CLINICAL INVESTIGATION

LUSTER-1 and -2: Two randomized controlled trials of the prostaglandin D_2 receptor 2 antagonist, fevipiprant, in asthma

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Abstract

The prostaglandin D_2 receptor 2 (DP_2) pathway has an important mechanistic role in the pathophysiology of asthma; specifically, the potential benefits of blockage of this pathway as a treatment for asthma are of considerable interest. The DP_2 receptor is expressed on cells involved in the inflammatory cascade, including T-helper type 2 (Th2) cells, eosinophils, type 2 innate lymphoid cells (ILC2), monocytes and basophils, as well as on airway epithelial and smooth muscle cells. Fevipiprant is an oral, highly selective DP_2 receptor antagonist that has shown potent inhibitory effects on human eosinophils and Th2 cells *in vitro*. In Phase II clinical trials of patients with asthma, fevipiprant showed improvements in lung function, asthma control and quality of life. Furthermore, fevipiprant showed a reduction in sputum eosinophils, a biomarker for asthma exacerbations, as well as an effect on the airway epithelium and airway smooth muscle mass in patients with moderate-to-severe persistent asthma. In Phase II studies, fevipiprant showed a favorable safety profile. LUSTER-1 and -2 are replicate Phase III studies whose aim is to determine the efficacy, safety and tolerability of fevipiprant (150 mg and 450 mg once daily) added to standard-of-care asthma treatment in patients with symptomatic severe asthma over a one-year period.

Keywords: fevipiprant • prostaglandin D_2 • prostaglandin D_2 receptor 2 • DP_2 receptor • LUSTER-1 • LUSTER-2 • asthma • exacerbations • randomized controlled trial • phase III

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Abbreviations

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; AE: Adverse Events; ASM: Airway Smooth Muscle; BALF: Bronchoalveolar Lavage Fluid; DP_1: Prostaglandin D_2 Receptor 1; DP_2: Prostaglandin D_2 Receptor 2; FEV_1: Forced Expiratory Volume in One Second; GINA: Global Initiative for Asthma; ICS: Inhaled Corticosteroid; ILC2: Type 2 Innate Lymphoid Cells; LABA: Long-Acting β_2-Agonist; LAMA: Long-Acting Muscarinic Antagonist; LTRA: Leukotriene Receptor Antagonist; PGD_2: Prostaglandin D_2; QTcF: QT Fridericia Correction Formula; $tFEV_1$: Trough Forced Expiratory Volume in One Second; Th2: T Helper Type 2

Introduction

The prostaglandin D_2 receptor 2 (DP_2) pathway is a target of significant interest for the treatment of asthma. Fevipiprant is an oral, non-steroidal, highly selective, reversible and competitive DP_2 receptor antagonist with potent inhibitory effects on human eosinophils, and Th2 cells *in vitro* [1], currently in Phase III of clinical development. Fevipiprant is expected to provide benefit in asthma by preventing the binding of prostaglandin D_2 (PGD_2) to prostaglandin D_2 receptor 2 (DP_2) receptors on key cells and tissues involved in the inflammatory cascade [2]. Binding of fevipiprant to the DP_2 receptor prevents pro-inflammatory functional effects on effector cells [3]. *In vitro*, fevipiprant reduces IL-4, IL-5, and IL-13 cytokine release from Th2 cells [1,4] and ILC2 [5], inhibits eosinophil migration towards mast cells [6] and prevents eosinophil activation [4].

Here we describe the protocol for the fevipiprant pivotal Phase III LUSTER-1 and LUSTER-2 studies.

The DP_2 Receptor Pathway

Prostaglandins are key pro-inflammatory mediators. PGD_2 is released through both allergen-dependent (acquired) and non-allergen-dependent (innate) immune responses [7,8]. Early studies in patients with asthma showed that PGD_2 is a major mediator found in bronchoalveolar lavage fluid (BALF) [9-11] and is released after segmental allergen challenge into the airways of patients with asthma.

PGD_2 binds to and activates two diverse receptors, PGD_2 receptor 1 (DP_1) and DP_2 [12]. The DP_1 receptor mediates the vascular effects of PGD_2 and has anti-inflammatory properties in some tissues [13,14]. The DP_2 receptor, a G-protein-coupled receptor, is a principal regulator of the inflammatory cascade with a key role in the pathophysiology of asthma [15]. The DP_2 receptor pathway is stimulated by allergic and non-allergic triggers and therefore is involved in both the allergen-dependent and -independent immune responses [5]. The DP_2 receptor is expressed on several cells involved in the inflammatory cascade, including T helper type 2 cells (Th2), eosinophils, type 2 innate lymphoid cells (ILC2), monocytes and basophils, (Figure 1) [16,17]. Activation of this receptor stimulates type 2 cytokine (IL-4, IL-5, and IL-13) release from ILC2 [5] and Th2 cells [18,19]. Furthermore, the DP_2 receptor is expressed on airway epithelial cells, where it is involved in their migration and differentiation [20], and on the cell surface of airway smooth muscle (ASM) cells. DP_2 receptor antagonism reduces the filamentous actin (microfilament) content and migration of ASM cells, thereby contributing to reduced smooth muscle mass in people with asthma [21].

The DP_2 receptor pathway magnifies the effect of the inflammatory cascade, suggesting that in the absence of the DP_2 receptor pathway, there would be reduced inflammation. Evidence for this comes from *in vitro* studies of several pro-inflammatory cells which showed: amplification of cytokine release from Th2 cells [22]; a synergistic effect on cytokine production from ILC2 in response to IL-25 and IL-33 stimuli [5]; an additive effect on ILC2 migration [23], and activation of eosinophils measured by shape change [24]. Based on the evidence, the DP_2 receptor represents an appropriate therapeutic target in asthma. In BALF studies, both asthma severity and incidence of exacerbations were correlated with up-regulation of the PGD_2/DP_2 receptor pathway, which may imply higher potential therapeutic benefit of DP_2 receptor antagonism in more severe patients [9-11,25].

Fevipiprant 'Proof of Concept' Study

A double-blind, randomized, placebo-controlled, 28-day, 'proof-of-concept' study of fevipiprant 500 mg once daily in 170 patients showed that, while there was no statistically significant difference between fevipiprant and placebo for trough forced expiratory volume in one second ($tFEV_1$) in the total study population, patients with a baseline $tFEV_1$ <80% showed a numerical difference in favor of fevipiprant, and those with FEV_1 <70% of predicted at baseline showed a significant treatment difference in $tFEV_1$ from placebo of 207 mL (90% CI: 96,–319; p=0.002). Patients in this subgroup also had a significant

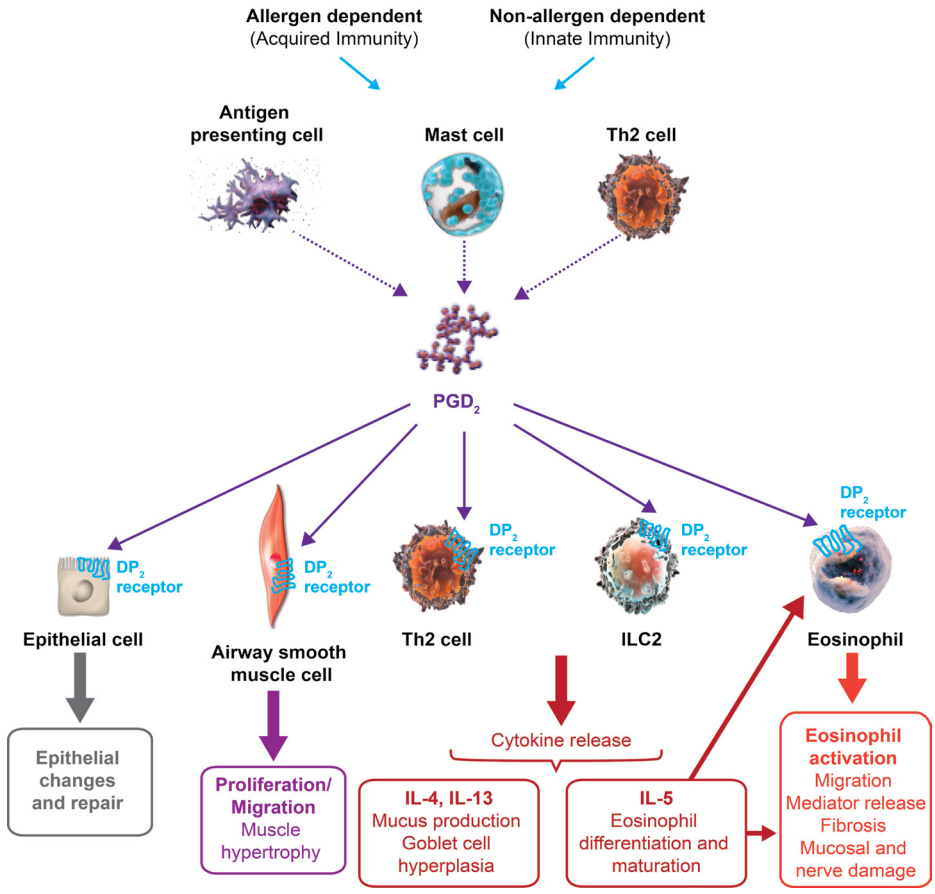

Figure 1: The DP_2 receptor pathway and effect of fevipiprant on the DP_2 receptor pathway.
The DP_2 receptor mediates the inflammatory response through the binding of PGD_2 [5,17]. PGD_2 is released in large quantities from antigen presenting cells [39], mast cells [40], and to a lesser degree Th2 cells [41] through acquired (allergen-dependent) and innate (non-allergen-dependent) immune responses [7]. The DP_2 receptor is expressed on effector cells involved in the inflammatory process in asthma, including Th2 cells [42], eosinophils [43], ILC2s [44] and on the cell surface of epithelial [20] and ASM cells [21] with subsequent downstream effects. Fevipiprant acts by preventing the binding of PGD_2 to DP_2 receptors on these key cells, thereby reducing the inflammatory response, promoting epithelial repair and reducing ASM mass [3].

improvement in Asthma Control Questionnaire (ACQ)-7 with a treatment difference of –0.41 (90% CI: –0.69, –0.13; p=0.009) for fevipiprant compared with placebo [2]. This indicated a relationship between baseline pulmonary function reduction and efficacy of fevipiprant, with lower lung function correlating with greater drug effects, which could potentially be related to the increasing importance of DP_2 receptor antagonism in patients with more severe disease. In this study, most adverse events (AEs) were mild or moderate and were balanced between the drug and placebo groups with no serious AEs reported.

Fevipiprant Dose-Response Study

The dose-response of fevipiprant was investigated in a 12-week double-blind, randomized, placebo-controlled study of 1058 patients with allergic asthma inadequately controlled by low-dose inhaled corticosteroid (ICS) therapy [26]. Pre-dose FEV_1, the primary endpoint, increased significantly in patients treated with fevipiprant plus low-dose budesonide, compared with placebo plus low-dose budesonide, with a maximum model-averaged difference of 0.112 L (95% CI: 0.004, 0.175; p=0.0035). The greatest differences from placebo were observed with the 75 mg dose administered twice daily (+0.179 L, 95%: CI 0.052, 0.307; p=0.0059) and with 150 mg fevipiprant administered once daily (+0.164 L, 95% CI: 0.044, 0.285; p=0.0075). AEs in this study were of mild or moderate severity overall and were distributed similarly across doses and treatments.

Fevipiprant Sputum Eosinophils Study

Sputum eosinophil count is a biomarker associated with asthma exacerbations [27]. A third Phase II randomized, double-blind, parallel-group, placebo-controlled, single-center study determined the effect of fevipiprant 225 mg administered twice daily on

sputum eosinophil count and other biomarkers in 61 adults with persistent, moderate-to-severe asthma [3]. Patients were treated with ICS or ICS plus a long-acting β_2-agonist (LABA) at the time of the study, had sputum eosinophil counts of ≥ 2% at screening and either a score of ≥ 1.5 on the ACQ-7 at randomization or at least one severe exacerbation in the previous 12 months [3]. After 12 weeks of treatment, there was a 3.5-fold greater reduction in sputum eosinophils in the fevipiprant group compared with the placebo group (p=0.0014) [3]. This reduction in sputum eosinophils (72%) is in the same range as that observed with the anti-IL-5 monoclonal antibodies, mepolizumab (57%) [28] and benralizumab (70%) [29]. The blood eosinophil count did not change after treatment with fevipiprant.

In a bronchoscopy sub-study of 26 patients, the ratio of change in bronchial submucosal eosinophil numbers in the fevipiprant group to the change in the placebo group was 0.4 (95% CI: 0.2, 1.0; p=0.04) [3]. In patients treated with fevipiprant, the proportion of intact epithelium in the bronchial biopsies was increased with fevipiprant, and decreased with placebo, a difference of 27.8% (95% CI: 2.9, 52.7; p=0.03). The proportion of denuded epithelium was 26.6% lower in the fevipiprant group, compared with the placebo group (p=0.0062) at the end of the study [3]. Furthermore, in patients treated with fevipiprant, ASM mass was reduced by (mean ± SEM) 13 ± 5%, compared with an increase of 4 ± 5% with placebo (p=0.034) [30]; to our knowledge, this is the first time that any drug therapy has shown an effect on ASM mass. These data suggest that fevipiprant may influence airway healing by having direct effects on the airway epithelium, associated with a reduction of smooth muscle mass [3,30].

In a prespecified subgroup of patients with symptomatic asthma (ACQ-7 ≥ 1.5 at baseline; n=40), there was a clinically and statistically significant difference of –0.56 points (95% CI: –1.12–0.01) between those treated with fevipiprant and placebo at 12 weeks (p=0.046) [3]. Fevipiprant also showed a clinically significant difference between the fevipiprant and placebo groups of 0.59 points in the standardised Asthma Quality of Life Questionnaire (AQLQ[S]; (95% CI: 0.16, 1.03; p=0.008). Furthermore, there was a significant difference in post-bronchodilator FEV_1 between the fevipiprant group and placebo group of 0.16 L (95% CI: 0.03, 0.30; p=0.021). In this study, AEs were balanced between treatment groups and there were no deaths or severe AEs.

The Rationale for LUSTER-1 and -2 Studies

High sputum eosinophil counts are a recognized predictor of exacerbations and poor control in asthma [31]. Previous studies have shown that some asthma treatments that reduce sputum eosinophilia also reduce asthma exacerbations [28,32,33]. For fevipiprant, the Phase II sputum eosinophil study established that there was a 3.5-fold greater reduction in sputum eosinophil numbers in patients treated with fevipiprant compared with those treated with placebo [3]. Furthermore, fevipiprant was efficacious across key clinical endpoints, including lung function, symptom control and quality of life, and showed a favorable safety and tolerability profile in all three Phase II studies [2,3,26]. Thus, the LUSTER-1 and -2 studies were developed to test the hypothesis that fevipiprant would reduce asthma exacerbations in patients with severe asthma, as well as specifically in those with severe asthma and elevated blood eosinophil counts. Peripheral blood eosinophil counts are used to classify asthma or to predict treatment response.

LUSTER-1 and -2 Objectives and Study Design

The LUSTER-1 (ClinicalTrials.gov number, NCT02555683) and LUSTER-2 (ClinicalTrials.gov number, NCT02563067) studies are replicate Phase III studies. These are 52-week, multicenter, double-blind, placebo-controlled, parallel-group studies of fevipiprant 150 mg and 450 mg once daily in patients aged ≥ 12 years with inadequately controlled severe asthma receiving Global Initiative for Asthma (GINA) steps 4 and 5 [34] standard-of-care asthma therapy. The aim of the studies is to determine the efficacy, safety and tolerability of fevipiprant (150 mg and 450 mg once daily) added to standard-of-care asthma therapy, in 846 patients with symptomatic, severe asthma [35].

The studies included a screening period of up to two weeks to assess eligibility, a run-in period of approximately two weeks to collect baseline data for efficacy variables and compliance with an Electronic Peak Flow/eDiary device, a treatment period of 52 weeks; a follow-up period of 4 weeks, investigational and drug-free, following the last dose of study drug (Figure 2). If a patient experienced an asthma exacerbation during the run-in period, the run-in period was extended to six weeks to permit the resolution of the exacerbation before randomization.

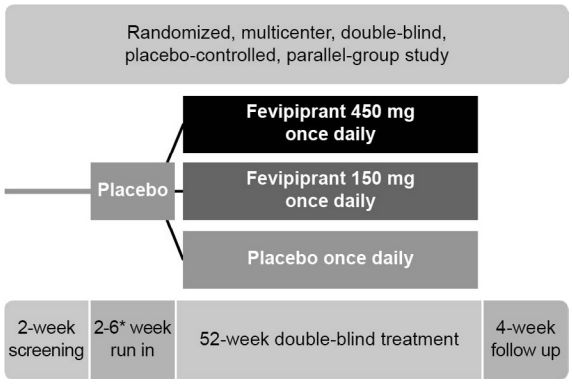

Figure 2: LUSTER-1 and -2 study design.
Patients ≥ 12 years with inadequately controlled severe asthma receiving Global Initiative for Asthma (GINA) steps 4 and 5 standard-of-care asthma therapy were randomized (1:1:1) to receive either fevipiprant 450 mg, fevipiprant 150 mg or placebo once daily. The study includes a two-week screening period, a run-in period of 2-6 weeks to collect baseline data for efficacy variables and to measure compliance with an Electronic Peak Flow/eDiary device, a 52-week treatment period and a 4-week follow-up period after the last dose of study drug.
*Flexible 2-6 week run-in period to accommodate patients with asthma exacerbations.

Regulatory and Ethical Compliance

The LUSTER-1 and LUSTER-2 studies were designed, are being implemented and will be reported in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Study Population

The patient population of both studies consists of approximately 846 males and females aged ≥ 12 years with inadequately controlled severe asthma. Recruitment was stratified so that two-thirds of randomized patients had a blood eosinophil count ≥ 250 cells/μL and one-third a blood eosinophil count <250 cells/μL (inclusion in one of the groups was stopped once the quota was reached).

Key inclusion criteria

Patients were males and females aged ≥ 12 years who provided written informed consent and assent (if applicable) within 14 days, before or at screening before any assessment was carried out. Patients had a diagnosis of asthma [34] of at least 24 months before screening and had been treated with one of the following, with or without maintenance oral corticosteroids for at least 3 months before screening (doses must have been stable for at least 4 weeks before screening) with medium or high doses of ICS: ICS + LABA; ICS + leukotriene receptor antagonist (LTRA); ICS + theophylline; ICS + long-acting muscarinic antagonist (LAMA); ICS + LABA + LAMA; ICS + LABA + LTRA; ICS + LABA + theophylline.

Patients had a clinical diagnosis of asthma supported by at least one of the following: an increase of ≥ 12% and ≥ 200 mL in FEV_1 approximately 10 to 15 minutes after administration of 400 μg of salbutamol/albuterol (or equivalent dose) before randomization. If reversibility was not shown at screening, documented evidence either of reversibility in the previous two years, [36] or a positive bronchial responsiveness test within the two years before the run-in period was considered evidence for an asthma diagnosis. Patients aged ≥ 18 years had FEV_1 of ≤ 80% of predicted, after withholding bronchodilators both at screening and at the beginning of the run-in period. Patients aged 12 to <18 years, had FEV_1 of ≤ 90% of predicted after withholding bronchodilators both at screening and at the beginning of the run-in period. Patients demonstrated inadequate control of asthma based on an ACQ score ≥ 1.5 at screening and a history of two or more asthma exacerbations within the 12 months before screening that required either treatment with systemic corticosteroids or hospitalization.

Key exclusion criteria

Patients were excluded for use of other investigational drugs within five half-lives of enrollment, or within 30 days, whichever was longer, or for participation in another trial of fevipiprant, as were those on >20 mg simvastatin, >40 mg atorvastatin, >40 mg pravastatin, or >2 mg pitavastatin daily or any statin therapy with a creatine kinase level >2 X upper limit of normal at screening. Patients with a resting QT interval measure (Fridericia Correction Formula; QTcF) ≥ 450 msec (male) or ≥ 460 msec (female) at screening or randomization were excluded, as well as those with a history of malignancy of any organ with the exception of local basal cell carcinoma of the skin, and those with other serious comorbidities. Pregnant or lactating women were excluded, as were women of child-bearing potential unless they were using effective means of contraception during dosing of study treatment.

Doses

Two doses are included in the LUSTER studies: 150 mg and 450 mg once daily. Fevipiprant's half-life of approximately 20 h supports once-daily dosing [37]. The 450 mg once-daily dose was included because at 450 mg once daily >98% DP_2 receptor occupancy is expected for the entire dosing interval in a 'typical patient' at steady state. Furthermore, a 500 mg daily dose was effective in improving pre-dose FEV_1 in patients with $tFEV_1$ <70% of predicted at baseline in the 'proof of concept' study [2]; a 450 mg dose was also efficacious on the endpoint of pre-dose FEV_1 in the dose-finding study [26]. Finally, in the sputum eosinophil study, fevipiprant 450 mg daily (225 mg twice-daily dose) caused a significant reduction in sputum eosinophils in patients with severe eosinophilic asthma [3]. The 150 mg once-daily dose was included because the dose-finding study identified this dose as the lowest dose with "maximal efficacy" on the endpoint of pre-dose FEV_1 in patients with moderate-to-severe asthma [26].

Outcome Measures

Efficacy endpoints

The primary endpoint of both studies is the rate of moderate-to-severe asthma exacerbations over the 52-week treatment period in patients with severe asthma and elevated blood eosinophil counts (≥ 250 cells/μL) and in the total study population. Severe asthma exacerbation is defined as treatment with 'rescue' systemic corticosteroids for ≥ 3 days and hospitalization, or treatment with 'rescue' systemic corticosteroids for ≥ 3 days and an emergency department visit (>24 hours); or death due to asthma. Moderate asthma exacerbation is defined as treatment with 'rescue' systemic corticosteroids for ≥ 3 days, either as an outpatient or in an emergency department visit of ≤ 24 hours. The secondary endpoints are: change in asthma quality of life (measured by the AQLQ+12); asthma control (measured by the ACQ-5), and FEV_1 (average of the two pre-dose FEV_1 assessments at the end of the 52-week treatment period.

Safety/tolerability

Safety of fevipiprant in terms of AEs, electrocardiograms, vital signs, and laboratory tests will also be assessed.

Data analysis

The primary variable (number of moderate-to-severe asthma exacerbations experienced by each patient per patient-year of follow-up) will be analyzed using a negative binomial regression model with the natural logarithm of the duration of follow-up as an offset variable, treatment group, randomization strata and region as fixed class effects, as well as the natural logarithm of the number of asthma exacerbations in the 12 months before screening and the baseline pre-dose FEV_1 as continuous linear covariates. Missing data will be imputed assuming no further treatment effect versus placebo for patients on fevipiprant that discontinue treatment and are lost to follow-up because of (or after treatment discontinuation because of) lack of efficacy, AEs or death. In contrast, a continued treatment effect for patients on fevipiprant lost to follow-up for reasons likely to be unrelated to study treatment will be imputed. The superiority of fevipiprant over placebo will be considered confirmed if at least one of four primary null hypotheses regarding the exacerbation rates is rejected in favor of the respective two-sided superiority alternative hypothesis.

A closed testing procedure will be used to control the family-wise type I error rate at the two-sided 5% level across the primary and key secondary null hypotheses. In this closed testing procedure the primary null hypotheses about exacerbations for each dose and population act as gatekeepers for the key secondary null hypotheses for the same dose and the total sample size of 846 patients (188 patients per arm in the subpopulation with blood eosinophils ≥ 250 cells/μL and 282 patients per arm in the overall population) provides greater than 80% power for demonstrating the superiority of each dose of fevipiprant, compared with placebo, both in the subpopulation with blood eosinophils ≥ 250 cells/μL and in the overall population.

The key secondary variables of this trial are AQLQ+12, ACQ-5 and pre-dose FEV_1 assessments at the end of the 52-week treatment period. Each variable will be analyzed using an analysis of covariance. Before analysis, missing values for key secondary variables will be imputed in a similar manner to the primary variable.

Discussion

Fevipiprant, an oral DP_2 receptor antagonist, was developed to address the unmet needs in patients whose asthma is not controlled under current guidelines (GINA Step 3, 4, or 5) [38] as well as those for whom these therapies are unsuitable, or result in side effects. Preventing asthma exacerbations and hospitalizations are important therapeutic goals

for asthma management according to the GINA guidelines [38]. The LUSTER studies described will determine whether once-daily, orally administered fevipiprant, added to standard-of-care therapy, reduces exacerbations and improves symptoms in patients with symptomatic severe asthma and investigate whether this therapy is well tolerated over the 1-year treatment period [35].

The Phase III program of fevipiprant is composed of three other studies besides LUSTER-1 and LUSTER-2: ZEAL-1/ZEAL-2 (ClinicalTrials.gov number, NCT03215758; ClinicalTrials.gov number, NCT03226392); and SPIRIT (ClinicalTrials.gov number: NCT03052517), a safety study. ZEAL-1 and ZEAL-2 are randomized, double-blind, parallel-group, placebo-controlled, 12-week studies of fevipiprant in 650 patients aged 12 years or older with moderate-to-severe asthma (GINA steps 3 and 4) [34]. The primary endpoint of both studies is change from baseline in pre-dose FEV_1 at the end of the first 12-week treatment period. SPIRIT is a randomized, placebo-controlled multicenter parallel group study over an initial 52-week treatment period, with an optional 104-week follow-on treatment period in patients aged 12 years and older who are inadequately controlled on treatment at GINA steps 3, 4 and 5 [34]. The aim of SPIRIT is to provide long-term safety data for fevipiprant 150 mg once daily and 450 mg once daily, compared with placebo, when added to the GINA steps 3, 4, and 5 standard-of-care asthma therapy [34], in patients with moderate-to-severe asthma.

The goal of the Phase III program is to provide evidence for the efficacy of once-daily fevipiprant for the improvement of asthma control based on a reduction in the rate of asthma exacerbations and improvement in lung function and other key endpoints, including asthma quality of life, as well as long-term safety data. The LUSTER-1 and LUSTER-2 studies are the most advanced of the five studies, and the expectation is that these studies will provide a further understanding of the role that that fevipiprant may play in improving exacerbation rates in patients with severe asthma.

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Competing and Conflicting Interests

CEB has received grants and consultancy funding from Novartis paid to his Institution.

ERB has undertaken clinical trials through his employer, Wake Forest School of Medicine and University of Arizona, for AstraZeneca, MedImmune, Boehringer Ingelheim, Genentech, Johnson and Johnson (Janssen), Novartis, Regeneron, and Sanofi Genzyme. ERB has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Glaxo Smith Kline, Novartis, Regeneron, and Sanofi Genzyme, outside the submitted work. VJE is a former employee of Novartis Pharma AG and holds shares in the company. CB is a full-time employee of Novartis Pharma AG. SF and PA are full-time employees of Novartis Pharmaceuticals Corporation. DL and BK are full-time employees of Novartis Pharmaceuticals Corporation and hold shares in the company.

Executive summary

The prostaglandin D_2 receptor 2 (DP_2) pathway has an important mechanistic role in the pathophysiology of asthma; specifically, the potential benefits of blockage of this pathway as a treatment for asthma are of considerable interest. The DP_2 receptor is expressed on cells involved in the inflammatory cascade, including T-helper type 2 (Th2) cells, eosinophils, type 2 innate lymphoid cells (ILC2), monocytes and basophils, as well as on airway epithelial and smooth muscle cells. Fevipiprant is an oral, highly selective DP_2 receptor antagonist that has shown potent inhibitory effects on human eosinophils and Th2 cells *in vitro*. In Phase II clinical trials of patients with asthma, fevipiprant showed improvements in lung function, asthma control and quality of life. Furthermore, fevipiprant showed a reduction in sputum eosinophils, a biomarker for asthma exacerbations, as well as an effect on the airway epithelium and airway smooth muscle mass in patients with moderate-to-severe persistent asthma. In Phase II studies, fevipiprant showed a favorable safety profile. LUSTER-1 and -2 are replicate Phase III studies whose aim is to determine the efficacy, safety and tolerability of fevipiprant (150 mg and 450 mg once daily) added to standard-of-care asthma treatment in patients with symptomatic severe asthma over a one-year period.

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