



Research Paper

Efficacy and safety of fevipiprant in patients with uncontrolled asthma: Two replicate, phase 3, randomised, double-blind, placebo-controlled trials (ZEAL-1 and ZEAL-2)

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ABSTRACT

Background: These studies assessed the efficacy and safety of fevipiprant, an oral antagonist of the prostaglandin D₂ (PGD₂) receptor (DP₂), compared with placebo when added to standard-of-care (SoC) asthma therapy in patients with uncontrolled asthma.

Methods: ZEAL-1 (NCT03215758) and ZEAL-2 (NCT03226392) are two replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies in which fevipiprant 150 mg once daily (o.d.) or placebo was added to SoC asthma therapy in patients aged ≥12 years with uncontrolled asthma. Primary endpoint: change from baseline in pre-dose forced expiratory volume in 1 s (FEV₁) after 12 weeks' treatment. Key secondary endpoints: daytime asthma symptom score, short-acting β₂-agonist (SABA) use and Asthma Quality-of-Life Questionnaire (AQLQ+12) score after 12-weeks treatment.

Findings: 662 patients in ZEAL-1 and 685 patients in ZEAL-2 completed the treatment period. In ZEAL-1, the least squares (LS) mean change from baseline in pre-dose FEV₁ was 112 mL in fevipiprant vs 71 mL in placebo group (difference [Δ]: 41 mL; 95% CI: -6, 88; adjusted p-value 0.088). In ZEAL-2, the LS mean change in pre-dose FEV₁ was 126 mL and 157 mL in the fevipiprant and placebo groups, respectively (Δ: -31 mL; 95% CI: -80, 18; adjusted p-value 0.214). For both studies, there were no statistically significant differences in the key secondary objectives between the treatment groups.

Interpretation: The ZEAL studies did not demonstrate significant improvement in lung function or other clinical outcomes. These results suggest that DP₂ receptor inhibition with fevipiprant is not effective in the studied patient population.

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1. Introduction

Asthma is a chronic inflammatory disease of the airways associated with airway hyper-responsiveness and structural remodelling, and is characterised by respiratory symptoms such as wheezing,

breathlessness, chest tightness and cough [1]. The goals of asthma therapy are to attain asthma control and to reduce the risk of asthma worsening [2]. For patients who remain uncontrolled on low-dose inhaled corticosteroid (ICS) therapy (step 2), the Global Initiative for Asthma (GINA) recommends progression to step 3: a combination of low-dose ICS plus long-acting β₂-agonist (LABA), medium-/high-dose ICS, or low-dose ICS plus leukotriene receptor antagonist (LTRA). Asthma patients who are uncontrolled on low-dose ICS plus LABA (step 3) may benefit from increasing to medium-/high-dose ICS

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Research in context

Evidence before this study

In asthma, stimulation of the prostaglandin D₂ (PGD₂) receptor 2 (DP₂) pathway by PGD₂ mediates the activation and migration of key inflammatory cells such as Th2 cells, ILC2s, basophils, and eosinophils, as well as stimulating the release of Type 2 cytokines from these cells. Fevipiprant (QAW039), an oral, non-steroidal, highly selective, reversible antagonist of the DP₂ receptor showed promise in three phase 2 studies. The ZEAL-1 and -2 studies (phase 3 studies) reported here investigated the effect of fevipiprant on lung function (pre-dose FEV₁) in patients with uncontrolled asthma.

Added value of this study

ZEAL-1 and -2 are two replicate, randomised, multicentre, double-blind, placebo-controlled, parallel-group, phase 3 studies of fevipiprant 150 mg once daily added to standard-of-care asthma therapy in patients with uncontrolled asthma. These studies tested the premise that the improvement in lung function demonstrated in the phase 2 programme would be observed as improvement in pre-dose FEV₁ in patients participating in these phase 3 trials. The ZEAL-1 and ZEAL-2 studies did not demonstrate significantly improved lung function or other clinical outcomes.

Implications of all the available evidence

The ZEAL-1 and ZEAL-2 studies demonstrated that fevipiprant did not improve lung function in this patient population with uncontrolled asthma. Fevipiprant demonstrated a well-balanced safety profile compared with placebo. These results suggest that DP₂ receptor inhibition with fevipiprant is not effective in the studied patient population.

uncontrolled asthma with respect to change from baseline in lung function (FEV₁) after 12 weeks of treatment.

2. Methods

2.1. Study design

ZEAL-1 (NCT03215758) and ZEAL-2 (NCT03226392) were replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies in which fevipiprant or placebo was added to SoC asthma therapy (Fig. 1, Supplementary Appendix). Both were outpatient studies; ZEAL-1 took place in 9 countries at 88 sites; ZEAL-2 took place in 15 countries at 117 sites (see Supplementary Appendix Section 1, Table 1 for list of countries).

Patients were randomised (1:1) to receive either fevipiprant 150 mg or placebo once daily in the morning, plus SoC asthma therapy. Patients received SoC asthma therapy (either medium- or high-dose ICS, low- or medium-dose ICS plus LABA, or low-dose ICS plus LTRA) throughout the study. The study design included: (i) a screening period of up to 2 weeks; (ii) a placebo run-in period of 1 week to collect baseline data; (iii) a treatment period of 12 weeks; and (iv) a follow-up period of 4 weeks after the last dose of study drug (Fig. 1, Supplementary Appendix). The study protocol (Supplementary Appendix, Section 4), amendments, informed consent forms, and other relevant documents were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre. The studies were designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles described in the Declaration of Helsinki. Informed consent (and assent for adolescents) was obtained from each patient or legal guardian in writing before or at screening, and before any study specific procedure was performed. An independent Data Monitoring Committee (DMC) conducted monitoring of patient safety data for both studies.

2.2. Patients

Eligible patients were those with prior diagnosis of asthma (GINA 2016 [11]) for at least 6 months, treatment with medium- or high-dose ICS, low-dose ICS plus either LABA or LTRA, or medium-dose ICS plus LABA for at least 3 months prior to first (screening) visit and the doses had to be stable for at least 4 weeks prior to first visit, and pre-bronchodilator FEV₁ ≤ 85% of predicted normal for patients ≥ 18 years (or ≤ 90% of predicted normal for patients 12 to < 18 years). Patients demonstrated reversible airway obstruction defined as an increase of ≥ 12% and ≥ 200 mL in FEV₁ approximately 10–15 min after administration of 400 µg of salbutamol/albuterol (or equivalent), patients also had an ACQ score ≥ 1.5 at the end of the run-in period. Key exclusion criteria were a history of conditions other than asthma or allergic rhinitis that could result in elevated eosinophils (eg, hypereosinophilic syndromes, Churg-Strauss Syndrome, eosinophilic esophagitis). Full inclusion and exclusion criteria are reported in the Supplementary Appendix (Section 2.1).

2.3. Randomisation and masking

Patients were randomised via Interactive Response Technology (IRT) to one of the two treatment arms (fevipiprant 150 mg or placebo once daily) in a 1:1 ratio within each of the randomisation strata: patient age (< 18 or ≥ 18 years), and use or non-use of a second asthma controller medication. Further details on randomisation may be found in the Supplementary Appendix (Section 2.2). Patients, investigator staff, those performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomisation until database lock, as follows: firstly, randomisation data were kept confidential until the time of unblinding and were

plus LABA, high-dose ICS plus LTRA, or the addition of tiotropium (step 4) [2]. Despite current guidelines and available treatments, asthma control remains suboptimal in a large percentage of patients and additional oral add-on therapies are needed [3,4].

Fevipiprant (QAW039) is an oral, highly selective, competitive, reversible antagonist of the prostaglandin D₂ (PGD₂) receptor. PGD₂ is a major prostanoid inflammatory mediator identified in asthma. By binding to the DP₂ receptor, fevipiprant inhibits the migration and activation of eosinophils, basophils, ILC-2 (type 2 innate lymphoid cells) and T lymphocytes into the airway tissues and blocks the PGD₂-driven release of Th2 cytokines [5,6]. In a phase 2 'proof-of-concept' study in a subgroup of patients with reduced lung function at baseline, treatment with fevipiprant 500 mg once daily showed significant improvements in pre-dose trough FEV₁ and Asthma Control Questionnaire (ACQ) scores compared with placebo [7]. A phase 2 dose-finding study showed significant differences in FEV₁ with fevipiprant compared with placebo, with the largest difference being observed with fevipiprant 150 mg total daily dose [8]. In a third phase 2 study, patients treated with fevipiprant 225 twice daily showed a 3.5 times greater reduction in sputum eosinophils compared with placebo [9,10].

The objective of these two replicate phase 3, randomised, controlled trials (ZEAL-1 and ZEAL-2) was to assess the efficacy and safety of fevipiprant 150 mg once daily (dose based on results from the dose-ranging study of fevipiprant [8]), when added to standard-of-care (SoC) asthma therapy (GINA steps 3 and 4) compared with placebo, in adults and adolescents (aged ≥ 12 years) with

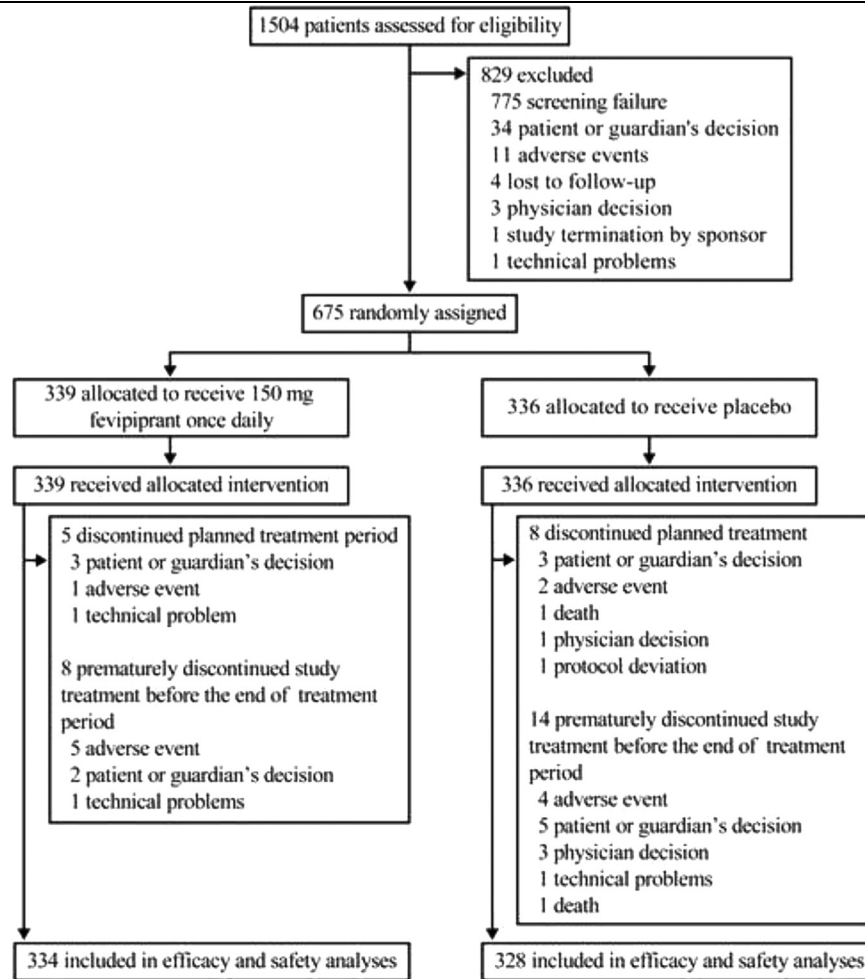


Fig. 1. Patient flow through both studies (A) ZEAL-1 (B) ZEAL-2

*ZEAL-2 Patients did not receive the allocated intervention (misrandomisation or patient not given drug).

not accessible to anyone involved in the study apart from the external DMC; secondly, the identity of the treatment was concealed by the use of placebo with identical packaging, labelling, schedule of administration, appearance, taste and odour to fevipirant Supplementary Appendix (Sections 2.3 and 2.4).

2.4. Procedures

Asthma patients who were already receiving ICS or ICS with one additional asthma controller medication were the target population for these studies. Patients continued the SoC asthma medication that they were receiving prior to screening throughout the study. Patients took their investigational treatment (fevipirant or placebo) once daily in the morning regardless of timing of food intake. During the run-in period, all patients received placebo for approximately 1 week and were instructed on how to take the drug. During the treatment period, each randomised patient entered the 12-week treatment period where they received one of the following two treatments: (1) fevipirant 150 mg once daily given orally or (2) matching placebo once daily given orally. The dosing was selected based on the dose-ranging study for fevipirant, which included FEV₁ as the primary endpoint [8]. The study drug was dispensed in kits at each site visit during the treatment period and covered the treatment period between patient visits and also allowed for late visits and other unforeseen events. All dosages prescribed and dispensed during the study were recorded on the dosage administration record CRF. All

kits of the study drug assigned by IRT were recorded/databased in the IRT system (Supplementary Appendix Sections 2.5 and 2.6).

2.5. Outcomes

The primary efficacy endpoint was the change from baseline in pre-dose pre-bronchodilator FEV₁ at the end of the 12-week treatment period with fevipirant 150 mg once daily compared with placebo, both in addition to SoC asthma therapy.

The secondary endpoints were: change from baseline in daytime asthma symptom score and total daily short-acting β -agonist (SABA) use over 12 weeks of treatment; and change from baseline in AQLQ +12 score at week 12.

Exploratory endpoints included: (i) change from baseline in ACQ at week 12; (ii) proportion of patients with a change from baseline (improvement) in ACQ-5 score of at least -0.5 and -1.0 at week 12; (iii) change from baseline in pre-dose FEV₁% predicted at week 12; (iv) change from baseline in Patient Global Impression of Change (PGIC) at week 12; (v) change from baseline in morning and evening peak expiratory flow (PEF) at week 12; (vi) change from baseline in night-time asthma symptom score over 12 weeks of treatment; (vii) rate of asthma exacerbations over 12 weeks of treatment; and (viii) healthcare utilisation over 12 weeks of treatment.

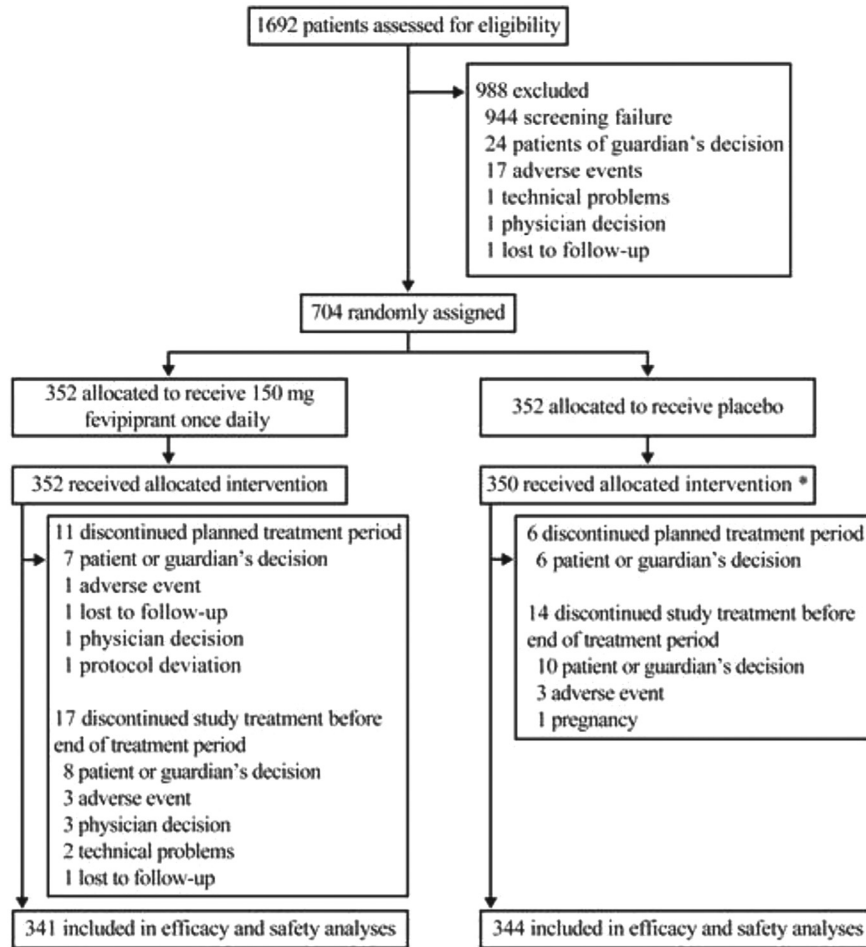


Fig. 1. Continued.

2.6. Safety

The tolerability of the two treatment arms was compared with respect to adverse events (AEs), electrocardiogram (ECGs), vital signs, and laboratory tests.

2.7. Statistical analysis

For each ZEAL study, it was calculated that a sample size of 650 patients –325 patients per arm–would provide approximately 90% power for demonstrating the superiority of fevipiprant 150 mg once daily compared with placebo, assuming a difference of 112 mL in pre-dose FEV₁ at week 12 between fevipiprant and placebo groups. Depending on the rejection of primary and other secondary null hypotheses, the study sample sizes were also expected to provide at least 74 or 83% power to detect between-group differences in the key secondary endpoints (mean change from baseline of –0.26 in daytime asthma symptoms and mean change from baseline of –1.34 point in the number of daily SABA puffs over the 12 weeks of treatment, and improvements of 0.5 points in AQLQ+12 at Week 12). Efficacy analyses included all patients who underwent randomisation and received at least one dose of study medication; data were analysed according to the assigned treatment. The change from baseline in pre-dose FEV₁ at week 12 was analysed using an analyses of covariance (ANCOVA) model with factors for treatment group, randomisation strata [age (< 18 vs ≥ 18 years), use or non-use of a second asthma controller medication at study entry, and region], as well

as the baseline daytime asthma symptom score, baseline total daily SABA use and baseline pre-dose FEV₁ as continuous linear covariates. The change from baseline in daytime asthma symptom score and total daily use of SABA over the 12 weeks of treatment were analysed using an ANCOVA model with the same factors as the primary endpoint. The change from baseline in AQLQ+12 at Week 12 was analysed using an ANCOVA model with factors described above and baseline AQLQ+12 as continuous linear covariates. Patients who discontinued randomised treatment were encouraged to return to the clinic for all remaining visits. For patients who discontinued randomised treatment and remained in the trial, measurements after treatment discontinuation were included in the analysis. Where patients discontinued the trial, missing data for the primary and key secondary endpoints were imputed using a multiple imputation framework based on the jump to reference imputation approach [12]. In each study, in order to control the family-wise type I error at a two-sided 5% significance level for the primary and key secondary endpoints, a closed testing procedure using a graphical method of Bretz et al. 2009 [13] was applied. Endpoints included within the closed testing procedure are presented with 95% confidence intervals and adjusted p-values. The other efficacy endpoints that were not listed in the closed testing procedure were not controlled for multiplicity and are also presented with 95% confidence intervals. Nominal P-values for these endpoints are reported but have not been adjusted for multiple testing and should be considered descriptive only. Full statistical methods are summarised in the statistical analysis plan (Supplementary Appendix, Section 2.7).

Table 1
Patients' baseline demographics and characteristics (full analysis set).

Characteristic	ZEAL-1		ZEAL-2	
	Fevipirant 150 mg N = 339	Placebo N = 336	Fevipirant 150 mg N = 352	Placebo N = 350
Age, years	48.1 ± 15.15	47.7 ± 15.40	50.4 ± 14.87	50.2 ± 14.39
Sex, n (%)				
Male	122 (36.0)	120 (35.7)	136 (38.6)	132 (37.7)
Female	217 (64.0)	216 (64.3)	216 (61.4)	218 (62.3)
Age of onset of asthma, years	24.6 ± 17.95	23.8 ± 17.70	29.1 ± 19.32	29.9 ± 18.86
Duration of asthma, years	24.1 ± 15.83	24.4 ± 15.40	21.9 ± 16.06	20.8 ± 15.44
Atopic status ^a , n (%)				
Yes	222 (65.5)	236 (70.2)	242 (68.8)	223 (63.7)
No	116 (34.2)	98 (29.2)	110 (31.3)	126 (36.0)
Smoking status, n (%)				
Never smokers	264 (77.9)	268 (79.8)	303 (86.1)	292 (83.4)
Former smokers	75 (22.1)	68 (20.2)	49 (13.9)	58 (16.6)
ICS monotherapy, n (%)	37 (10.9)	30 (8.9)	47 (13.4)	41 (11.7)
ICS plus LABA	294 (86.7)	299 (89.0)	296 (84.1)	303 (86.6)
ICS plus LTRA	4 (1.2)	5 (1.5)	5 (1.4)	6 (1.7)
ICS dose				
Low	73 (21.5)	84 (25.0)	75 (21.3)	63 (18.0)
Medium	241 (71.1)	229 (68.2)	216 (61.4)	236 (67.4)
High	24 (7.1)	22 (6.5)	59 (16.8)	51 (14.6)
Missing	1 (0.3)	1 (0.3)	2 (0.6)	0
Pre-bronchodilator FEV ₁ , L	1.8 ± 0.59	1.9 ± 0.62	1.8 ± 0.63	1.8 ± 0.62
Pre-bronchodilator FEV ₁ , % predicted	59.4 ± 13.83	61.1 ± 13.14	59.9 ± 14.14	61.0 ± 13.88
FEV ₁ reversibility, %	28.6 ± 15.00	27.9 ± 17.21	30.9 ± 19.45	30.4 ± 18.73
Baseline daytime asthma symptom score	2.0 ± 0.84	2.0 ± 0.89	1.9 ± 0.78	2.0 ± 0.84
Baseline AQLQ+12 score	4.4 ± 0.98	4.3 ± 0.96	4.4 ± 0.87	4.4 ± 0.91
Baseline ACQ-5 score	2.6 ± 0.64	2.6 ± 0.68	2.5 ± 0.56	2.6 ± 0.57
Baseline SABA use (puffs/day)	3.14 ± 1.81	3.18 ± 2.0	3.01 ± 1.85	2.92 ± 1.71
Baseline night symptoms	0.80 ± 0.52	0.77 ± 0.57	0.71 ± 0.51	0.72 ± 0.49
Baseline blood eosinophils cells/μL	343.8 ± 280.4	352.2 ± 281.9	337.3 ± 284.5	331.3 ± 290.4
Screening blood eosinophil counts - n (%)				
Eos <250 cells/μL	148 (43.7)	141 (42.0)	161 (45.7)	170 (48.6)
Eos ≥ 250 cells/μL	182 (53.7)	190 (56.5)	174 (49.4)	172 (49.1)
Missing	9	5	17	8
Morning PEF (L/min)	304.89 ± 107.73	315.20 ± 107.98	296.48 ± 116.90	300.18 ± 112.60
Evening PEF (L/min)	315.08 ± 107.15	325.68 ± 108.95	307.10 ± 116.25	310.96 ± 115.83

^a For Specific IgE (ImmunoCap), the allergen panel was: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Cockroach (American/German/Oriental), Cat dander, Dog dander, *Alternaria alternata* (mould).

Data are presented as mean ± SD, unless specified otherwise

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality-of-Life Questionnaire; Eos, eosinophil; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; PEF, peak expiratory flow; SABA, short-acting β-agonists; SD, standard deviation.

2.8. Role of the funding source

The sponsor (Novartis) developed the protocol. Data were collected by the investigators and analysed by statisticians (DL, WW) from the sponsor. The first draft of the manuscript was prepared by medical writers at Novartis Business Services CONEXTS, with input from all the authors. All authors had full access to the data, provided contributions to the interpretation of the data, participated in review of the manuscript, provided edits, and approved the final version to be published. The corresponding author had the final responsibility for the decision to submit the manuscript for publication. All authors agree to be accountable for the accuracy and integrity of the work.

3. Results

3.1. Patients

Across both studies, a total of 1379 patients were randomised. For ZEAL-1, between November 2017 and July 2019, patients were

screened for eligibility and 675 patients from 9 countries at 88 sites worldwide were randomised, and for ZEAL-2, between October 2017 and August 2019, patients were screened for eligibility and 704 patients from 15 countries at 117 sites worldwide were randomised (listed in Table 1 of Section 1, Supplementary Appendix).

In ZEAL-1, a total of 1504 patients were screened and 829 were excluded (screening failure [*n* = 775], subject/guardian decision [*n* = 34], AEs [*n* = 11], lost to follow-up [*n* = 4], physician decision [*n* = 3], termination by sponsor [*n* = 1], and technical problems [*n* = 1]). Therefore, 675 patients were randomized and 662 patients (98.1%) completed the 12-week treatment period (Fig. 1).

In ZEAL-2, a total of 1692 patients were screened and 988 were excluded (screening failure [*n* = 944], subject/guardian decision [*n* = 24], AEs [*n* = 17], lost to follow-up [*n* = 1], physician decision [*n* = 1], and technical problems [*n* = 1]). Therefore, 704 patients were randomized and 685 patients (97.3%) completed the 12-week treatment period (Fig. 1).

For both studies, patients' baseline demographics and characteristics were balanced between the treatment groups. Nearly two-thirds of

patients were female, and the majority were Caucasian (82.2% for ZEAL-1 and 61.5% for ZEAL-2) (Table 1). In ZEAL-1, the mean age was 47.9 years, 4.4% of patients were adolescents and 13.6% were aged 65 years or older. In ZEAL-2, the mean age was 50.3 years, 1.9% were adolescents and 18.2% were aged 65 years or older. Baseline clinical characteristics were similar for patients with high eosinophils and the overall population in ZEAL-1 and ZEAL-2 studies. Use of asthma medication was comparable between the treatment groups and in line with the required background therapy as per the eligibility criteria (Table 1).

3.2. Primary endpoint

Neither study met the primary endpoint. The change in pre-dose FEV₁ from baseline to week 12 was not statistically significantly different between fevipiprant and placebo (Fig. 2). In ZEAL-1, the LS mean change from baseline in pre-dose FEV₁ was 112 mL in the fevipiprant group vs 71 mL in the placebo group (difference of 41 mL; 95% CI: -6, 88; adjusted p-value 0.088). In ZEAL-2, the LS mean change from baseline in pre-dose FEV₁ was 126 mL in the fevipiprant group and 157 mL in the placebo group (difference of -31 mL; 95% CI: -80, 18; adjusted p-value 0.214). There was no evidence in either study of a differential treatment effect in pre-defined subgroups based on age, sex, race, geographical region, use of second controller medication, FEV₁, or predicted FEV₁ (Fig. 2, Supplementary Appendix). In addition, there was little evidence of a differential treatment effect in post hoc analysis of additional sub-groups (subgroups based on exacerbation history, ICS dose at baseline, atopic status, screening blood eosinophil level, and degree of reversibility) (Fig. 3, Supplementary Appendix).

3.3. Secondary endpoints (daytime asthma symptoms, SABA use, and AQLQ+12)

For both ZEAL-1 and ZEAL-2, there were no statistically significant differences in mean daytime asthma symptom scores (Fig. 3A). The daytime asthma symptoms were scored on a 7-item scale generating at least 7 possible responses from 0 ("none of the time") to 6 ("most of the time"). In ZEAL-1, the LS mean change from baseline in mean day time asthma symptoms was -0.56 vs 0.51 for fevipiprant vs placebo (lower scores denote less severe symptoms), respectively, with a LS mean difference of -0.06 (95% CI: -0.16, 0.05; adjusted p-value 0.567) over the 12-week treatment period. In ZEAL-2 the LS mean change from baseline was -0.55 in the fevipiprant group vs -0.45 in the placebo group, with a LS mean difference of -0.10 (95% CI: -0.19, -0.01; adjusted p-value 0.214) over the 12-week treatment

period. There were no statistically significant differences in mean daily SABA use between the fevipiprant and placebo groups in both ZEAL-1 and ZEAL-2 (Fig. 3B). In ZEAL-1, the LS mean change from baseline in the daily number of puffs over 12 weeks was -1.11 in the fevipiprant group vs -1.02 in the placebo group, with a LS mean difference of -0.08 (95% CI: -0.30, 0.13; adjusted p-value 0.567). In ZEAL-2 the LS mean change from baseline in the daily number of puffs was -0.89 in the fevipiprant group vs -0.88 in the placebo group, with a LS mean difference of -0.01 (95% CI: -0.20, 0.17; adjusted p-value 0.911) over the 12-week treatment period. There was no statistically significant difference in AQLQ+12 scores between the fevipiprant and placebo groups in either study (Fig. 3C). In ZEAL-1, the LS mean change from baseline in the AQLQ+12 at week 12 was 0.91 in the fevipiprant group vs 0.89 in the placebo group, with a LS mean difference of 0.02 (95% CI: -0.12, 0.15; adjusted p-value 0.777). In ZEAL-2, the LS mean change from baseline in the AQLQ+12 at week 12 was 0.77 in the fevipiprant group vs 0.72 in the placebo group, with a LS mean difference of 0.05 (95% CI: -0.07, 0.17; adjusted p-value 0.911). In ZEAL-1 and ZEAL-2, the proportion of patients who had an improvement in AQLQ+12 score of ≥ 0.5 (minimally important difference) at week 12 was similar for fevipiprant and placebo (ZEAL-1: 66.8% and 65.5%, respectively; ZEAL-2: 55.8% and 57.5%, respectively).

3.4. Morning and mean evening PEF

In ZEAL-1, the LS mean change from baseline in mean morning PEF was 12 vs 3 L/min for fevipiprant vs placebo, respectively, with a LS mean difference of 8.7 L/min (95% CI: 2.028, 15.381; p-value 0.011) over the 12-week treatment period. The results of the corresponding analyses for mean evening PEF were similar to those for mean morning PEF. In ZEAL-2, the LS mean change from baseline in mean morning PEF was 11 L/min vs 7 L/min for fevipiprant vs placebo, respectively, with a LS mean difference of 3.3 L/min (95% CI: -3.434, 10.013; p-value 0.337) over the 12-week treatment period. The results for the corresponding analyses for mean evening PEF were similar to those for mean morning PEF.

3.5. Night-time asthma symptom score

The change from baseline in mean night-time asthma symptom score (scored on a 4-item scale, generating at least 4 possible responses from 0 ["no awakening with asthma symptoms"] to 3 ["awake all night"]) was similar for the fevipiprant and placebo groups in both ZEAL-1 and ZEAL-2: in ZEAL 1, the LS mean change from

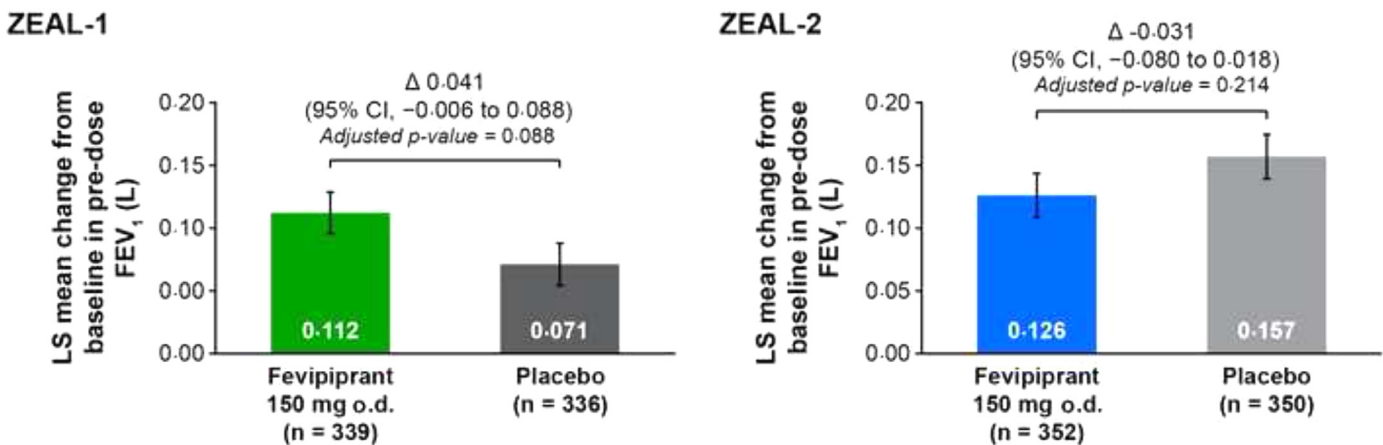


Fig. 2. Change from baseline in pre-dose FEV₁ in patients receiving fevipiprant or placebo in the ZEAL-1 and ZEAL-2 studies. Error bars represent SE; Δ , treatment difference between fevipiprant 150 mg o.d. and placebo FEV₁, forced expiratory volume in 1 s; LS, least squares; o.d., once daily.

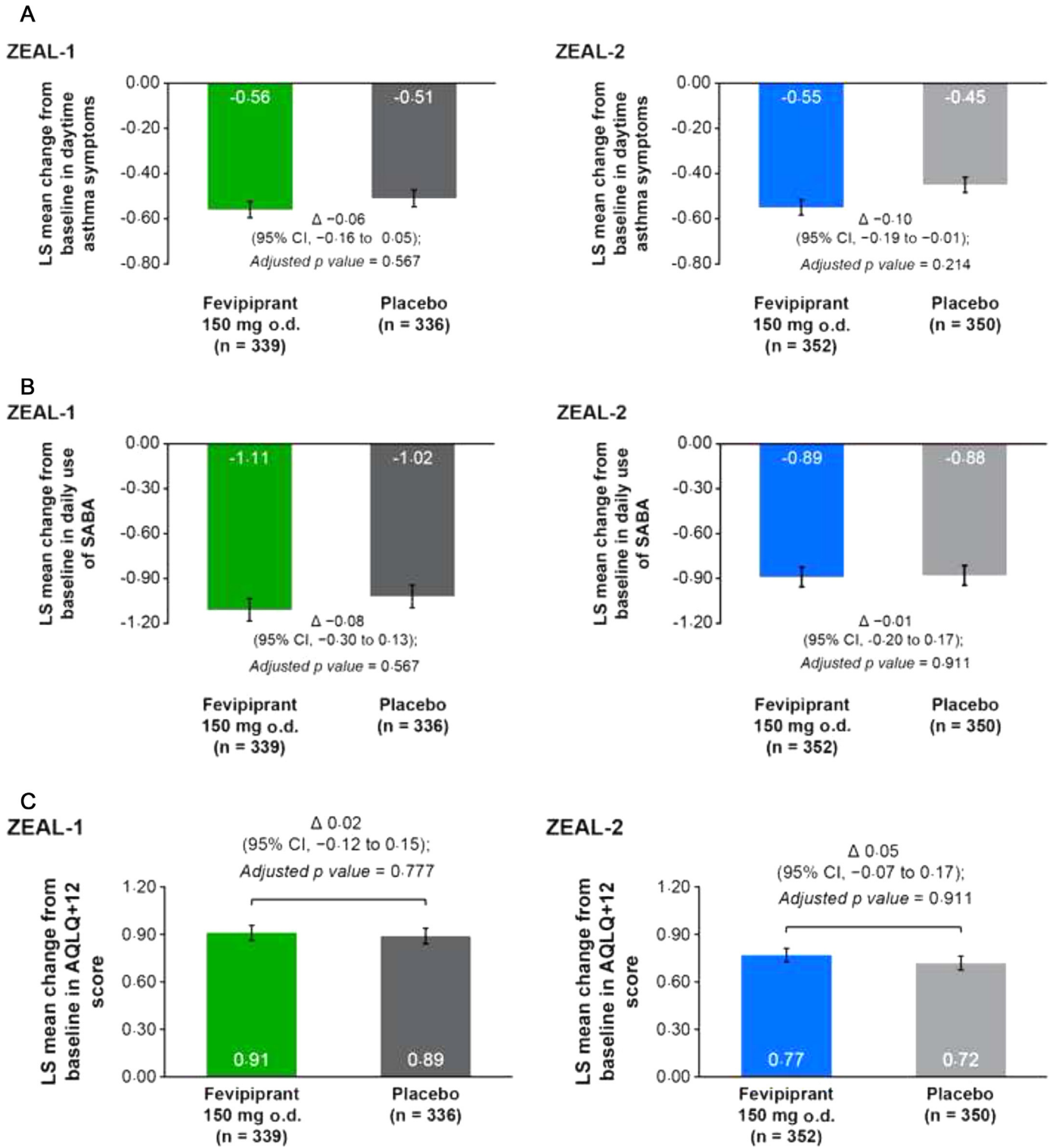


Fig. 3. Change from baseline in: (A) daytime symptom score; (B) daily SABA use; and (C) AQLQ-12 score in patients receiving fevipiprant or placebo in the ZEAL-1 and ZEAL-2 studies

Error bars represent SE; Δ, treatment difference between fevipiprant 150 mg o.d. and placebo

AQLQ, Asthma Quality of Life Questionnaire; LS, least squares; o.d., once daily; SABA, short-acting β_2 -agonist.

baseline was -0.29 vs -0.30 for fevipiprant vs placebo, respectively, with a LS mean difference of 0.01 (95% CI: -0.05, 0.07; p-value 0.711) over the 12-week treatment period. In ZEAL-2 the LS mean change from baseline was -0.24 in both groups with a LS mean difference of -0.00 (95% CI: -0.05, 0.05; p-value 0.935) over the 12-week treatment period.

3.6. ACQ-5 score

There was no statistically significant difference in ACQ-5 scores between the fevipiprant and placebo groups in either study. In ZEAL-1, the LS mean change from baseline in the ACQ-5 at week 12 was -1.16 in the fevipiprant group vs -1.04 in the placebo group, with a

with a LS mean difference of -0.12 (95% CI: $-0.25, 0.01$; p -value 0.070). In ZEAL-2, the LS mean change from baseline in the ACQ-5 at week 12 was -0.95 in the fevipiprant group vs -0.91 in the placebo group, with a LS mean difference of -0.05 (95% CI: $-0.17, 0.07$; p -value 0.450). In ZEAL-1 and ZEAL-2, the proportion of patients who had an improvement in ACQ-5 score of ≥ 0.5 (minimally important difference) at week 12 was similar for fevipiprant and placebo (ZEAL-1: 78.0% and 69.6%, respectively; ZEAL-2: 64.1% and 67.2%, respectively).

3.7. Asthma exacerbations

In both ZEAL-1 and ZEAL-2 studies, the majority of patients did not experience a moderate-to-severe asthma exacerbation during the 12-week treatment period. In ZEAL-1, one asthma exacerbation occurred in 9.1% patients in the fevipiprant group vs 8.0% in the placebo group, 2 exacerbations occurred in 0.9% patients in the fevipiprant group vs 2.7% in the placebo group, and 3 asthma exacerbations in 0 patient in the fevipiprant group vs 0.3% in the placebo group and in ZEAL-2, one asthma exacerbation occurred in 5.7% patients in the fevipiprant group vs 10.0% in the placebo group, and 2 exacerbations occurred in 0.6% patients in the fevipiprant group vs 1.1% in the placebo group.

3.8. Healthcare resource utilisation

Summary statistics for healthcare resource utilisation between the treatment groups in both ZEAL-1 and ZEAL-2 studies are reported. In ZEAL-1, the proportion of patients with any unplanned healthcare resource utilisation was 5.6% vs 5.1% for fevipiprant vs placebo, respectively; these were primarily related to asthma exacerbations (5.3% vs 4.5%). In ZEAL-2, the proportion of patients with any unplanned healthcare resource utilisation was 4.3% vs 7.1% for fevipiprant vs placebo, respectively; again, these were also primarily related to asthma exacerbations (3.7% vs 5.1%).

See supplementary appendix Section 3, for more information on the pre-dose FEV₁% predicted (Section 3.1) and PGIC (Section 3.2).

3.9. Safety

Fevipiprant was well tolerated with a safety profile comparable to that of placebo in terms of type, severity and frequency of AEs in both the ZEAL-1 and ZEAL-2 studies (Table 2). Asthma exacerbation was the most frequent AE in both studies (ZEAL-1 study: 13% of patients in both treatment groups: ZEAL-2 study: 13.9% in fevipiprant vs 17.4% in placebo group). Most AEs were mild or moderate in intensity. In the ZEAL-1 study, no deaths occurred in the fevipiprant group, while one death occurred in the placebo group: the patient died due to pulmonary embolism one day after starting study treatment. In the ZEAL-2 study, there were no deaths. Few patients in either study had AEs that led to discontinuation. In ZEAL-1, AEs leading to discontinuation of study drug occurred in 4 patients in the fevipiprant group and 5 patients in the placebo group. In ZEAL-2, AEs leading to

discontinuation of study drug occurred in 4 patients in the fevipiprant group and 3 patients in the placebo group. Please see table 2 of supplementary appendix which summarises the overall treatment-emergent AEs and SAEs in pooled ZEAL-1 and ZEAL-2 studies.

4. Discussion

Neither the ZEAL-1 nor the ZEAL-2 study met their primary endpoint. Fevipiprant 150 mg once daily resulted in similar increases in pre-dose FEV₁ in both ZEAL-1 and ZEAL-2 (112 and 126 mL, respectively); however, the increased pre-dose FEV₁ observed in the placebo treatment group in ZEAL-2 was considerably larger than that seen in ZEAL-1 (157 vs 71 mL, respectively). The reason for this large placebo response in ZEAL-2 is difficult to elucidate, particularly because the two studies were replicates. In addition, there is a possibility that the discrepancy in placebo response may come from random variation.

It is worth noting that the increase in pre-dose FEV₁ observed with fevipiprant in the two ZEAL studies was similar to the effect observed in a phase 2 study of fevipiprant in patients with moderate-severe asthma [8]. However, in this phase 2 dose-ranging study, fevipiprant produced a statistically significant improvement in the primary endpoint of change in pre-dose FEV₁ at week 12 ($p = 0.0035$) with a maximum model-averaged difference to placebo of 112 mL [8]. In the 12-week dose-ranging study, 150 mg daily was the optimal dose; doses above 150 mg did not provide additional efficacy on the primary endpoint of pre-dose FEV₁ [8]. While the dose-ranging study had no placebo run-in period and recruited patients receiving any dose of ICS, followed by dose-adjustment to low-dose ICS monotherapy (budesonide 200 μ g twice daily) without concomitant LABA or LTRA prior to randomization, the ZEAL studies had a placebo run-in period and recruited patients already on low- and medium-dose ICS, with the majority of subjects continuing on dual ICS with LABA and/or LTRA therapies on ZEAL-1 and ZEAL-2.⁸ It is possible that the use of concomitant LABA or LTRA with ICS in the ZEAL studies may have reduced the ability of fevipiprant to demonstrate an effect on FEV₁.

Several prostaglandin D₂ receptor (DP₂ receptor) antagonists have been developed and investigated in clinical trials of asthma and other inflammatory conditions, none of which has completed phase 3 trials to date, either because of absence of efficacy or because of an adverse safety profile. Fevipiprant showed promising results (improved FEV₁, enhanced asthma control, and reduced sputum eosinophilia) in phase 2 trials [8,7,14]. It is important to note that DP₂ receptor inhibitors are not direct bronchodilators but have an inhibitory effect on cells and pathways that can influence airway smooth muscle tone; this, combined with the results of these studies [8,7,14] would suggest that the direct effects of a bronchodilator plus ICS therapy are the driving factors in affecting airway bronchodilation.

The ZEAL studies were not able to determine whether there might be subpopulations of asthma patients with "treatable traits" that might be more responsive to DP₂ receptor blockade. The ZEAL studies did not enrich for patients with severe asthma and prior asthma exacerbations. Importantly, data on exhaled nitric oxide (FeNO)

Table 2
Adverse and severe adverse events in ZEAL-1 (safety set).

Characteristic	ZEAL-1		ZEAL-2	
	Fevipiprant 150 mgN = 339	PlaceboN = 336	Fevipiprant 150 mgN = 352	PlaceboN = 350
Patients with ≥ 1 AE	152 (44.8)	143 (42.6)	145 (41.2)	168 (48.0)
Patients with ≥ 1 SAE	1 (0.3)	5 (1.5)	7 (2.0)	3 (0.9)
Patients with AEs leading to discontinuation	4 (1.2)	5 (1.5)	4 (1.1)	3 (0.9)
Fatality, n	0	1	0	0

Data are presented as n (%), unless specified otherwise.
AE, adverse event; SAE, serious adverse event.

levels and other biomarkers were not captured. The pre-bronchodilator FEV₁ values in ZEAL were similar to the findings from the LUSTER studies [15] (LUSTER-1: NCT02555683; LUSTER-2 NCT02563067) conducted in patients with severe asthma. Increased asthma exacerbation rates predict increased response to biologic therapy [16] (anti-IL-5 etc.), therefore, it is possible that there may have been a greater response to treatment if the ZEAL studies had recruited patients with more severe asthma prone to asthma exacerbations. Increased production of PGD₂ is observed in severe eosinophilic asthmatics, but not in patients with mild-to-moderate asthma [17,18]. This would be another reason why DP₂ antagonists may exhibit a greater response in patients with severe and eosinophilic asthma. The 52-week LUSTER [15] studies (LUSTER-1: NCT02555683; LUSTER-2 NCT02563067) did include patients with more severe asthma and prior exacerbations, but these studies did not show a significant effect with fevipirant on exacerbation rate and lung function.

Poorly controlled asthma has a negative impact on health-related quality of life, and is a major contributor to asthma-related health-care costs, and time lost from work and school [19]. In both ZEAL-1 and ZEAL-2 there were no improvements observed in daytime asthma symptom scores and AQLQ scores with fevipirant treatment compared with placebo. Patient-reported outcomes can sometimes demonstrate a greater placebo response than 'functional' outcomes, especially in situations such as this where patients are already receiving maintenance medication. Therefore, inclusion of these patients in a clinical trial might improve treatment compliance to the controller medication contributing to an improvement in the placebo group.

Strengths of the studies include the enrolment of patients on GINA 3 and GINA 4 therapies who still showed evidence of uncontrolled asthma to assess the potential benefits of added fevipirant. The studies achieved high rates of treatment completion and assessed multiple endpoints for efficacy. A limitation was that these studies did not require prior exacerbations or high blood eosinophil levels, which may have impacted appropriate phenotype selection for a DP₂ antagonist. In addition, the studies did not measure baseline FeNO levels or other biomarkers, so the identification of further subsets of T2-enriched patients that may have responded to DP₂ antagonism was not possible.

ZEAL-1 and ZEAL-2 studies demonstrated that fevipirant did not improve lung function in the studied patient population with uncontrolled asthma receiving SoC asthma therapy (GINA steps 3 and 4). Fevipirant demonstrated a well-balanced safety profile compared with placebo.

Declaration of Competing Interest

MC receives University Grant Funding from NIH, American Lung Association, PCORI. **MC** receives Pharmaceutical Grant Funding from AstraZeneca, GSK, Novartis, Pulmatrix, Sanofi-Aventis, Shionogi. **MC** is a consultant for Genentech, Teva, Sanofi-Aventis, Novartis. **MC** is a speaker for AstraZeneca, Genentech, GSK, Regeneron, Sanofi, Teva. **MC** receives royalties from Elsevier. **EK** reports personal fees from Crisor LLC Research, other from Amphastar, other from AstraZeneca, other from Boehringer Ingelheim, other from Forest, other from GlaxoSmithKline, other from Mylan, other from Novartis, other from Pearl, other from Sunovion, other from Teva, other from Theravance, other from Cipla, other from Chiesi, outside the submitted work. **AP** and **DM** declared no conflict of interest. **PC** and **BK** reports employment by the pharmaceutical company [Novartis Pharmaceuticals Corporation] (sponsor study CQAW039A2316 [ZEAL-1] and CQAW039A2317 [ZEAL-2]) and personal fees and other from Novartis Pharmaceuticals Corporation, outside the submitted work. **PC** and **BK** also hold stock/shares [Novartis Pharmaceuticals Corporation]. **DL** reports employment by the pharmaceutical company [Novartis Pharma AG] (sponsor study CQAW039A2316 [ZEAL-1] and CQAW039A2317 [ZEAL-2]) and personal fees and other from Novartis

Pharma AG, outside the submitted work. **DL** also hold stock/shares [Novartis Pharma AG]. **DO** reports employment by the pharmaceutical company [Novartis Pharma AG] (sponsor study CQAW039A2316 [ZEAL-1] and CQAW039A2317 [ZEAL-2]) and personal fees and other from Novartis Pharma AG, outside the submitted work. **DO** also hold stock/shares [Novartis Pharma AG]. **WW** reports personal fees from Novartis Institutes for Biomedical Research Co., Ltd, Shanghai, during the conduct of the study, outside the submitted work; and is an employee of Novartis Institutes for Biomedical Research Co., Ltd, Shanghai. **JM** reports personal fees from Novartis, grants from Novartis, during the conduct of the study; personal fees from AstraZeneca, grants and personal fees from Sanofi, personal fees from IMMUNOTEK, personal fees from SANOFI, outside the submitted work. **LS** reports grants from Regeneron, Sanofi-Genzyme and Novartis outside the submitted work.

Contributors

All authors substantially contributed to the design of the ZEAL studies, and/or the collection, analysis, and/or interpretation of the data for the studies, and have been involved in drafting the manuscript and revising it for important intellectual content. All authors have approved the final version of the manuscript to be published and agree to be accountable for the accuracy and integrity of the work.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of subjects who have participated in the trial in line with applicable laws and regulations. Result summaries have been posted on the Novartis clinical trial database and other online public databases. More information on Novartis' position on access to clinical trial results and patient-level data is available at <https://www.novartis.com/our-science/clinical-trials/clinical-trial-information-disclosure>

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Supplementary materials

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