Fevipiprant, an oral prostaglandin DP_2 receptor (CRTh2) antagonist, in allergic asthma uncontrolled on low-dose inhaled corticosteroids

Eric D. Bateman[1], Alfredo G. Guerreros[2], Florian Brockhaus[3], Björn Holzhauer[3], Abhijit Pethe[4], Richard A. Kay[3] and Robert G. Townley[5†]

Affiliations: [1]Division of Pulmonology, Dept of Medicine, University of Cape Town, Cape Town, South Africa. [2]Clinica Internacional, Lima, Peru. [3]Novartis Pharma AG, Basel, Switzerland. [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. [5]Internal Medicine/Allergy, Creighton University, Omaha, NE, USA.

Correspondence: Eric D. Bateman, Division of Pulmonology, Dept of Medicine, University of Cape Town, George Street, Mowbray 7700, Cape Town, South Africa. E-mail: eric.bateman@uct.ac.za

@ERSpublications
Fevipiprant, an oral DP_2 receptor antagonist, is effective (dose 150 mg *q.d.*) in allergic asthma uncontrolled on ICS http://ow.ly/Ns5d30dlAFd

Cite this article as: Bateman ED, Guerreros AG, Brockhaus F, *et al*. Fevipiprant, an oral prostaglandin DP_2 receptor (CRTh2) antagonist, in allergic asthma uncontrolled on low-dose inhaled corticosteroids. *Eur Respir J* 2017; 50: 1700670 [https://doi.org/10.1183/13993003.00670-2017].

ABSTRACT Dose-related efficacy and safety of fevipiprant (QAW039), an oral DP_2 (CRTh2) receptor antagonist, was assessed in patients with allergic asthma uncontrolled by low-dose inhaled corticosteroids (ICS).

Adult patients were randomised to 12 weeks' treatment with once-daily (1, 3, 10, 30, 50, 75, 150, 300 or 450 mg *q.d.*) or twice-daily (2, 25, 75 or 150 mg *b.i.d.*) fevipiprant (n=782), montelukast 10 mg *q.d.* (n=139) or placebo (n=137). All patients received inhaled budesonide 200 µg *b.i.d.*

Fevipiprant produced a statistically significant improvement in the primary end-point of change in pre-dose forced expiratory volume in 1 s at week 12 (p=0.0035) with a maximum model-averaged difference to placebo of 0.112 L. The most favourable pairwise comparisons to placebo were for the fevipiprant 150 mg *q.d.* and 75 mg *b.i.d.* groups, with no clinically meaningful differences between *q.d.* and *b.i.d.* Montelukast also demonstrated a significant improvement in this end-point. No impact on other efficacy end-points was observed. Adverse events were generally mild/moderate in severity, and were evenly distributed across doses and treatments.

Fevipiprant appears to be efficacious and well-tolerated in this patient population, with an optimum total daily dose of 150 mg. Further investigations into the clinical role of fevipiprant in suitably designed phase III clinical trials are warranted.

Received: March 30 2017 | Accepted after revision: June 30 2017

R.G. Townley sadly passed away before the submission of this manuscript.

This article has supplementary material available from erj.ersjournals.com

Support statement: This study was funded by Novartis Pharma AG (Basel, Switzerland). Funding information for this article has been deposited with the Crossref Funder Registry.

The study is registered with ClinicalTrials.gov as NCT01437735.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Introduction

Several classes of asthma medications, such as inhaled corticosteroids (ICS), long-acting β_2-adrenergic agonists (LABA), or leukotriene receptor antagonists (LTRA) are advocated by internationally accepted management guidelines for achieving control of asthma [1]. However, asthma control remains suboptimal for many patients, with nearly half (45%) of all respondents in a recent European survey of 8000 people with asthma having uncontrolled asthma [2]. Even aggressive asthma management using maximal doses of available conventional therapies (fluticasone propionate or salmeterol/fluticasone combination therapy) fails to achieve total control in 38% of patients [3]. Failure to achieve and maintain control of asthma is associated with symptoms such as night-time awakenings, an increased risk of severe exacerbations, need for emergency care and hospitalisations, and even death [4]. Poor asthma control is also a major contributor to asthma-related healthcare costs [5], lost time from work [6], and can have profound effects on quality-of-life [7]. Consequently, there is a need for new treatment options for patients with uncontrolled asthma.

A promising target for new therapeutic agents in asthma is prostaglandin D_2 (PGD_2), which acts *via* the DP_2 receptor, also known as the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2). DP_2 is a G-protein coupled receptor, which mediates the activation and migration of Th2 cells and eosinophils, effector mechanisms that lie at the core of inflammatory processes in allergic asthma. Fevipiprant (QAW039) is a potent and highly selective oral DP_2 (CRTh2) receptor antagonist that targets PGD_2. Because it is orally administered, fevipiprant works systemically and is therefore thought to be able to reach all areas of the lungs, including the smaller, lower airways.

This phase IIb study (study QAW039A2206) was designed to characterise the dose–response relationship among fevipiprant once-daily (*q.d.*) and twice-daily (*b.i.d.*) doses and placebo in patients with allergic asthma inadequately controlled by low-dose ICS therapy. It is registered with ClinicalTrials.gov as NCT01437735.

Methods

Study patients

This study enrolled non-smoking patients, aged 18–65 years, whose asthma was being managed with ICS therapy. Patients demonstrated reversible airway obstruction or airway hyperreactivity (AHR), or had shown either of such responses in previous test(s) within the last 5 years. They had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) value of 40–80% of individual predicted value at screening and at randomisation. Allergic status was determined by patient history, or by either a skin prick test ($\geqslant$3 mm diameter above background) or a positive specific IgE (*e.g.* RAST/CAP) test ($\geqslant$0.35 IU eq·mL^{-1}) at screening visit 3. Patients' asthma control questionnaire (ACQ) score was required to be $\geqslant$1.5 at randomisation.

Key exclusion criteria included a history of life-threatening asthma, including hypercapnia (carbon dioxide tension >45 mmHg), prior intubation, respiratory arrest, or seizures as a result of asthma, history of long QT syndrome or current QTc interval (Fridericia's) prolongation (>450 ms) at screening. Detailed inclusion and exclusion criteria are available in the online supplement.

The study protocol was approved by the local ethics committees and was undertaken in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

Study design

This double-blind, randomised, placebo-controlled, dose-ranging, multicentre study investigated the effects of fevipiprant in patients with allergic asthma inadequately controlled with ICS therapy. It was conducted at 188 centres in 22 countries worldwide (listed in the online supplement). The study commenced on August 25, 2011 and was completed on November 12, 2013. It had 15 parallel treatment arms: 13 doses of fevipiprant, montelukast as a positive control, and placebo (figure 1).

After enrolment, patients taking more than 800 µg budesonide daily (or the equivalent of another ICS) had their LABA stopped (if they were taking one) and were placed on budesonide 400 µg *b.i.d.* for 2 weeks from visit 2. After 2 weeks, patients who remained eligible were placed on budesonide 200 µg *b.i.d.* for another 2 weeks. Patients taking 800 µg or less of budesonide were directly placed on 200 µg *b.i.d.* at visit 3 (having stopped other controller medications).

2 weeks later, at visit 4, all eligible patients who were uncontrolled on ICS therapy alone were randomised to one of the 15 treatment arms and entered a 12-week treatment period (figure 1). Patients received either once-daily fevipiprant (1, 3, 10, 30, 50, 75, 150, 300 or 450 mg *q.d.*), twice-daily fevipiprant (2, 25, 75 or 150 mg *b.i.d.*), montelukast 10 mg *q.d.* or a matching placebo. From visit 4, until the study end, all randomised patients continued treatment with inhaled budesonide 200 µg *b.i.d.*

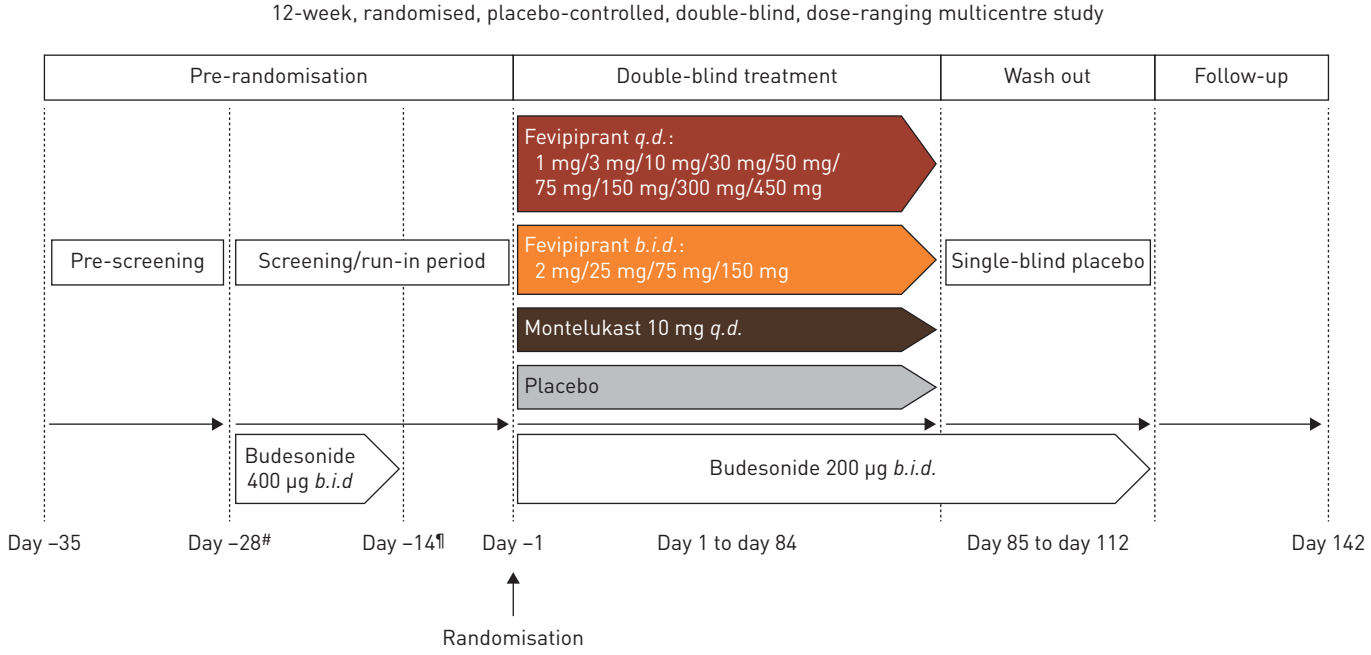

FIGURE 1 Study design. #: inhaled corticosteroid (ICS) weaning begins here if pre-trial ICS is >800 µg budesonide daily (or equivalent). ¶: ICS weaning begins here if pre-trial ICS is ⩽800 µg budesonide daily (or equivalent). Study sites were split into two groups for randomisation. Patients in each group were allocated equally to either fevipiprant 450 mg *q.d.*, montelukast 10 mg *q.d.*, placebo, or to one of six other fevipiprant doses as follows: Group 1: 1, 10, 50 or 150 mg *q.d.* or 2 mg or 75 mg *b.i.d.* Group 2: 3, 30, 75 or 300 mg *q.d.* or 25 or 150 mg *b.i.d.* In addition, approximately 90 patients at pre-selected sites were planned to be randomised equally to 3 treatment arms (fevipiprant 450 mg *q.d.*, montelukast 10 mg *q.d.* or placebo) in a sputum collection sub-study. However, insufficient numbers of patients were recruited into this sub-study. Some patients not participating in the sub-study were therefore selected to be randomised to one of these three treatment groups in order to maintain the overall pre-specified distribution of patients to different treatments.

Efficacy outcomes

The primary efficacy end-point was change in pre-dose (trough) FEV_1 (24 h post-morning dose) after 12 weeks' treatment with fevipiprant compared to placebo. Secondary efficacy end-points were asthma symptom control compared to placebo measured by the ACQ and Juniper Asthma Control Diary (JACD); onset of efficacy as measured by spirometry and ACQ after 2, 4, 8 and 12 weeks' treatment; to characterise the fevipiprant dose–response relationship with respect to pre-dose FEV_1 after 12 weeks' treatment and to compare the efficacy of fevipiprant and montelukast to placebo as add-on therapy to low-dose ICS.

Pharmacokinetics

All subjects with evaluable pharmacokinetic data were included in a pharmacokinetic analysis. The details of this analysis are not reported here as they are beyond the scope of this paper.

Safety assessments

Safety was assessed by collecting all adverse events, serious adverse events, with their severity and relationship to study drug, and pregnancies, laboratory data, vital signs and ECG data. Following the 12-week treatment period, all patients were allocated placebo and followed up for a further 4 weeks. Safety assessments were completed 30 days after this period through a telephone call.

Exploratory outcomes

Exploratory outcomes included changes in health-related quality-of-life, as measured by the standardised Asthma Quality of Life Questionnaire (AQLQ), work productivity and daily activities (using the Work Productivity and Activity Impairment – Allergic Asthma (WPAI-AA) questionnaire), and fractional exhaled nitric oxide (F_{ENO}) levels.

Asthma worsening/exacerbations

A *post hoc* analysis was performed on adverse events that satisfied the protocol definition of exacerbations (worsening of asthma as judged clinically significant by the physician, requiring treatment with rescue oral or intravenous corticosteroids for 3 days or more) and asthma worsening episodes reported by

investigators but not severe enough to satisfy the protocol definition of an exacerbation (based on diary data, clinic visit spirometry and investigator's clinical judgment).

Statistical analysis

The primary FEV1 dose–response analysis was performed using the generalised multiple comparisons procedures and modelling (MCP-Mod) approach [8, 9] on the modified full analysis set (mFAS), which consisted of all randomised patients that took at least one dose of study drug and had valid baseline and post-baseline spirometry data as confirmed by a quality control process. The analysis was adjusted for region, the average of two baseline FEV1 measurements and centre as a random effect nested within region. p-values were adjusted to account for the multiple dose response contrasts. Missing FEV1 values and those recorded up to 6 h after rescue medication were imputed using last-observation-carried-forward.

For the modelling part of MCP-Mod, uncertainty was reflected by generating 10 000 parametric bootstrap samples and using the generalised Akaike information criterion to select the best fitting model from a set of monotonic candidate models for each bootstrap sample [9, 10]. Each model included a model parameter that describes what multiple of the same total daily dose given once daily corresponds to the same total daily dose given twice daily. The median of the predicted differences to placebo for each dose based on the selected model for each sample was used as the estimated dose response curve with 95% confidence intervals based on the 2.5th and 97.5th percentiles.

A sensitivity analysis using a repeated measures model that implicitly imputes data under a missing at random assumption was also conducted. An expanded set of dose–response models including non-monotonic ones was fitted and the primary analysis repeated for a per-protocol set. Safety data were summarised for all patients who received at least one dose of study drug according to the treatment patients actually received.

Further details on statistical methods and sample size calculations are provided as online supplementary material.

Results

Patients

Of 2598 patients screened, 1058 patients were randomised to receive either fevipiprant (n=782), montelukast (n=139) or placebo (n=137). Details on the reasons for screen failures are provided in the supplementary appendix. The number of patients who comprised the various fevipiprant dose groups is shown in table 1. The most common reason for patient withdrawal in the fevipiprant (7.4%) and placebo (11.7%) groups was adverse events, and for the montelukast group was withdrawal of consent (7.2%). The proportions of patients completing the study were 83.5%, 81.3% and 81.0% in the fevipiprant, montelukast and placebo groups, respectively. Patient demographics and disease characteristics were well-balanced between treatment groups (tables 1 and 2).

TABLE 1 Patient demographics (safety set)

Variable	Placebo (n=136)	Fevipiprant low-dose[#] (n=201)	Fevipiprant mid-dose[¶] (n=219)	Fevipiprant high-dose[+] (n=212)	Fevipiprant 450 mg *q.d.* (n=133)	Fevipiprant total[§] (n=765)	Montelukast 10 mg *q.d.* (n=133)	Total (n=1034)
Age years	44.6±12.5	45.2±12.1	45.6±12.1	43.5±12.3	45.8±12.5	45.0±12.3	44.5±11.2	44.9±12.2
Male	57 (41.9)	82 (40.8)	100 (45.7)	83 (39.2)	60 (45.1)	325 (42.5)	55 (41.4)	437 (42.3)
Race								
Caucasian	82 (60.3)	119 (59.2)	124 (56.6)	110 (51.9)	74 (55.6)	427 (55.8)	78 (58.6)	587 (56.8)
Asian	28 (20.6)	49 (24.4)	50 (22.8)	52 (24.5)	29 (21.8)	180 (23.5)	27 (20.3)	235 (22.7)
Black	2 (1.5)	2 (1.0)	5 (2.3)	11 (5.2)	7 (5.3)	25 (3.3)	2 (1.5)	29 (2.8)
Native American	8 (5.9)	10 (5.0)	15 (6.8)	12 (5.7)	5 (3.8)	42 (5.5)	8 (6.0)	58 (5.6)
Other	16 (11.8)	21 (10.4)	25 (11.4)	27 (12.7)	18 (13.5)	91 (11.9)	18 (13.5)	125 (12.1)
Weight kg	75.3±15.6	76.7±19.0	75.1±16.5	75.5±17.9	76.8±16.6	75.9±17.6	76.1±17.5	75.9±17.3
Height cm	165.7±9.94	164.6±10.21	166.7±10.11	165.7±10.60	165.9±10.71	165.7±10.39	165.8±10.21	165.7±10.30
BMI kg·m^{-2}	27.4±5.1	28.1±5.7	26.9±5.0	27.4±5.5	27.8±5.0	27.5±5.3	27.5±5.4	27.5±5.3

Data are presented as mean±SD or n (%). BMI: body mass index. Height and weight are taken from visit 1 vital signs evaluations. [#]: fevipiprant low-dose: combination of 1 mg *q.d.*, 3 mg *q.d.*, 2 mg *b.i.d.*, 10 mg *q.d.*; [¶]: fevipiprant mid-dose: combination of 30 mg *q.d.*, 50 mg *q.d.*, 25 mg *b.i.d.*, 75 mg *q.d.*; [+]: fevipiprant high-dose: combination of 150 mg *q.d.*, 75 mg *b.i.d.*, 300 mg *q.d.*, 150 mg *b.i.d.*; [§]: fevipiprant total: combination of all fevipiprant doses.

Primary efficacy end-points

There was a statistically significant improvement in the primary end-point; pre-dose FEV_1 increased with fevipiprant on top of low-dose ICS compared with placebo after 12 weeks' treatment, with a maximum model-averaged difference to placebo of 0.112 L (95% CI 0.004–0.175; p=0.0035). There was no evidence of higher efficacy in terms of FEV_1 in any subgroup (which included predicted FEV_1, baseline ACQ scores, blood eosinophilia level, regions and countries). A significant improvement in pre-dose FEV_1 was observed with montelukast compared to placebo (0.134 L, 95% CI 0.045–0.222; p=0.0033) (table 3).

Secondary efficacy end-points

Characterisation of dose response for FEV_1

The dose–response curve obtained from the primary analysis is shown in figure 2a. Figure 2b shows the pre-specified sensitivity analysis, in which a beta model capable of capturing bell-shaped dose response was selected in 66% of bootstrap samples. Consistent with this, the point estimates of pre-dose FEV_1 after 12 weeks' treatment with fevipiprant, using the primary linear mixed effects model, showed that the greatest differences from placebo occurred at doses of 75 mg *b.i.d.* (0.179 L, 95% CI 0.052–0.307; p=0.0059) and 150 mg *q.d.* (0.164 L, 95% CI 0.044–0.285; p=0.0075). The fevipiprant 150 mg *b.i.d.* (0.064 L, 95% CI −0.054–0.181), 300 mg *q.d.* (0.120 L, 95% CI 0.003–0.237) and 450 mg *q.d.* (0.077 L, 95% CI −0.012–0.167) groups had numerically better results compared with placebo. Total daily doses of fevipiprant less than 150 mg had FEV_1 differences compared with placebo between −0.014 L to 0.145 L. The dose responses for *q.d.* and *b.i.d.* dosing were similar (figure 2a, primary analysis; figure 2b, sensitivity analysis allowing for a bell-shaped dose response).

Change in FEV_1 over time

The largest effects of the 75 mg *b.i.d.* and 150 mg *q.d.* doses of fevipiprant were seen by week 4 (0.190 L; p=0.0022; and 0.233 L; p<0.0001, *versus* placebo, respectively). These persisted through the remainder of the study (figure 3). Montelukast demonstrated a statistically significant improvement in FEV_1 compared with placebo throughout the course of the study (range: 0.102–0.141 L; p=0.0054 to p=0.0029 between weeks 2 and 12).

TABLE 2 Patient disease characteristics (safety set)

Variable	Placebo (n=136)	Fevipiprant low-dose[#] (n=201)	Fevipiprant mid-dose[¶] (n=219)	Fevipiprant high-dose[+] (n=212)	Fevipiprant 450 mg *q.d.* (n=133)	Fevipiprant total[§] (n=765)	Montelukast 10 mg *q.d.* (n=133)	Total (n=1034)
Duration of asthma years	20.7±13.7	20.5±14.5	20.5±14.9	18.4±14.0	21.2±15.0	20.0±14.6	22.2±15.5	20.4±14.6
ACQ score	2.2±0.5 (n=136)	2.2±0.5 (n=199)	2.3±0.6 (n=219)	2.2±0.6 (n=210)	2.2±0.5 (n=132)	2.2±0.5 (n=760)	2.3±0.6 (n=133)	2.2±0.5 (n=1029)
AQLQ score	4.8	4.9	4.7	4.8	4.9	4.8	4.7	4.8
ICS dose at enrolment								
⩽800 µg per day budesonide[f]	131 (96.3)	188 (93.5)	203 (92.7)	205 (96.7)	122 (91.7)	718 (93.9)	125 (94.0)	974 (94.2)
>800 µg per day budesonide[f]	5 (3.7)	13 (6.5)	16 (7.3)	7 (3.3)	11 (8.3)	47 (6.1)	8 (6.0)	60 (5.8)
Change in ICS dose during run-in								
ICS dose maintained	38 (27.9)	63 (31.3)	58 (26.5)	65 (30.7)	34 (25.6)	220 (28.8)	39 (29.3)	297 (28.7)
Stepped up	33 (24.3)	51 (25.4)	49 (22.4)	53 (25.0)	27 (20.3)	180 (23.5)	40 (30.1)	253 (24.5)
Stepped down	65 (47.8)	87 (43.3)	112 (51.1)	94 (44.3)	72 (54.1)	365 (47.7)	54 (40.6)	484 (46.8)
FEV_1 L	1.98±0.6	1.90±0.6	1.97±0.6	1.96±0.6	1.92±0.6	1.94±0.6	1.96±0.5	1.95±0.6
FEV_1 % pred	65.3±9.0	64.4±9.6	64.1±10.1	64.5±9.7	63.7±10.5	64.2±9.9	64.8±9.7	64.4±9.8
FVC L	3.22±0.9	3.04±0.9	3.11±0.9	3.09±0.9	3.16±1.0	3.09±0.9	3.08±0.9	3.11±0.9

Data are presented as mean±SD or n (%), unless otherwise stated. ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; ICS: inhaled corticosteroids; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. Duration of asthma is calculated as date of asthma first diagnosed until visit 1. ACQ score is the average of all seven questions. The baseline ACQ score is the last available non-missing pre-dose value. ICS stepped down: patient was controlled at screening receiving medium-dose ICS±LABA (long-acting β_2-adrenergic agonist) or high-dose ICS±LABA. ICS dose maintained: Patient was controlled at screening receiving low-dose ICS+other (*e.g.* LABA, leukotriene receptor antagonists, *etc.*). The shown FEV_1, FEV_1 % predicted and FVC values are the single pre-bronchodilator measurement of these parameters taken in the clinic during screening. [#]: fevipiprant low-dose: combination of 1 mg *q.d.*, 3 mg *q.d.*, 2 mg *b.i.d.*, 10 mg *q.d.*; [¶]: fevipiprant mid-dose: combination of 30 mg *q.d.*, 50 mg *q.d.*, 25 mg *b.i.d.*, 75 mg *q.d.*; [+]: fevipiprant high-dose: combination of 150 mg *q.d.*, 75 mg *b.i.d.*, 300 mg *q.d.*, 150 mg *b.i.d.*; [§]: fevipiprant total: combination of all fevipiprant doses; [f]: or an equivalent dose of another ICS.

TABLE 3 Change in forced expiratory volume in 1 s (FEV_1) after 12 weeks of treatment

Treatment group	Difference to placebo L (95% CI)	p-value
Fevipiprant 1 mg *q.d.*	0.075 (−0.048, 0.198)	0.2296
Fevipiprant 3 mg *q.d.*	0.087 (−0.035, 0.209)	0.1609
Fevipiprant 10 mg *q.d.*	0.002 (−0.125, 0.129)	0.9760
Fevipiprant 30 mg *q.d.*	0.091 (−0.027, 0.210)	0.1311
Fevipiprant 50 mg *q.d.*	0.052 (−0.071, 0.175)	0.4072
Fevipiprant 75 mg *q.d.*	0.111 (−0.007, 0.230)	0.0652
Fevipiprant 150 mg *q.d.*	0.164 (0.044, 0.285)	0.0075
Fevipiprant 300 mg *q.d.*	0.120 (0.003, 0.237)	0.0442
Fevipiprant 450 mg *q.d.*	0.077 (−0.012, 0.167)	0.0901
Fevipiprant 2 mg *b.i.d.*	−0.014 (−0.135, 0.107)	0.8230
Fevipiprant 25 mg *b.i.d.*	0.145 (0.030, 0.260)	0.0133
Fevipiprant 75 mg *b.i.d.*	0.179 (0.052, 0.307)	0.0059
Fevipiprant 150 mg *b.i.d.*	0.064 (−0.054, 0.181)	0.2871
Montelukast 10 mg	0.134 (0.045, 0.222)	0.0033

p-values are not adjusted for multiplicity. All estimates are based on a linear mixed effects model with treatment and region as fixed class effects, centre nested within region as a random class effect and absolute baseline FEV_1 as a covariate. The baseline FEV_1 was defined as the average of two pre-bronchodilator FEV_1 assessments taken in the clinic at 50 min and 15 min prior to the first study drug administration.

Asthma symptom control

Asthma symptom control was not significantly affected by any fevipiprant dose compared to montelukast or placebo as measured by the ACQ using a linear mixed model. Symptom control was also assessed by the JACD; however, no statistical differences were observed between fevipiprant and placebo.

Exploratory outcomes

Neither fevipiprant nor montelukast had any effect on patient quality of life, work productivity and daily activities as measured by the AQLQ and WPAI-AA questionnaire respectively, or on F_{ENO} levels in this study. Further information is available in the online supplement.

Asthma worsening/exacerbations

Numerical reductions were observed in the cumulative incidence of asthma exacerbations or asthma worsening adverse events following treatment with either fevipiprant or montelukast compared with placebo (figure 4). However, this study was not powered for the assessment of asthma worsening and there were insufficient events for formal statistical analyses.

Safety

Overall, 498 (48.2%) patients experienced at least one adverse event during the treatment period. Most adverse events were mild or moderate in severity, and their incidence was similar and evenly distributed across treatment groups (table 4). No clinically significant abnormalities were observed in haematological, clinical, vital signs and ECG parameters.

An imbalance in the frequency of post-randomisation cardiac adverse events was observed; one (angina pectoris) occurred in the placebo group (0.7%), the remainder of these events were in patients receiving fevipiprant (n=13, 1.7%) (described in detail in the online supplement). Cardiac adverse events comprised different non-serious arrhythmias, and one serious adverse events of pericarditis not considered to be study drug-related by the investigator. Three events in the fevipiprant groups occurred during the washout period and nine resolved with continued active treatment. All cardiac adverse events were mild or moderate in severity. Based on the inability to identify trends with fevipiprant dose or dosing, time-of-onset, patient age and gender, concomitant medication or event type, it was considered that these were coincidental events without a causal association to study drug.

Serious adverse events (including asthma exacerbations) during treatment occurred in 1.6% (12/765) of patients in the fevipiprant group, and 1.5% (2/136) and 0.8% (1/133) in the placebo and montelukast groups, respectively. Only one patient in the study had a serious adverse event (vertigo) that was suspected to be related to study drug; this was in the placebo group. Most serious adverse events (12/16) resolved under treatment. None led to death.

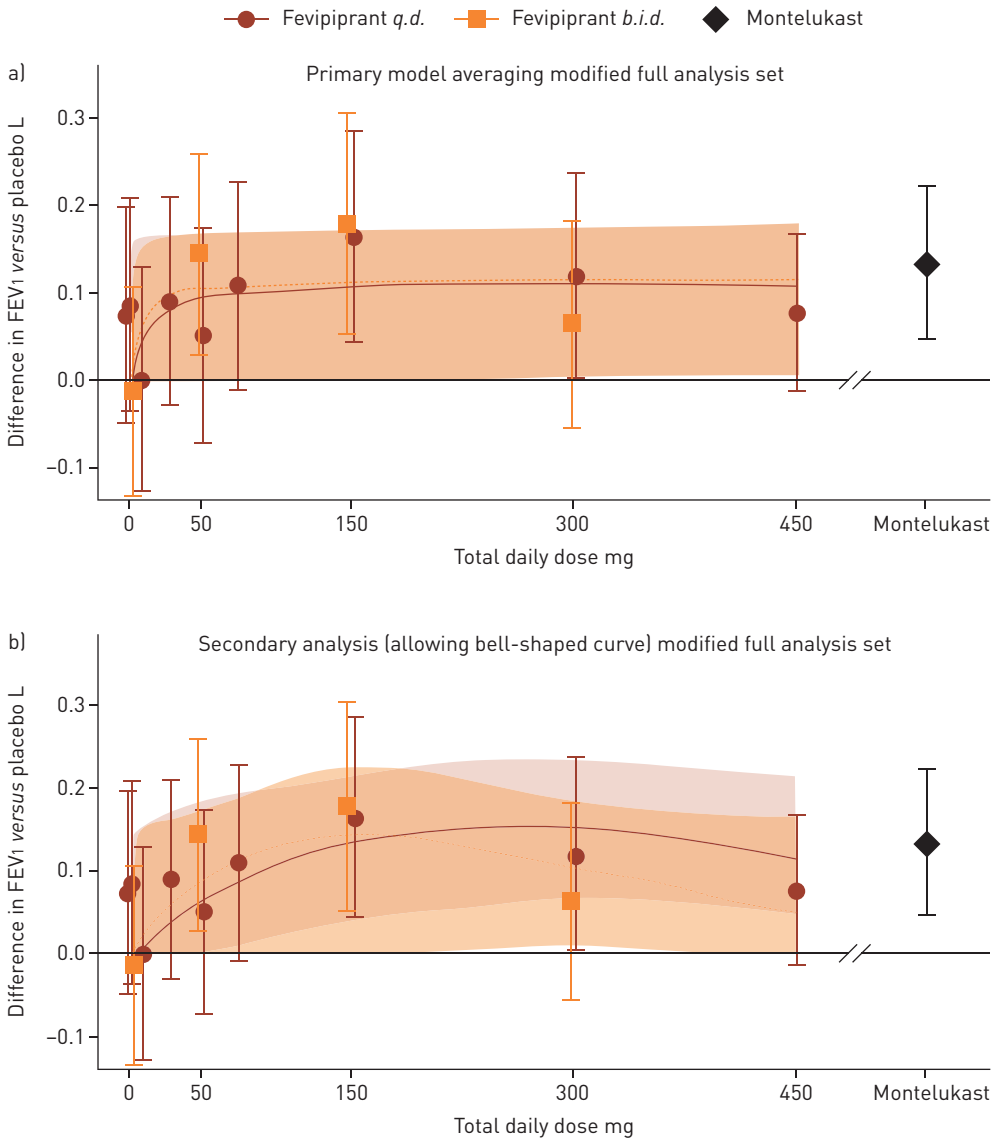

FIGURE 2 Dose-response curves based on model-averaging along with ANCOVA estimates of difference to placebo for pre-dose forced expiratory volume in 1 s (FEV_1) after 12 weeks of treatment (modified full analysis set). The primary analysis based on model averaging between monotonic dose–response models resulted in the dose–response curve shown in (a). A pre-specified sensitivity analysis allowing for a bell-shaped dose–response curve is shown in (b).

Discontinuations due to adverse events occurred in 81 patients (7.8%); 7.8% in the fevipiprant, 11.8% in the placebo and 3.8% in the montelukast group. The majority of adverse events leading to discontinuation were non-serious (76 patients; 7.4%), with discontinuations due to serious adverse events reported for 5 (0.5%) patients (4 (0.5%) fevipiprant and 1 (0.7%) placebo). There were no dose-related trends for discontinuations as a result of adverse events in the fevipiprant treatment group.

Discussion

This phase II study of the oral DP_2 receptor antagonist, fevipiprant, achieved its primary objective by demonstrating a statistically significant improvement in pre-dose FEV_1 *versus* placebo after 12 weeks' treatment in patients with asthma uncontrolled on low-dose ICS (GINA step 2 requiring step 3 treatment). These findings support those of other phase II studies where fevipiprant has been shown to be effective in asthma patients with severe airflow limitation (subgroup with FEV_1 <70% predicted) (study 2201) [11], and in asthma patients with sputum eosinophilia (study 2208) [12]. Importantly, the safety profile of fevipiprant was also favourable in this study. Together, these findings point to a potential benefit of fevipiprant as an add-on controller therapy in patients with asthma.

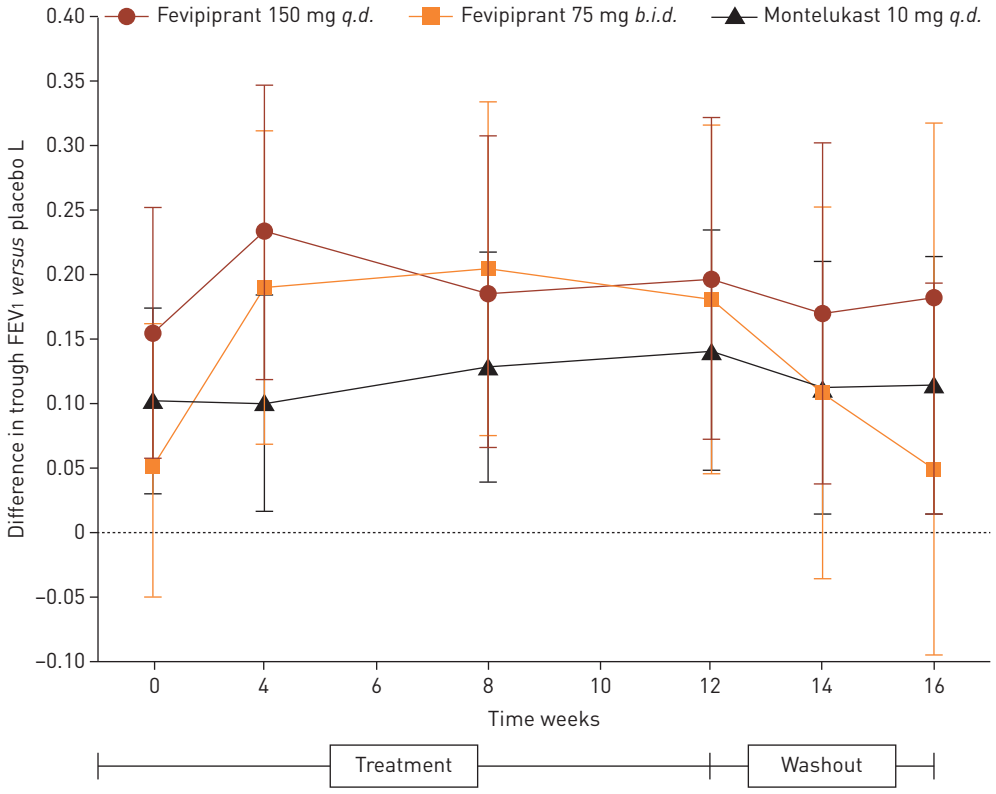

FIGURE 3 Change in forced expiratory volume in 1 s (FEV_1) compared to placebo over time. Change in FEV_1 (L) over time compared to placebo based on a mixed effects model for repeated measures with model terms for treatment, visit, treatment by visit interaction, baseline FEV_1, baseline FEV_1 by visit interaction, region and centre nested within region as a random effect (modified full analysis set). The baseline FEV_1 was defined as the average of two FEV_1 assessments taken in the clinic at 50 min and 15 min prior to the first study drug administration.

In the current study, the observed improvement in FEV_1 with fevipiprant *versus* placebo (0.112 L) was similar to that achieved with montelukast (0.134 L), the active control; however, the study was not powered for this comparison. Lung function improvement should be considered in light of the fact that this was a phase II dose-ranging study rather than a phase III efficacy study, and was restricted to an

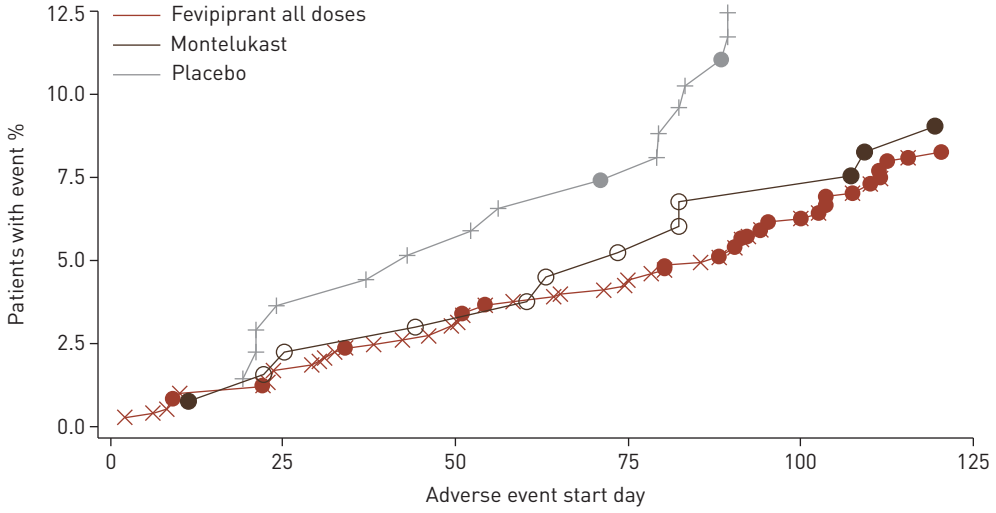

FIGURE 4 Cumulative distribution of asthma worsening (including exacerbations) over time by pooled treatment (safety set). Distribution of adverse events in the fevipiprant, montelukast and placebo groups are represented. Filled circles represent events occurring after treatment cessation.

TABLE 4 Patients reporting common adverse events (≥5% in any group) by preferred term during treatment (safety set)

Preferred term	Placebo (n=136)	Fevipiprant low-dose[#] (n=201)	Fevipiprant mid-dose[¶] (n=219)	Fevipiprant high-dose[+] (n=212)	Fevipiprant 450 mg *q.d.* (n=133)	Fevipiprant total[§] (n=765)	Montelukast 10 mg *q.d.* (n=133)
Any adverse event	68 (50.0)	104 (51.7)	103 (47.0)	95 (44.8)	65 (48.9)	367 (48.0)	63 (47.4)
Nasopharyngitis	6 (4.4)	11 (5.5)	21 (9.6)	15 (7.1)	5 (3.8)	52 (6.8)	8 (6.0)
Headache	8 (5.9)	9 (4.5)	9 (4.1)	9 (4.2)	10 (7.5)	37 (4.8)	8 (6.0)
Asthma exacerbation[f]	6 (4.4)	9 (4.5)	8 (3.7)	11 (5.2)	6 (4.5)	34 (4.4)	6 (4.5)
Upper respiratory tract infection	4 (2.9)	9 (4.5)	7 (3.2)	8 (3.8)	3 (2.3)	27 (3.5)	11 (8.3)
Asthma[f]	10 (7.4)	4 (2.0)	5 (2.3)	11 (5.2)	6 (4.5)	26 (3.4)	4 (3.0)
Pharyngitis	4 (2.9)	9 (4.5)	8 (3.7)	4 (1.9)	1 (0.8)	22 (2.9)	5 (3.8)
Influenza	3 (2.2)	6 (3.0)	4 (1.8)	8 (3.8)	2 (1.5)	20 (2.6)	4 (3.0)
Diarrhoea	2 (1.5)	3 (1.5)	8 (3.7)	4 (1.9)	1 (0.8)	16 (2.1)	1 (0.8)
Sinusitis	3 (2.2)	5 (2.5)	2 (0.9)	4 (1.9)	3 (2.3)	14 (1.8)	5 (3.8)
Viral upper respiratory tract infection	0 (0.0)	6 (3.0)	2 (0.9)	1 (0.5)	3 (2.3)	12 (1.6)	1 (0.8)
Nausea	4 (2.9)	2 (1.0)	5 (2.3)	1 (0.5)	3 (2.3)	11 (1.4)	4 (3.0)
Cough	0 (0.0)	2 (1.0)	4 (1.8)	2 (0.9)	0 (0.0)	8 (1.0)	1 (0.8)
Dizziness	1 (0.7)	1 (0.5)	1 (0.5)	4 (1.9)	1 (0.8)	7 (0.9)	1 (0.8)
Abdominal pain	1 (0.7)	2 (1.0)	4 (1.8)	0 (0.0)	0 (0.0)	6 (0.8)	2 (1.5)
Gastroesophageal reflux disease	0 (0.0)	0 (0.0)	2 (0.9)	3 (1.4)	0 (0.0)	5 (0.7)	1 (0.8)

Data are presented as n (%). Note that the ≥5% cut-off also applies to treatment arms that are not shown; this table only displays the largest of these treatment groups. The safety set included all patients who received at least one dose of study drug whether or not they were randomised. Patients were analysed according to the treatment they received. Adverse events were coded using the medical dictionary for regulatory activities (MedDRA) terminology (Version 16.1). A subject with multiple adverse events is counted only once in the "any adverse event" row. A subject with multiple occurrences of an adverse event under one treatment is counted only once in that adverse event category for that treatment. [#]: fevipiprant low-dose: combination of 1 mg *q.d.*, 3 mg *q.d.*, 2 mg *b.i.d.*, 10 mg *q.d.*; [¶]: fevipiprant mid-dose: combination of 30 mg *q.d.*, 50 mg *q.d.*, 25 mg *b.i.d.*, 75 mg *q.d.*; [+]: fevipiprant high-dose: combination of 150 mg *q.d.*, 75 mg *b.i.d.*, 300 mg *q.d.*, 150 mg *b.i.d.*; [§]: fevipiprant total: combination of all fevipiprant doses; [f]: asthma and asthma exacerbation adverse event terms could both be reported for the same patient. Asthma and/or asthma exacerbation were reported for 55 (7.2%) fevipiprant total doses, 12 (6.0%) fevipiprant low-dose, 12 (5.5%) fevipiprant mid-dose, and 19 (9.0%) fevipiprant high-dose, 12 (9.0%) fevipiprant 450 mg *q.d.*, 14 (10.3%) placebo and nine (6.8%) montelukast patients.

intended target population. Importantly, however, the FEV1 response is comparable to that seen in other phase II and phase III studies of new treatments added to ICS. For example, Laviolette *et al.* [13] reported an FEV1 improvement of 0.14 L in a large phase III trial of montelukast *versus* placebo. In another phase III trial, the addition of 5 µg and 2.5 µg of the long-acting bronchodilator, tiotropium (a muscarinic receptor antagonist), resulted in a 0.122 L and 0.110 L improvement in FEV1, respectively *versus* placebo [14]. It is worth noting that other DP_2 receptor antagonists added to ICS have also demonstrated similar lung function improvements. Hall *et al.* [15] reported an improvement in pre-dose FEV1 of 0.142 L *versus* placebo with BI671800. In the same study, a similar improvement in FEV1 was also observed in patients receiving inhaled fluticasone in addition to BI671800 therapy compared to placebo. It is important to note, however, that as DP_2 receptor inhibitors are not bronchodilators, FEV1 improvement may not the most appropriate clinical outcome to study. Thus, lung function improvement with fevipiprant, whilst confirming efficacy in asthma, may not reflect the full potential of the drug.

No effect on asthma symptom control, quality of life, or work productivity and daily activities was demonstrated; however, the study groups were small and the trial was of short duration. In the past, longer trials have been required to demonstrate montelukast efficacy on these end-points [16, 17]. The *post hoc* findings relating to asthma exacerbations suggest a potential benefit of fevipiprant on other clinical outcomes. The reason for the absence of an effect of fevipiprant on *F*eNO is unclear, but this finding is consistent with that reported by Gonem *et al.* [18] in a 12-week trial of fevipiprant treatment in patients with persistent, moderate-to-severe asthma and an elevated sputum eosinophil count (≥2%). The apparent dissociation between the effects of fevipiprant upon airway eosinophils and *F*eNO is of interest, but needs to be confirmed in trials of longer duration.

In this study, subgroup analyses failed to show evidence of characteristics that predicted a greater clinical response. Recent studies with fevipiprant have suggested greater responses in patients with more severe airflow restriction (in whom improvements in asthma control were also observed) [11], and efficacy in patients with sputum eosinophilia (>2%), uncontrolled on ICS treatment. In the latter study, target engagement was suggested by reductions in sputum eosinophils and improved asthma control was also observed in the subgroup uncontrolled at baseline [12].

A point of interest in our study is the possibility that the dose–response curve for DP_2 receptor antagonists may be bell-shaped rather than monotonic, a finding suggested previously by KRUG *et al.* [19] in a study of BI671800 in allergic rhinitis. In our study, there was no indication that doses above 150 mg per day were needed to achieve maximal effects on FEV_1, and there appeared to be little difference between once-daily and twice-daily dosing.

The high screen failure rate observed in this study reflected the fact that only those who continued to satisfy the inclusion criteria after treatment reduction during run-in were eligible for randomisation. As in previous studies [11, 12], fevipiprant was well-tolerated, with adverse events consistent with those anticipated in moderate-to-severe asthma. The higher incidence of post-randomisation cardiac non-serious adverse events seen in the fevipiprant group were considered to be coincidental and not causally associated with the study drug. This view was based on our inability to identify discernible trends with respect to fevipiprant dose, regimen (*q.d.* or *b.i.d.* dosing), time-of-onset, patient age and gender, concomitant medication, event type and following a detailed ECG review.

In conclusion, our study confirms the efficacy of the oral DP_2 receptor antagonist, fevipiprant, in achieving sustained improvement in pre-dose FEV_1 in patients with allergic asthma who remain uncontrolled despite low-dose ICS therapy, and support its further development for this indication. Changes in FEV_1 were similar to those of the positive control, montelukast. Further research is required to assess the potential of fevipiprant for achieving asthma symptom control, improving quality of life and reducing the risk of exacerbations in patients with asthma.

Acknowledgements

The authors thank Eman Zaman and Gillian Lavelle of Novartis Product Lifecycle Services, for providing medical writing and editorial support, which was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (www.ismpp.org/gpp3).

References

1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2015. Date last accessed: March 31, 2016. www.ginasthma.org
2 Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med* 2014; 24: 14009.
3 Bateman ED, Boushey HA, Bousquet J, *et al.* Can guideline-defined asthma control be achieved? *Am J Respir Crit Care Med* 2004; 170: 836–844.
4 Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy* 2009; 39: 193–202.
5 Barranco P, Pérez-Francés C, Quirce S, *et al.* Consensus document on the diagnosis of severe uncontrolled asthma. *J Investig Allergol Clin Immunol* 2012; 22: 460–475.
6 Accordini S, Corsico A, Cerveri I, *et al.* The socio-economic burden of asthma is substantial in Europe. *Allergy* 2008; 63: 116–124.
7 Juniper EF, Wisniewski ME, Cox FM, *et al.* Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J* 2004; 23: 287–291.
8 Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics* 2005; 61: 738–748.
9 Pinheiro J, Bornkamp B, Glimm E, *et al.* Model-based dose finding under model uncertainty using general parametric models. *Stat Med* 2014; 33: 1646–1661.
10 Schorning K, Bornkamp B, Bretz F, *et al.* Model selection versus model averaging in dose finding studies. *Stat Med* 2016; 35: 4021–4040.
11 Erpenbeck VJ, Popov TA, Miller D, *et al.* The oral CRTh2 antagonist QAW039 (fevipiprant): A phase II study in uncontrolled allergic asthma. *Pulm Pharmacol Ther* 2016; 39: 54–63.
12 Gonem S, Berair R, Singapuri A, *et al.* Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016; 4: 699–707.
13 Laviolette M, Malmstrom K, Lu S, *et al.* Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999; 160: 1862–1868.
14 Paggiaro P, Halpin DMG, Buhl R, *et al.* P260 Tiotropium Respimat® add-on to inhaled corticosteroids improves lung function in patients with symptomatic mild asthma: results from a phase III trial. *Thorax* 2014; 69: Suppl 2, A191.
15 Hall IP, Fowler AV, Gupta A, *et al.* Efficacy of BI 671800, an oral CRTH2 antagonist, in poorly controlled asthma as sole controller and in the presence of inhaled corticosteroid treatment. *Pulm Pharmacol Ther* 2015; 32: 37–44.

16 Bjermer L, Bisgaard H, Bousquet J, *et al.* Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *BMJ* 2003; 327: 891.
17 Korn D, Van den Brande P, Potvin E, *et al.* Efficacy of add-on montelukast in patients with non-controlled asthma: a Belgian open-label study. *Curr Med Res Opin* 2009; 25: 489–497.
18 Gonem S, Berair R, Singapuri A, *et al.* Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016; 4: 699–707.
19 Krug N, Gupta A, Badorrek P, *et al.* Efficacy of the oral chemoattractant receptor homologous molecule on TH2 cells antagonist BI 671800 in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2014; 133: 414–419.