83 (69.2)	65 (54.2)	68 (57.6)	86 (70.5)
Nasal polyps	28 (23.3)	16 (13.3)	24 (20.3)	23 (18.9)
Smoking history				
Never	89 (74.2)	98 (81.7)	97 (82.2)	95 (77.9)
Former	31 (25.8)	22 (18.3)	21 (17.8)	27 (22.1)
ICS dose at randomization				
High	71 (59.2)	69 (57.5)	71 (60.2)	72 (59.0)
Medium	49 (40.8)	51 (42.5)	47 (39.8)	50 (41.0)
ACQ-5 score	2.39 ± 0.796	2.51 ± 0.895	2.43 ± 0.901	2.38 ± 0.985
Evidence of uncontrolled asthma[c]				
1 exacerbation and ACQ-5 score ≥ 1.5	61 (50.8)	63 (52.5)	60 (50.8)	64 (52.5)
≥ 2 exacerbations in prior 12 mo	58 (48.3)	57 (47.5)	58 (49.2)	58 (47.5)
Pre-bronchodilator FEV_1, L	1.924 ± 0.563	1.843 ± 0.557	1.917 ± 0.650	1.985 ± 0.653
Pre-bronchodilator FEV_1, % predicted	62.17 ± 12.229	61.25 ± 12.145	61.73 ± 13.890	61.81 ± 11.442
Post-bronchodilator FEV_1, L	2.257 ± 0.680	2.206 ± 0.730	2.272 ± 0.770	2.340 ± 0.697
FEV_1 reversibility, %	20.52 ± 14.418	24.18 ± 17.720	23.65 ± 18.055	20.22 ± 13.051
AM PEF, L/min	292.083 ± 101.918	288.424 ± 106.445	292.694 ± 110.950	318.123 ± 118.154
Rescue medication use, puffs/d	2.059 ± 1.998	2.188 ± 2.062	2.338 ± 2.515	2.009 ± 1.978
Qualifying blood eosinophils, cells/ μL	502 ± 236	502 ± 295	511 ± 352	486 ± 230
Blood eosinophils at baseline, cells/μL	486 ± 472	471 ± 419	434 ± 248	463 ± 308
F_{ENO}, ppb	47.88 ± 46.963	44.26 ± 40.865	37.03 ± 26.148	42.78 ± 31.108
IgE, IU/mL	552.15 ± 1,084.171	516.01 ± 2,119.107	464.45 ± 1,012.470	452.96 ± 889.813

Data are presented as mean ± SD for continuous parameters and No. (%) for categorical parameters. ACQ-5 = Asthma Control Questionnaire-5; AM PEF = morning peak expiratory flow; F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; ppb = parts per billion.

[a]Asian, Native Hawaiian or other Pacific Islander, and other.

[b]Reported in medical history as ongoing at screening.

[c]Patients who qualified for both categories are counted only in the second category.

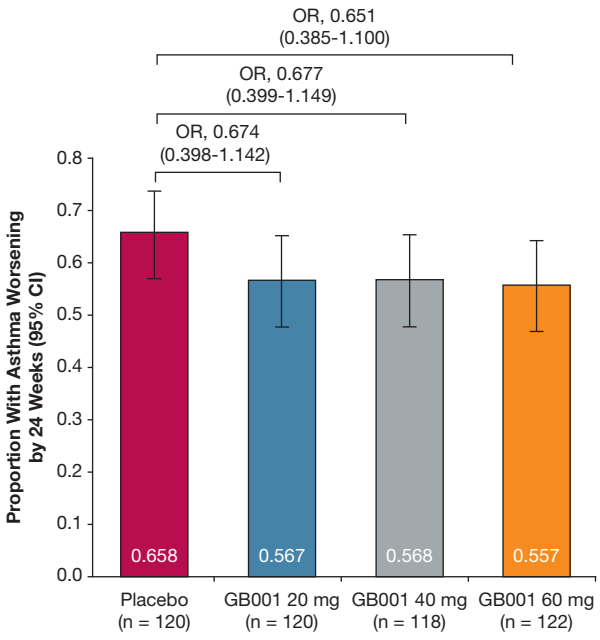

Figure 3 – *Primary end point: proportion of patients who experienced asthma worsening by 24 weeks (intention-to-treat population). ORs and 95% CIs for each GB001 group vs placebo are shown.*

0.385-1.100]) for GB001 20 mg, 40 mg, and 60 mg, respectively (Fig 3, Table 2). The proportion meeting each component of the asthma worsening composite exhibited numeric reductions for each GB001 group relative to placebo (e-Fig 1). Subgroup analyses of the primary end point according to baseline characteristics (eg, demographic characteristics, region, inhaled corticosteroid dose, prior exacerbations, pre-bronchodilator FEV_1, ACQ-5 score) did not indicate any clear heterogeneity in treatment effect across GB001 treatment groups. Analysis of the primary end point according to baseline blood eosinophil levels and/or FENO revealed no consistent pattern of differential treatment effect comparing high vs low values across different thresholds (e-Fig 2). Subgroups based on baseline blood eosinophil thresholds of 250 and 300 cells/μL were evaluated; higher thresholds were also assessed, with similar results (not shown). GB001 20 mg and 60 mg resulted in a significant delay in the time to first asthma worsening relative to placebo (HRs of 0.719 [95% CI, 0.519-0.995] and 0.698 [95% CI, 0.505-0.967]) (Fig 4). There was a numeric reduction for GB001 40 mg relative to placebo (HR, 0.773; 95% CI, 0.558-1.071), which was not statistically significant. The annualized rate of asthma worsening revealed significant reductions relative to placebo for all GB001 groups, 20 mg, 40 mg, and 60 mg (rate ratio [RR], 0.557 [95% CI, 0.389-0.796]; RR, 0.650 [95% CI, 0.455-0.928]; and RR, 0.677 [95% CI, 0.478-0.959]) (Fig 5A, Table 2) in a post hoc analysis.

GB001 groups showed numeric reductions in the annualized rate of severe asthma exacerbations relative to placebo (RR, 0.797 [95% CI, 0.501-1.268]; RR, 0.748 [95% CI, 0.469-1.195]), and RR, 0.889 [95% CI, 0.565-1.397]), respectively), which were not statistically significant (Fig 5B, Table 2). Notably, a substantially higher proportion of patients administered GB001 60 mg discontinued study treatment but continued on study relative to other groups. Other secondary end points included change from baseline to 24 weeks in pre-bronchodilator FEV_1, AM PEF, and ACQ-5 score; all showed modest numeric improvements that were not statistically significant.

In an exploratory analysis in a subset of 121 patients (25.2%) for whom biomarkers were collected that were generally similar at baseline to the remainder of the study population, we found an increased baseline percentage of demethylated DP_2^+ cells in peripheral blood compared with healthy control subjects that was positively correlated with baseline blood eosinophil counts (e-Fig 3). There was a trend of decreasing percent DP_2^+ demethylation from baseline to 24 weeks in the GB001 60-mg group. In addition, expression levels of specific genes related to asthma (DP_2 [PTGDR2], C-C motif chemokine ligand 23 [CCL23], and serine protease 33 [PRSS33]) were correlated with baseline blood eosinophil counts and the presence of nasal polyps, an important comorbidity in moderate to severe asthma, reported in medical history. Improvements in lung function at 24 weeks (defined as the proportion of patients with an improvement from baseline in observed pre-bronchodilator $FEV_1 \geq 80$ mL) were more frequently observed in the overall population in patients with high vs low baseline DP_2 expression levels (OR, 2.74; 95% CI, 1.25-6.03), irrespective of treatment group (e-Fig 4). A better understanding is needed of the potential value of DP_2 messenger RNA expression level as a prognostic marker in relation to clinical end points; nonetheless, these exploratory findings support target engagement of GB001.

Safety

The overall incidence of AEs was similar across treatment groups (Table 3). The most common AEs with a greater incidence in GB001-treated patients than patients receiving placebo included nasopharyngitis,

TABLE 2] Summary of Primary and Secondary Efficacy End Points (Intention-to-Treat Population)

End Point	Placebo (n = 120)	GB001 20 mg (n = 120)	GB001 40 mg (n = 118)	GB001 60 mg (n = 122)
Primary end point				
Proportion (n/nn) with asthma worsening by 24 wks (95% CI)	0.658 (79/120) (0.570 to 0.737)	0.567 (68/120) (0.477 to 0.652)	0.568 (67/118) (0.478 to 0.654)	0.557 (68/122) (0.469 to 0.642)
OR vs placebo (95% CI)[a,b]	...	0.674 (0.398 to 1.142)	0.677 (0.399 to 1.149)	0.651 (0.385 to 1.100)
Secondary end points				
Time to first asthma worsening (wk)				
Median (95% CI)[c]	10.57 (7.857 to 16.286)	17.43 (12.143 to NE)	17.57 (13.429 to 24.286)	19.86 (14.857 to NE)
Hazard ratio vs placebo (95% CI)[b,d]	...	0.719 (0.519 to 0.995)[e]	0.773 (0.558 to 1.071)	0.698 (0.505 to 0.967)[e]
Annualized rate of asthma worsening by 24 wks[b,f]				
Adjusted rate (95% CI)	5.799 (4.495 to 7.481)	3.227 (2.458 to 4.238)	3.769 (2.869 to 4.952)	3.928 (3.026 to 5.099)
Rate ratio vs placebo (95% CI)[b,f]	...	0.557 (0.389 to 0.796)[f]	0.650 (0.455 to 0.928)[e]	0.677 (0.478 to 0.959)[e]
Annualized rate of severe asthma exacerbations by 24 wks[f,g]				
Adjusted rate (95% CI)	0.933 (0.664 to 1.311)	0.744 (0.517 to 1.070)	0.698 (0.480 to 1.015)	0.829 (0.585 to 1.174)
Rate ratio vs placebo (95% CI)	...	0.797 (0.501 to 1.268)	0.748 (0.469 to 1.195)	0.889 (0.565 to 1.397)
Change from baseline to 24 wk in pre-bronchodilator FEV_1 (L)[b,h]				
LS mean (95% CI)	0.105 (0.027 to 0.182)	0.121 (0.041 to 0.200)	0.146 (0.064 to 0.227)	0.180 (0.102 to 0.257)
Difference in LS means vs placebo (95% CI)	...	0.016 (−0.091 to 0.123)	0.041 (−0.067 to 0.149)	0.075 (−0.030 to 0.180)
Change from baseline to 24 wks in AM PEF (L/min)[h,i]				
LS mean (95% CI)	8.993 (−1.514 to 19.499)	15.115 (4.779 to 25.451)	22.941 (12.042 to 33.839)	14.581 (4.140 to 25.021)
Difference in LS means vs placebo (95% CI)	...	6.122 (−8.007 to 20.251)	13.948 (−0.578 to 28.474)	5.588 (−8.522 to 19.698)

(Continued)

TABLE 2] *(Continued)*

End Point	Placebo (n = 120)	GB001 20 mg (n = 120)	GB001 40 mg (n = 118)	GB001 60 mg (n = 122)
Change from baseline to 24 wks in ACQ-5 score[b,h]				
LS mean (95% CI)	−0.89 (−1.05 to −0.73)	−1.04 (−1.20 to −0.89)	−1.04 (−1.20 to −0.88)	−1.08 (−1.24 to −0.92)
Difference in LS means vs placebo (95% CI)	…	−0.15 (−0.36 to 0.06)	−0.15 (−0.37 to 0.07)	−0.19 (−0.40 to 0.03)

ACQ-5 = Asthma Control Questionnaire-5; AM PEF = morning peak expiratory flow; LS = least squares; NE = not estimable due to an insufficient number of events.
[a]Analyzed by using a logistic regression model.
[b]Covariate adjustment for treatment group, inhaled corticosteroid dose (medium or high) at randomization, region, baseline pre-bronchodilator FEV_1, and baseline ACQ-5 score.
[c]Based on Kaplan-Meier estimates with CIs calculated based on the Brookmeyer and Crowley method using the log-log transformation.
[d]Based on a Cox proportional hazards model.
[e]95% CI excludes a null effect.
[f]Analyzed by using a negative binomial regression model.
[g]Covariate adjustment for treatment group, inhaled corticosteroid dose (medium or high) at randomization, region, age, and the number of exacerbations in the past 12 months.
[h]LS means, differences in LS means, and corresponding 95% CIs calculated based on an analysis of covariance model with multiple imputation using Rubin's rules.
[i]Covariate adjustment for treatment group, inhaled corticosteroid dose (medium or high) at randomization, region, baseline AM PEF, and baseline ACQ-5 score.

headache, increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and sinusitis. The incidence of AEs leading to study treatment discontinuation was higher in the GB001 60-mg treatment group (n = 18 [14.8%]) compared with the placebo (n = 4 [3.3%]), GB001 20-mg (n = 2 [1.7%]), and GB001 40-mg (n = 3 [2.5%]) groups and included liver chemistry abnormalities and pruritus with GB001 60 mg. The incidence of AEIs was higher for GB001 60 mg (n = 5 [4.1%]) relative to placebo (n = 1 [0.8%]) and GB001 20 mg (n = 1 [0.8%]) and GB001 40 mg (n = 2 [1.7%]), including increased ALT and AST levels and liver injury. A single treatment-related serious AE occurred in 1 (0.8%) patient in the GB001 60-mg group: an asymptomatic case of liver injury meeting Hy's law criteria for which recovery occurred following study treatment discontinuation on day 30. One death occurred in a patient receiving GB001 60 mg who completed study treatment; the patient died of small cell lung cancer 97 days following the last dose. The death was assessed as unrelated to study treatment and thought to be preexisting but unidentified prior to screening.

Discussion

The LEDA study found numeric reductions in the odds of asthma worsening by 24 weeks for GB001 add-on maintenance therapy ranging from 32% to 35%, with no dose response; these findings were not statistically significant. However, end points assessing various end point formulations of the asthma worsening outcome, including the secondary end point of time to first asthma worsening and the post hoc analysis of annualized rate of asthma worsening, showed nominally statistically significant treatment effects, corresponding to a median delay of approximately 7 to 9 weeks and a reduction of approximately 32% to 44% relative to placebo, respectively. These results indicate that GB001 extended the time to asthma worsening and reduced the rate of asthma worsening over 24 weeks, with more modest clinical activity in complete prevention of asthma worsening by 24 weeks.

Over the past two decades, several trials of DP_2 antagonists in mild to moderate asthma have generally found DP_2 antagonists to be safe and well tolerated. However, the overall efficacy results were underwhelming, with inconsistent reports of statistically significant but small improvements in lung function and quality of life measures.[11-13] These studies may have been affected by the selection of end points and patient

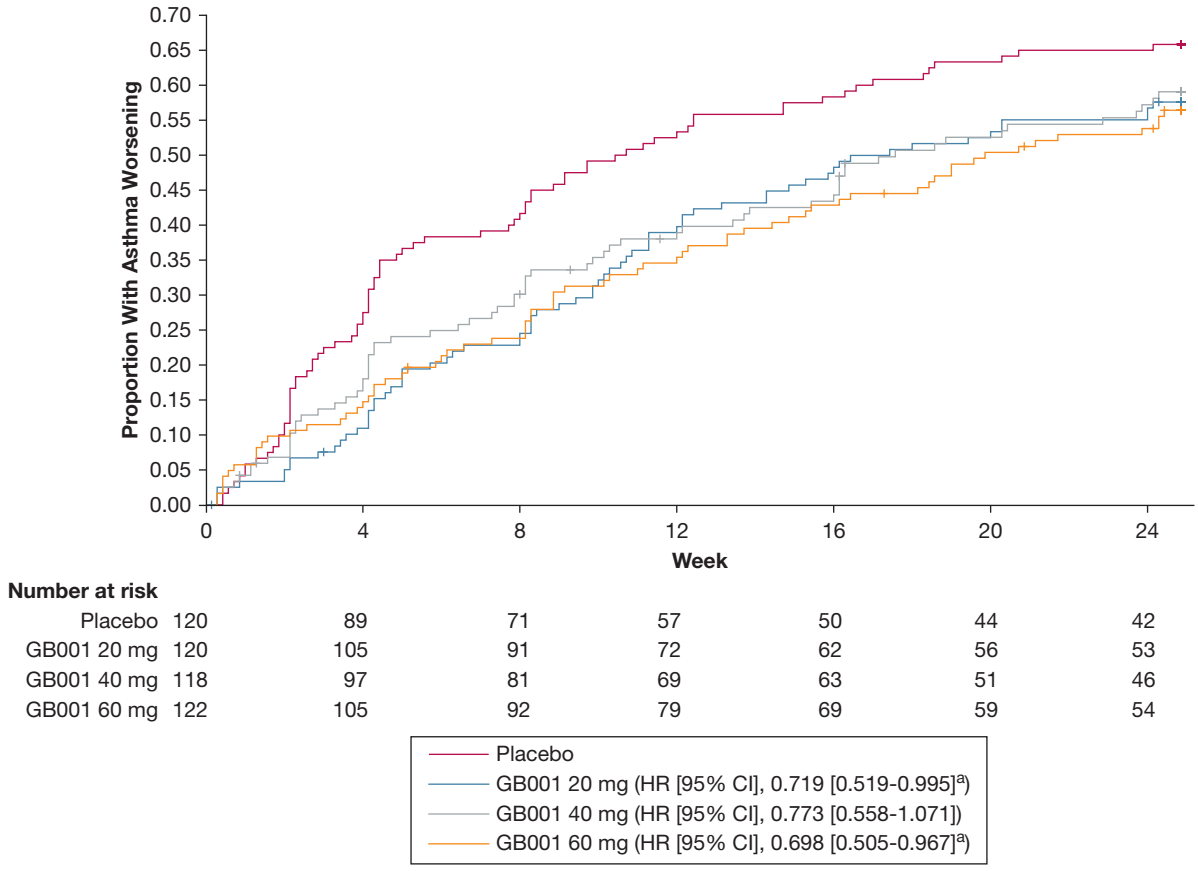

Figure 4 – *Time to first asthma worsening (intention-to-treat population).* [a]*95% CI excludes a null effect.*

characteristics. In a previous study that served as the basis for LEDA, GB001 20 mg showed a delay in time to asthma worsening in the overall population,[9] with an enhanced response in patients with type 2 phenotype (high baseline blood eosinophils and/or FENO), as observed with some biologics.[7,14] Specifically, patients with high blood eosinophil levels (≥ 300 cells/μL) experienced a greater delay in time to asthma worsening when treated with GB001 vs placebo, compared with patients without high blood eosinophil levels. Notably, standard-of-care treatment was withdrawn, and thus the clinical outcomes observed in a high eosinophil population may be related to this treatment modification.

Asthma worsening as an end point has been used successfully in previous studies in a treatment withdrawal setting,[15,16] including a 16-week phase II study of GB001.[9] Moreover, others have investigated similar end points (eg, CompEx) capturing clinically relevant deteriorations (diary events) that, when combined with severe exacerbations, provide a useful composite outcome.[17] These findings further support the use of the asthma worsening outcome in the context of LEDA, in which it served as a surrogate for asthma exacerbations. One limitation of LEDA was the lack of prior information on the performance of the asthma worsening outcome in an add-on maintenance therapy setting with respect to end point formulation and sample size assumptions. LEDA is one of the first studies meaningfully evaluating asthma worsening in an add-on setting and assessing this outcome according to various end point formulations (proportion, time to event, and annualized rate). Our results indicate that the end point formulation was sensitive in terms of treatment effect detection and suggest that the annualized rate end point may be most appropriate for future studies. Furthermore, our findings suggest that a 6-month, phase II, dose-ranging study using annualized asthma worsening rate as the primary end point and asthma exacerbation rate as a secondary end point can be achieved with a reasonable sample size to meaningfully inform phase III design for drug development in moderate to severe asthma.

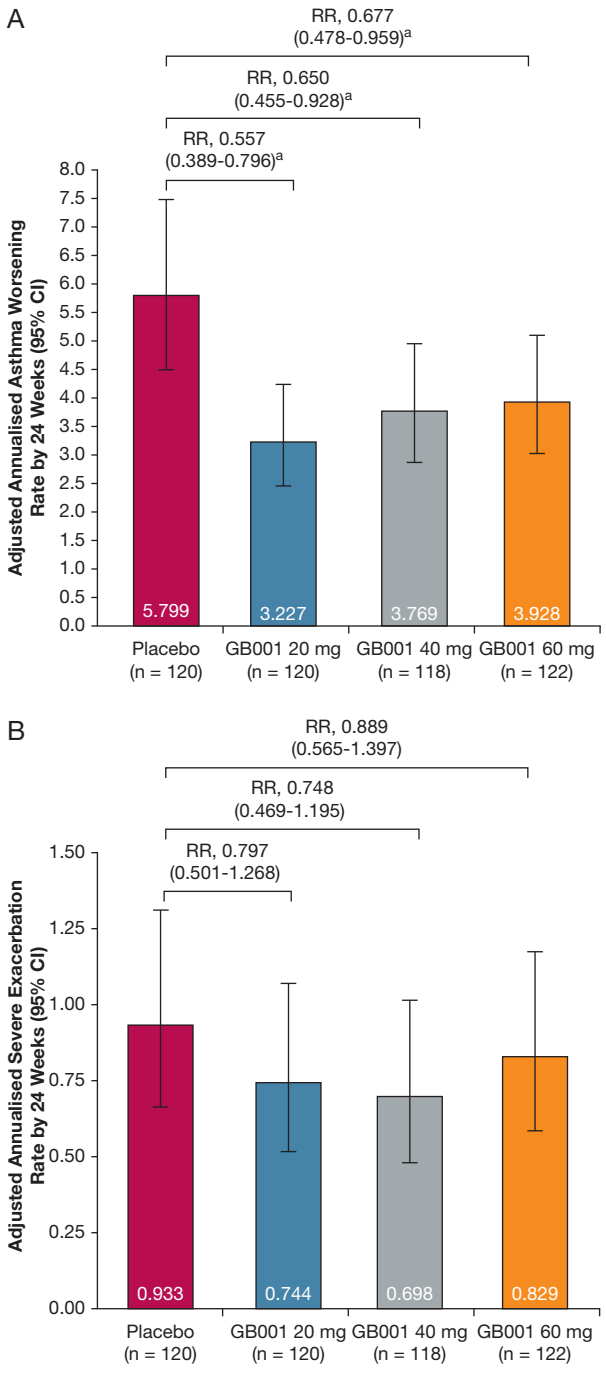

Figure 5 – *Annualized rate of asthma worsening (A) and severe asthma exacerbations (B) by 24 weeks (intention-to-treat population). RRs and 95% CIs for each GB001 group vs placebo are shown. [a]95% CI excludes a null effect. RR = rate ratio.*

The efficacy findings of the LEDA study seem to be independent of baseline blood eosinophils or FENO levels. These results are consistent with the recently completed LUSTER-1 and LUSTER-2 phase III studies[18] evaluating fevipiprant, another oral DP_2 antagonist, in patients with moderate to severe asthma. The primary end point in the LUSTER studies was the annualized rate of asthma exacerbations over 52 weeks in both high eosinophil (≥ 250 cells/μL) and overall populations.[17] Results showed consistent, modest reductions for the fevipiprant 450-mg dose relative to placebo in the annualized rate of asthma exacerbations in the high eosinophil subpopulation and in the overall populations, and modest improvement in lung function with both the 150-mg and 450-mg fevipiprant doses. These findings, however, were not statistically significant. The treatment effects for fevipiprant 450 mg in the two studies were 17% and 28% reductions in the high eosinophil subpopulation and 22% and 24% in the overall population, indicating no differential effect in patients regardless of type 2 phenotype (eosinophilic asthma). In LEDA, baseline blood eosinophils and/or FENO did not seem to be predictive of a greater treatment effect on asthma worsening. Of note, LEDA required patients to have elevated blood eosinophil levels (≥ 250 cells/μL) for qualification. The lack of enhanced treatment effects in patients with type 2 phenotype for the DP_2 antagonists GB001 and fevipiprant, as contrasted with the presence of such enhanced treatment effects for several biologic asthma treatments, underscores the importance of evaluating a potential predictive marker such as type 2 phenotype on a therapy-specific basis.

The overall safety profile in the current study was acceptable, as shown by similar rates of AEs across treatment groups. GB001 was associated with an increased incidence of liver chemistry abnormalities at the GB001 60-mg dose; in some cases, elevations resulted in study treatment discontinuation. The incidence of AEIs was higher in the GB001 60-mg group compared with other groups and included increased ALT and AST levels and liver injury. In a previous study,[19] another DP_2 antagonist, AZD1981, showed transaminase levels ≥ 3 times the upper limit of normal (ULN) in a small proportion of patients. Notably, the highest proportion occurred with the highest dose. Four cases of transaminase elevations ≥ 3 × ULN or total bilirubin ≥ 2 × ULN may have been related to AZD1981. Transaminase levels returned to baseline values after AZD1981 was stopped.[19] Although liver chemistry abnormalities have been observed with two DP_2 antagonists (GB001 and AZD1981), this is not a class effect phenomenon, given the safety profiles observed with other DP_2 antagonists (fevipiprant, AMG 853, OC000459, and BI671800). Generally, DP_2 antagonists have exhibited an acceptable safety profile.

TABLE 3] Summary of Adverse Events (Safety Population)

Adverse Event	Placebo (n = 120)	GB001 20 mg (n = 120)	GB001 40 mg (n = 118)	GB001 60 mg (n = 122)
Any adverse event	79 (65.8)	79 (65.8)	82 (69.5)	83 (68.0)
Any serious adverse event[a]	8 (6.7)	3 (2.5)	4 (3.4)	5 (4.1)
Any adverse event leading to discontinuation of study treatment	4 (3.3)	2 (1.7)	3 (2.5)	18 (14.8)
Any adverse event leading to death	0	0	0	1 (0.8)
Any adverse event of interest[b]	1 (0.8)	1 (0.8)	2 (1.7)	5 (4.1)
Adverse events occurring in ≥ 5% of patients in any treatment group[c]				
Nasopharyngitis	19 (15.8)	23 (19.2)	29 (24.6)	17 (13.9)
Headache	11 (9.2)	14 (11.7)	14 (11.9)	13 (10.7)
Increased AST	2 (1.7)	2 (1.7)	4 (3.4)	13 (10.7)
Increased ALT	1 (0.8)	2 (1.7)	3 (2.5)	13 (10.7)
Sinusitis	3 (2.5)	4 (3.3)	11 (9.3)	3 (2.5)
Hypertension	2 (1.7)	3 (2.5)	7 (5.9)	5 (4.1)
Upper respiratory tract infection	7 (5.8)	3 (2.5)	8 (6.8)	4 (3.3)
Diarrhea	3 (2.5)	6 (5.0)	1 (0.8)	4 (3.3)
Pruritus or allergic pruritus[d]	1 (0.8)	2 (1.7)	2 (1.7)	8 (6.6)
Rhinitis	6 (5.0)	1 (0.8)	2 (1.7)	7 (5.7)
Bronchitis	6 (5.0)	4 (3.3)	1 (0.8)	1 (0.8)

Data are presented as number (%) of patients. ALT = alanine aminotransferase; AST = aspartate aminotransferase.
[a]Excludes asthma-worsening-related serious adverse events.
[b]Includes adverse events of increased ALT or AST levels in all groups and liver injury (Hy's law) in the GB001 60-mg group.
[c]Coded by using Medical Dictionary for Regulatory Activities version 23.0.
[d]The incidence of pruritus or allergic pruritus leading to discontinuation of study treatment was 0, 1 (0.8%), 0, and 5 (4.1%) in the placebo group and GB001 20-mg, 40-mg, and 60-mg groups, respectively.

Interpretation

Although LEDA did not meet its primary end point, there were signs of clinical activity. GB001 showed numeric reductions in the odds of and significant delays in time to asthma worsening. The overall safety profile was acceptable, as indicated by similar rates of AEs across treatment groups; however, the highest dose of GB001 60 mg was associated with risk for liver injury. An unmet medical need remains for nonbiologic, oral therapies for patients with moderate to severe asthma that show a positive benefit-risk profile. LEDA also highlighted the value in using the outcome of asthma worsening for signal seeking prior to the conduct of large phase III studies and the importance of the end point formulation of this outcome. These results provide added value to the exploration of this complex PGD_2/DP_2 pathway in the context of airway inflammation and asthma worsening.

Acknowledgments

Author contributions: H. O. is the guarantor of the content of the manuscript. All authors provided substantial contribution to the conception or design of the work or the acquisition, analysis, or interpretation of data for the content contained in the manuscript; and contributed to drafting, revising, and/or critically reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding/support: This work was supported by GB001, Inc., a wholly owned subsidiary of Gossamer Bio, Inc.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: N. L. L. received consulting fees for advisory board participation from Amgen, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi, and Teva; honoraria for non-speaker bureau presentations from GSK and Astra Zeneca; travel support from Astra Zeneca; and her institution received research support from Amgen, AstraZeneca, Avillion, Gossamer Bio, Genentech, GSK, Regeneron, Sanofi, and Teva. M. C. has received grants from the National Institutes of Health, American Lung Association, the Patient-Centered Outcomes Research Institute, AstraZeneca, GSK, Novartis, PULMATRiX, Sanofi-Aventis, and Shionogi; royalties from Elsevier; consulting fees from Genentech, Teva, Sanofi-Aventis, and Novartis; and honoraria for speaking engagements from AstraZeneca, Genentech, GSK, Regeneron, Sanofi, and Teva. N. A. H. received honoraria for serving as consultant to or on advisory boards of AstraZeneca, Sanofi/Regeneron, Genentech/Roche, Novartis, Gossamer Bio, Teva, Amgen, Mylan, and Theravance; and his institution has received research support on his behalf from Novartis, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, Genentech, and Gossamer Bio. A. L.-S. has received research grants (paid to her institution) from AstraZeneca, GlaxoSmithKline, Sanofi, Teva, Avillion, Ionis, Boehringer Ingelheim, Chiesi, Verona, Insmed, and Novartis for participation in clinical trials. R. D. received consulting fees for advisory board participation from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi, and Novartis; honoraria for lectures from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Berlin Chemie Menarini, and Sandoz; travel support from AstraZeneca; and holds (unpaid) positions in the Polish Respiratory Society and European Respiratory Society. I. O. has received travel grants, consulting fees, talk fees, or research grants from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, MSD, GlaxoSmithKline, Menarini, Mundipharma, Novartis, TEVA, PureTech, and SANOFI; and is a researcher supported by the *Pla Estratègic de Recerca i Innovació en salut* (PERIS) 2016-2020. I. V. has received financial support from AstraZeneca, Chiesi Farmaceutica, Sanofi, and AB Science; is President of the Ukrainian Association for Clinical Research; and has worked with AstraZeneca, Pfizer, and MSD to obtain nonfinancial support for the organization. J.-M. B., R. O., C.-a. T., and K. R. are employees and stockholders of Gossamer Bio, Inc. K. D. and H. O. are former employees of Gossamer Bio, Inc. K. D. works at Chinook Therapeutics, Inc. and H. O. works at Nexstone Immunology, Inc. None declared (M. H. M., D. S.).

Role of sponsor: The sponsor took part in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All authors had the final decision to submit the manuscript for publication.

Other contributions: The authors thank the patients, investigators, and site research staff for support provided throughout the conduct of this study. They also gratefully acknowledge the support of Erin Elman (study conduct and execution), Lynn Katz, Mason Yamashita, and Greg Opiteck (protocol development), and Bhushan Kanumuri (statistical analyses and programming).

Additional information: The e-Appendix and e-Figures are available online under "Supplementary Data."

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Accessed July 2, 2021. https://ginasthma.org/reports
2. Fajt ML, Gelhaus SL, Freeman B, et al. Prostaglandin D2 pathway upregulation: relation to asthma severity, control, and TH2 inflammation. *J Allergy Clin Immunol*. 2013;131(6):1504-1512.
3. Peinhaupt M, Sturm EM, Heinemann A. Prostaglandins and their receptors in eosinophil function and as therapeutic targets. *Front Med (Lausanne)*. 2017;4:104.
4. Singh D, Ravi A, Southworth T. CRTH2 antagonists in asthma: current perspectives. *Clin Pharmacol*. 2017;9:165-173.
5. Wenzel SE. Eosinophils in asthma-closing the loop or opening the door? *N Engl J Med*. 2009;360(10):1026-1028.
6. Price DB, Bosnic-Anticevich S, Pavord ID, et al. Association of elevated fractional exhaled nitric oxide concentration and blood eosinophil count with severe asthma exacerbations. *Clin Transl Allergy*. 2019;9:41.
7. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
8. Shen J, Yamashita M, Opiteck GJ. Pharmacokinetics, pharmacodynamics, and safety of GB001 in healthy non-Asian, non-Japanese Asian and Japanese subjects [abstract]. *Am J Respir Crit Care Med*. 2020;201:A3019.
9. Asano K, Sagara H, Ichinose M, et al. A phase 2a study of DP_2 antagonist GB001 for asthma. *J Allergy Clin Immunol Pract*. 2020;8(40):1275-1283.
10. Asano K, Hirata M, Hanania N, et al. Effect of the DP2 antagonist, GB001, on asthma worsening in patients with mild-moderate asthma [abstract]. *J Allergy Clin Immunol*. 2020;145(suppl):AB20.
11. Farne H, Jackson JD, Johnston SL. Are emerging PGD2 antagonists a promising therapy class for treating asthma? *Expert Opinion Emerg Drugs*. 2016;21(4):359-364.
12. Kupczyk M, Kuna P. Targeting the PGD2/CRTH2/DP1 signaling pathway in asthma and allergic disease: current status and future perspectives. *Drugs*. 2017;77(12):1281-1294.
13. Yang J, Luo J, Yang J, et al. Efficacy and safety of antagonists for chemoattractant receptor-homologous molecule expressed on Th2 cells in adult patients with asthma: a meta-analysis and systematic review. *Respir Res*. 2018;19(1):217.
14. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord I. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. *Am J Resp Crit Care Med*. 2019;200(10):1308-1312.
15. Castro M, King TS, Kunselman SJ, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *JAMA*. 2014;311(20):2083-2091.
16. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455-2466.
17. Fuhlbrigge AL, Bengtsson T, Peterson S, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomized controlled trials. *Lancet Respir Med*. 2017;5(7):577-590.
18. Brightling CE, Gaga M, Inoue H, et al. Effectiveness of fevipiprant in reducing exacerbations in patients with severe asthma (LUSTER-1 and LUSTER-2): two phase 3 randomized controlled trials. *Lancet Respir Med*. 2021;9(1):43-56.
19. Bateman ED, O'Brien C, Rugman P, Luke S, Ivanov S, Uddin M. Efficacy and safety of the CRTh2 antagonist AZD1981 as add-on therapy to inhaled corticosteroids and long-acting β2-agonists in patients with atopic asthma. *Drug Des Devel Ther*. 2018;12:1093-1106.