Randomised controlled trial of the prostaglandin D2 receptor antagonist fevipiprant in persistent eosinophilic asthma

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Abstract

Background

Eosinophilic airway inflammation is often present in asthma and interventions that reduce it result in improved clinical outcomes. Antagonism of prostaglandin (PG) D_2 signalling via the chemoattractant receptor homologous molecule expressed on T-helper 2 cells (CRTH2) receptor is a possible means to reduce eosinophilic airway inflammation.

Methods

We performed a single-centre, 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial of the CRTH2 receptor antagonist fevipiprant (QAW039) 225mg twice per day orally in 61 subjects with persistent moderate-to-severe asthma and an elevated sputum eosinophil count. The primary outcome was the change in sputum eosinophil percentage from baseline to post-treatment. Secondary and exploratory outcomes included changes in Asthma Control Questionnaire score (ACQ-7), Standardized Asthma Quality of Life Score (AQLQ(S)), forced expiratory volume in one second (FEV_1), and bronchial submucosal inflammation. This trial is registered with ClinicalTrials.gov (NCT01545726).

Findings

Sputum eosinophil percentage fell from a geometric mean of 5·4% at baseline to 1·1% post-treatment in the fevipiprant group and from 4·7% at baseline to 3·9% post-treatment in the placebo group (between group difference 3·5-fold; 95% confidence interval 1·7 to 7·0; $p < 0·001$). Bronchial submucosal eosinophils were reduced 2.5-fold in the fevipiprant group compared to placebo ($p = 0.040$). AQLQ improved by 0.59 points and post-bronchodilator

FEV_1 by 0.16 L (p = 0.008) in the fevipiprant group compared to placebo. No serious adverse events were reported.

Interpretation

Fevipiprant reduces eosinophilic airway inflammation in patients with persistent asthma and sputum eosinophilia. This is associated with improved lung function and asthma-related quality of life, and a favourable safety profile.

Funding

This work was funded by Novartis Pharmaceuticals, Airway Disease Predicting Outcomes through Patient Specific Computational Modelling (AirPROM) project (funded through FP7 EU grant), Leicester National Institute for Health Research (NIHR) Biomedical Research Unit.

Research in context

Evidence before this study

We searched PubMed for reports published in English before February 1 2016, on the use of CRTH2 receptor antagonists in asthma with the terms “CRTH2”, “prostaglandin D2”, and “asthma”. We also searched the reference lists of identified reports. The most relevant reports identified were of two randomised controlled trials of the compound OC000459, which was found to improve forced expiratory volume in one second and asthma quality of life in steroid-naïve patients. The compound BI671800 was evaluated in two separate randomised controlled trials, one in steroid-naïve adults with asthma, and one in patients receiving inhaled fluticasone. In both cases, six weeks of treatment resulted in modest but statistically significant improvements in forced expiratory volume in one second compared to placebo.

Added value of this study

This is the first study to evaluate a CRTH2 receptor antagonist in a group of patients with moderate-to-severe asthma. We showed that fevipiprant reduces eosinophilic airway inflammation in his group of patients and is associated with improved lung function and asthma-related quality of life. Control of eosinophilic airway inflammation is an important goal of asthma treatment since it has been previously shown to reduce asthma exacerbation rates.

Implications of all the available evidence

Fevipiprant is potentially an important advance because it is a safe and well-tolerated orally acting agent which achieves significant reductions in eosinophilic airway inflammation in patients with moderate-to-severe asthma who are already receiving high-dose inhaled or oral corticosteroids.

Introduction

Asthma is a chronic inflammatory airway disease that is characterised by heterogeneity with respect to clinical phenotype and response to therapy[1]. Eosinophilic airway inflammation, mediated by type 2 immunity, is a common feature of asthma[1]. Treatment strategies that specifically target eosinophilic airway inflammation substantially reduce exacerbations of asthma in those patients with uncontrolled eosinophilic airway inflammation, and to a lesser extent improve lung function and asthma control[2–7].

There is increasing evidence that prostaglandin D2 (PGD_2), acting upon the chemoattractant receptor homologous molecule expressed on T-helper 2 cells (CRTH2/DP2), may play an important role in mediating eosinophilic airway inflammation in asthma. The CRTH2 receptor mediates the migration of T-helper 2 (T_H2) cells, delays their apoptosis and stimulates them to produce the cytokines IL-4, IL-5 and IL-13[8–10]. CRTH2 also influences the migration of and cytokine release from type 2 innate lymphoid cells[11], and the receptor is further expressed by eosinophils, and directly mediates their chemotaxis and degranulation[12,13]. The number of CRTH2+ cells in the bronchial submucosa increases with increasing severity of asthma[14]. CRTH2 is also expressed on airway epithelial cells and directly promotes their migration and differentiation[14]. CRTH2 is therefore a highly promising novel drug target in the treatment of asthma. Fevipiprant (QAW039) is an orally administered highly selective and potent antagonist of the CRTH2 receptor, but not to the more general homeostatic PGD_2 receptor DP1.

We tested the hypothesis that, in patients with sputum eosinophilia ($\geq$ 2%) and persistent, moderate-to-severe asthma, 12-weeks' treatment with fevipiprant at a dose of 225mg twice per day, on top of conventional treatment, reduces the levels of eosinophils in induced

sputum compared to placebo. Secondary objectives were to determine the effects of fevipiprant on asthma symptoms, as measured by the seven-point Asthma Control Questionnaire (ACQ-7)[15], and to assess safety and tolerability of fevipiprant. Exploratory objectives included assessment of the effect of fevipiprant on the forced expiratory volume in one second (FEV_1), lung volumes using body plethysmography, health-related quality of life as measured by the standardised Asthma Quality of Life Questionnaire (AQLQ(S))[16], airway inflammation and remodelling in bronchial biopsies and airway morphometry and lung density assessed by quantitative computed tomography (CT).

Methods

Subjects

Participants were older than 18 years of age and had a clinical diagnosis of asthma that was supported by one or more objective criteria, as described in the appendix. Participants were recruited from a regional refractory asthma clinic providing tertiary care for a population of 4 million people. Suitable participants were also identified from secondary care asthma and general respiratory clinics in the region, and through screening of local primary care databases. Inclusion criteria were current treatment with inhaled corticosteroids (ICS), a sputum eosinophil count of $\geq$ 2% at screening, and either an ACQ-7 score $\geq$ 1·5 at randomization or $\geq$ 1 severe exacerbations in the past 12 months requiring an increase in systemic corticosteroid therapy for three days or more. Exclusion criteria included serious coexisting illness and pregnancy or lactation, and are listed in full in the appendix. All subjects provided written informed consent. The study protocol was approved by the National Research Ethics Committee (Leicestershire, Northamptonshire and Rutland, approval no. 11/EM/0402) and the United Kingdom Medicines and Healthcare Products Regulatory

Agency. The trial was registered with ClinicalTrials.gov (NCT01545726) and EudraCT (2011-004966-13).

Design of the study

The study was a single-centre, randomised, double-blind, placebo-controlled, parallel-group clinical trial conducted from February 2012 through June 2013. The funding organisation (Novartis Pharmaceuticals) supplied the study drug and placebo.

The study design is illustrated in Figure 1a. Participants were given the option of undergoing bronchoscopy at the baseline and post-treatment visits as part of the study. Patients attended a screening visit (Visit 1, Day -21), at which inclusion and exclusion criteria were reviewed. Regular treatment was kept constant from this time point until the end of the study. One week later, a two-week single-blind placebo run-in period was commenced (Visit 2, Day -14). Following this, patients attended a baseline visit (Visit 3, Day 0), at which the inclusion and exclusion criteria were again assessed, taking into account the ACQ-7 score. If patients fulfilled the criteria, they proceeded to undertake the remainder of the study visit tests, and were then randomized in a 1:1 ratio to receive either fevipiprant at a dose of 225 mg twice per day, or an identical placebo. Patients attended a mid-treatment visit (Visit 4, Day 42), and a post-treatment visit (Visit 5, Day 84). At the post-treatment visit, patients began a six-week single-blind placebo washout period, and then attended an end-of-study visit (Visit 6, Day 126). Details of measurements and safety assessments performed at each study visit are shown in the appendix. Criteria for withdrawal from the study were defined *a priori*, and included withdrawal of informed consent, asthma exacerbation, pregnancy, and adverse events for which continued exposure to the study drug would be detrimental.

Randomisation and masking

Randomisation was performed by the trial pharmacist using previously generated treatment allocation cards, and was stratified by whether or not participants were receiving treatment with regular oral corticosteroids, and whether they were undergoing bronchoscopy. All other site staff, patients and sponsor personnel remained blinded to treatment allocation until the study had been completed and the trial database locked. Results of sputum and blood eosinophil counts subsequent to the baseline visit were not disclosed to the investigators during the study because of the expected anti-eosinophilic effects of fevipiprant.

Statistical analysis

The primary outcome of the study was the change in sputum eosinophil percentage between the baseline visit and the post-treatment visit. As sputum eosinophil percentage is known to follow a log-normal distribution, the analysis was based on a $\log_{10}$-transformed scale with differences expressed as a fold change. The secondary outcome was the change from baseline to post-treatment with respect to ACQ-7 score. Exploratory outcomes included the change from baseline to post-treatment with respect to ACQ-7 score in the subgroup with baseline score $\geq$ 1·5, AQLQ(S) score, FEV_1 and submucosal eosinophil count on bronchial biopsy. Statistical analyses were performed using SAS/STAT software, versions 9·3 and 9·4 of the SAS System for AIX (SAS Institute Inc., Cary, NC, USA) and Prism 6 (GraphPad, La Jolla, CA, USA). Changes in efficacy outcomes from the baseline to post-treatment visits were analysed using an analysis of covariance (ANCOVA) model, with treatment as the fixed effect. Randomisation stratum and baseline values of efficacy variables were entered as factors in the ANCOVA model for analysis of the primary outcome, secondary outcome and exploratory outcomes detailed in the statistical analysis plan (see appendix). Exploratory endpoints not explicitly detailed in the statistical analysis plan were analysed without

correction for randomisation stratum or baseline values. The sample size of 60 randomised patients was calculated so that at least 24 patients per arm would complete the post-treatment assessment in order to ensure 80% power at the two-sided 5% significance, assuming a 50% reduction in sputum eosinophil percentage with fevipiprant[17].

Role of the funding source

The sponsor contributed to the study design, data interpretation and writing of the report, and coordinated data collection and analysis. The authors had full access to the data and vouch for the accuracy of the findings. The corresponding author had final responsibility for the decision to submit for publication.

Results

Participants were recruited between Feb 10, 2012 and Jan 30, 2013. A total of 117 patients attended a screening visit, of which 61 fulfilled the inclusion and exclusion criteria and were randomised (Figure 1b). Thirty-one patients were assigned to receive placebo and 30 to receive fevipiprant. Four patients withdrew in the placebo group and three patients in the fevipiprant group, in each case due to an exacerbation of asthma. One patient was assigned to fevipiprant but incorrectly dispensed placebo at the mid-treatment visit. One patient was assigned to fevipiprant but incorrectly dispensed placebo throughout the course of the study. They were included in the fevipiprant group for efficacy analyses, but the latter patient was included in the placebo group for safety analyses. The randomised groups were well-matched for baseline characteristics, as shown in Table 1. Efficacy outcomes are shown in Figures 2-4, and in Tables S1-S3 in the appendix.

The geometric mean sputum eosinophil percentage fell from 5·4% at baseline to 1·1% post-treatment in the fevipiprant group, and from 4·7% at baseline to 3·9% post-treatment in the placebo group. The ratio of geometric means post-treatment to baseline for the sputum eosinophil percentage was 0·78 (1·3-fold reduction) in the placebo group and 0·22 (4·5-fold reduction) in the fevipiprant group, with a 3·5-fold (95% confidence interval [CI] 1·7 to 7·0-fold) greater reduction in the fevipiprant group compared to placebo ($p < 0·001$).

The mean ACQ-7 score fell by 0·32 points from baseline to post-treatment in the fevipiprant group compared to the change seen with placebo, but this improvement did not reach statistical significance (95% CI -0·78, 0·14; $p = 0·170$). However, among the subset of patients ($n = 40$) with an ACQ-7 score $\geq 1·5$ at baseline, the mean ACQ-7 score fell by 0·56 points compared to placebo, which was both clinically and statistically significant (95% CI -1·12, -0·01; $p = 0·046$). The mean AQLQ(S) score improved by 0·59 points in the fevipiprant group compared to placebo, which was both clinically and statistically significant (95% CI 0·16, 1·03; $p = 0·008$). The mean post-bronchodilator FEV_1 increased by 0·16L from baseline to post-treatment in the fevipiprant group compared to placebo, with a statistically significant difference between the groups (95% CI 0·03, 0·30; $p = 0·021$). There were no significant differences between the groups with respect to changes in pre-bronchodilator FEV_1. There were no significant changes in peripheral blood eosinophil count or exhaled nitric oxide in either group.

Paired bronchial biopsies (baseline and post-treatment) were obtained in 14 patients in the fevipiprant group and 12 patients in the placebo group. We observed a 2·5-fold greater reduction in bronchial submucosal eosinophil numbers from baseline to post-treatment in the fevipiprant group compared to the placebo group ($p = 0·040$). There was a 1·7-fold reduction

in bronchial epithelial eosinophil numbers from baseline in favour of fevipiprant, but the treatment difference did not reach statistical significance. Subjects treated with fevipiprant demonstrated a 27·8 percentage point increase in the proportion of intact epithelium (95% CI 2·9, 52·7; p = 0·030), and a 26·6 percentage point reduction in the proportion of denuded epithelium (95% CI -44·9, -8·3; p = 0·006), compared to the change seen with placebo. Changes in epithelial integrity were not significantly correlated with changes in sputum or bronchial mucosal eosinophilic inflammation, as shown in Figure S1 in the appendix.

Functional residual capacity (FRC) fell by 0·31 L in the fevipiprant group compared to the change seen with placebo (95% CI -0·62, -0·001; p = 0·049) and expiratory CT lung volume fell by 216 cm^3 in the fevipiprant group compared to the placebo group (95% CI -391, -40; p = 0·017), but no significant treatment differences were observed with respect to other quantitative CT parameters. Significant positive correlations were observed between changes in plethysmographic and CT-derived measures of expiratory air trapping, as shown in Figure S2 in the appendix.

Outcomes measured following the 6 week washout period returned to baseline without any significant differences between baseline and post-washout for any outcome.

Fevipiprant had an acceptable side-effect profile throughout the study period. There were no deaths or serious adverse events reported, and no patient withdrawals suspected by the investigator to be related to the study drug, as shown in Table S4 in the appendix.

Discussion

We found that fevipiprant significantly reduced eosinophilic inflammation in the sputum and bronchial submucosa compared to placebo in patients with persistent, moderate-to-severe asthma and sputum eosinophilia. This is clinically significant due to the known association between control of eosinophilic airway inflammation and reduction in asthma exacerbations. Fevipiprant significantly improved AQLQ(S) scores, ACQ-7 scores in the sub-group of patients who had poor asthma control at baseline (ACQ-7 ≥ 1·5 points), post-bronchodilator FEV_1 and functional residual capacity compared to placebo. Exploratory analyses of bronchial biopsies suggested that fevipiprant led to improvements in epithelial integrity, but did not affect epithelial goblet cell number or MUC5A expression.

The magnitude of reduction in eosinophilic inflammation reported here was comparable to that observed with mepolizumab[3,4]. Unlike mepolizumab[3,4], and other anti-IL5(R) targeted biologics reslizumab and benralizumab, fevipiprant did not have any significant effect on the blood eosinophil count. This suggests that CRTH2 receptor blockade attenuates the migration of eosinophils into the airway tissues, but does not affect the release of eosinophils from the bone marrow in humans. Previous interventional studies have shown that anti-eosinophilic treatments or strategies exert their major therapeutic effect through the reduction in asthma exacerbations[2–5,7], although effects on FEV_1 have also been observed, particularly in patients with blood eosinophilia[6,7]. The treatment period in this study was not long enough to observe a significant effect on exacerbations. Whether fevipiprant reduces the frequency of exacerbations in patients with eosinophilic asthma is an important question for future studies.

We noted a prompt return to baseline values following a six-week placebo wash-out period in the fevipiprant group with respect to sputum eosinophil percentage, ACQ-7 and AQLQ(S) scores, and FEV_1. This suggests that the short-term improvements in asthma quality of life

and FEV_1 seen with fevipiprant were driven by reversible processes rather than underlying disease modification. However, we observed significant improvements in epithelial integrity following 12 weeks of treatment with fevipiprant compared to placebo. Whether this effect was a consequence of reduced eosinophilic inflammation which is known to cause epithelial damage or a direct effect upon epithelial repair and differentiation as observed *in vitro*[14] remains uncertain, although the lack of an association between changes in sputum eosinophil counts and epithelial integrity in response to fevipiprant favours a direct mechanistic effect upon the epithelium.

Previous clinical trials of CRTH2 receptor antagonists in asthma have yielded mixed results. The compound OC000459 was found to improve FEV_1 and asthma quality of life in steroid-free patients[19], with a subsequent study finding that the beneficial effect was confined to patients with a baseline peripheral blood eosinophil count >250/μl[20]. However, this compound has not yet been tested in patients with moderate-to-severe asthma. AMG853, a dual CRTH2 and D-prostanoid receptor 1 (DP1) antagonist, was not effective in improving asthma symptoms or FEV_1 in patients with moderate-to-severe asthma[21], but there is evidence that CRTH2 and DP1 stimulation may have opposing effects on a number of inflammatory mechanisms[22]. The efficacy of BI671800 was evaluated in two separate randomised controlled trials, one in steroid-naïve adults with asthma, and one in patients receiving inhaled fluticasone[23]. In both cases, six weeks of treatment resulted in modest but statistically significant improvements in FEV_1 compared to placebo. In these previous studies patient selection was not based upon evidence of eosinophilic airway inflammation. Previous experience has shown that targeting anti-eosinophilic therapies to patients with evidence of uncontrolled type 2 inflammation is associated with more clear evidence of efficacy[3–7], and

the positive results obtained in our study should therefore not be extrapolated to an unselected group of patients with moderate-to-severe asthma.

One limitation of our study is the relatively small sample size undertaken in a single centre. However, the effect size in our primary outcome the sputum eosinophil count was large and other positive clinical outcomes showed both statistically and clinically important differences between the fevipiprant and placebo groups. Furthermore, our study design allowed a significant loss of efficacy to be demonstrated when fevipiprant was stopped. In contrast to many clinical trials the clinical outcomes in the group that received placebo were typically worse following intervention compared to their baseline, suggesting deterioration in this group. The lack of a positive placebo effect in this study may be explained by the fact that many of the participants were drawn from a tertiary refractory asthma clinic, and their treatment had previously been fully optimised. We also included a two-week single-blind placebo run-in period prior to the baseline visit specifically in order to minimise the placebo effect. Finally, our inclusion and exclusion criteria mandated a six-week period of clinical stability before patients could participate in the study, thus minimising the potential for changes to occur as a result of regression to the mean.

We conclude that the CRTH2 antagonist fevipiprant is effective at attenuating eosinophilic airway inflammation in patients with persistent eosinophilic asthma, and has a favourable safety profile. There is evidence that fevipiprant improves lung function and asthma-related quality of life, as well as expiratory air trapping and epithelial integrity. Longer-term multi-centre studies are required to confirm these findings and to investigate the effect of fevipiprant on asthma exacerbations.

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Table 1. Baseline Characteristics of Randomised Population		
Characteristic	**Fevipiprant (n = 30)**	**Placebo (n = 31)**
Sex (no. of subjects) Male Female	 18 12	 13 18
Age (yr) Mean Range	 50 20 – 80	 50 19 – 68
Duration of asthma (yr)	32 ± 16	29 ± 15
Body-mass index (kg/m^2)	31·0 ± 5·9	29·6 ± 6·0
Positive atopic status (% of subjects)‡	87	84
Total IgE (U/ml) Median Interquartile range	 414 216 – 863	 388 181 – 1121
FEV_1 before bronchodilator use (% of predicted value)	72·5 ± 23·8	75·1 ± 27·3
FEV_1/FVC before bronchodilator use (%) Median Interquartile range	 68·0 46·7 – 73·6	 69·2 52·1 – 73·5
Improvement in FEV_1 after bronchodilator use (%) Median Interquartile range	 9·3 5·5 – 12·6	 12·0 6·1 – 29·9
Eosinophil count in sputum (%) ¶	5·31 (2·77)	4·24 (4·03)
Eosinophil count in blood (×10^9/L) ¶	0·28 (1·31)	0·28 (0·79)
$FENO_{50}$ (ppb)	30 ± 24	48 ± 43
Score on Asthma Control Questionnaire	1·9 ± 0·8	2·2 ± 0·9
Score on Asthma Quality of Life Questionnaire	5·4 ± 1·1	5·0 ± 1·0

Use of long-acting beta-agonists (% of subjects)	90	84
Regular use of oral prednisolone (% of subjects)	23	23
Global Initiative for Asthma treatment step (number of patients)*		
Step 2	1	1
Step 3	1	4
Step 4	21	19
Step 5	7	7

FEV_1 denotes forced expiratory volume in one second, FVC forced vital capacity, and $FENO_{50}$ fraction of exhaled nitric oxide in exhaled air at a flow rate of 50 ml/s.

Plus-minus values are means ± standard deviation (SD) unless otherwise stated.

‡ Positive atopic status was defined as a positive skin test or radioallergosorbent test for any of a panel of specified aeroallergens (grass pollen, tree pollen [alder, silver birch, hazel], molds [*Aspergillus fumigatus*, *Alternaria tenius*, *Cladosporium*, *Penicillium notatum*], cat fur, dog dander, and house dust mite [*Dermatophagoides pteronyssimus*])

¶ Expressed as geometric mean (coefficient of variation)

* Global Initiative for Asthma treatment steps[18].

Figure 1

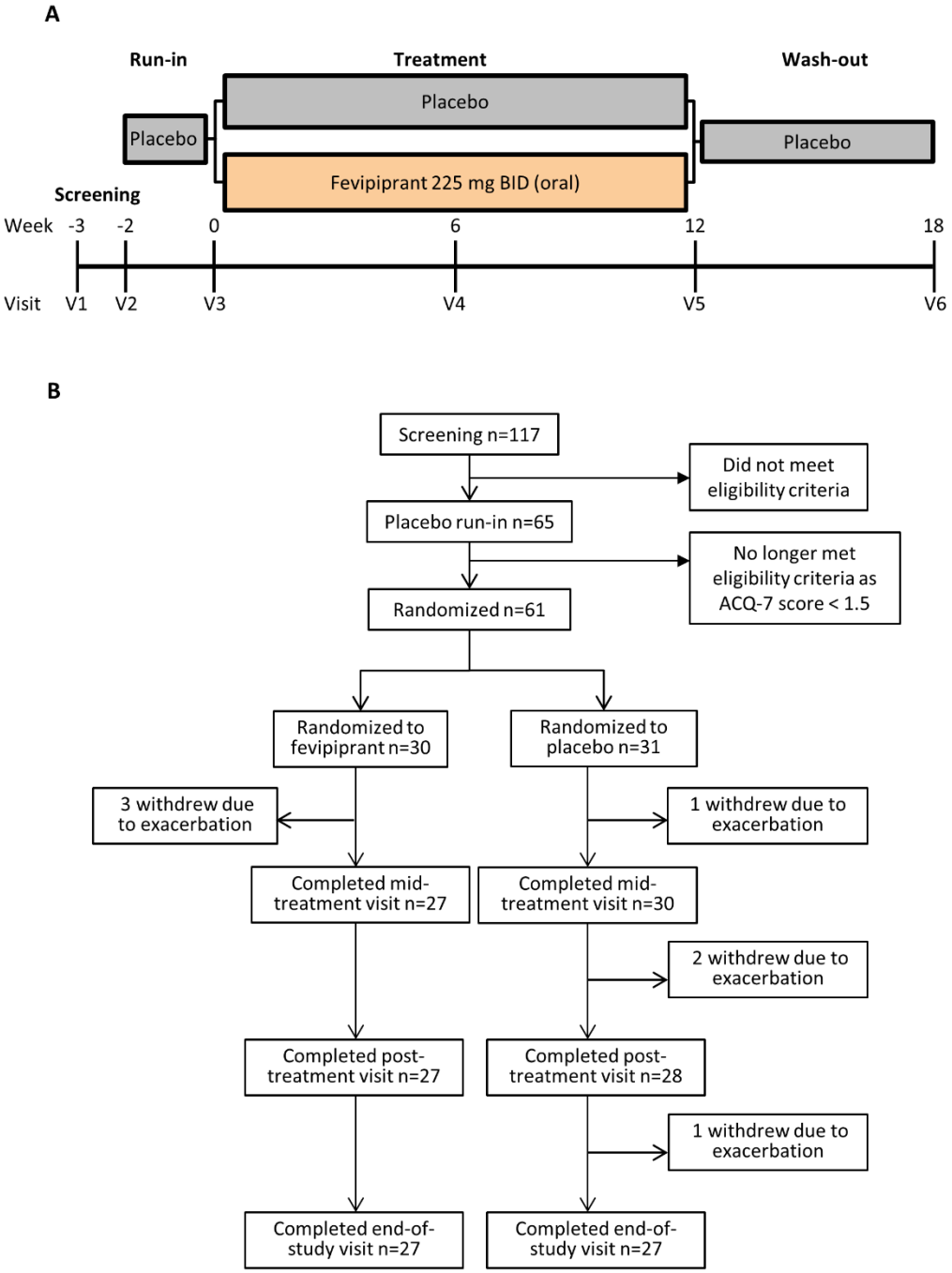
A
Run-in
Treatment
Wash-out
Placebo
Placebo
Placebo
Fevipiprant 225 mg BID (oral)
Screening
Week -3 -2 0 6 12 18
Visit V1 V2 V3 V4 V5 V6
B
Screening n=117
Did not meet eligibility criteria
Placebo run-in n=65
No longer met eligibility criteria as ACQ-7 score < 1.5
Randomized n=61
Randomized to fevipiprant n=30
Randomized to placebo n=31
3 withdrew due to exacerbation
1 withdrew due to exacerbation
Completed mid-treatment visit n=27
Completed mid-treatment visit n=30
2 withdrew due to exacerbation
Completed post-treatment visit n=27
Completed post-treatment visit n=28
1 withdrew due to exacerbation
Completed end-of-study visit n=27
Completed end-of-study visit n=27

Figure 2

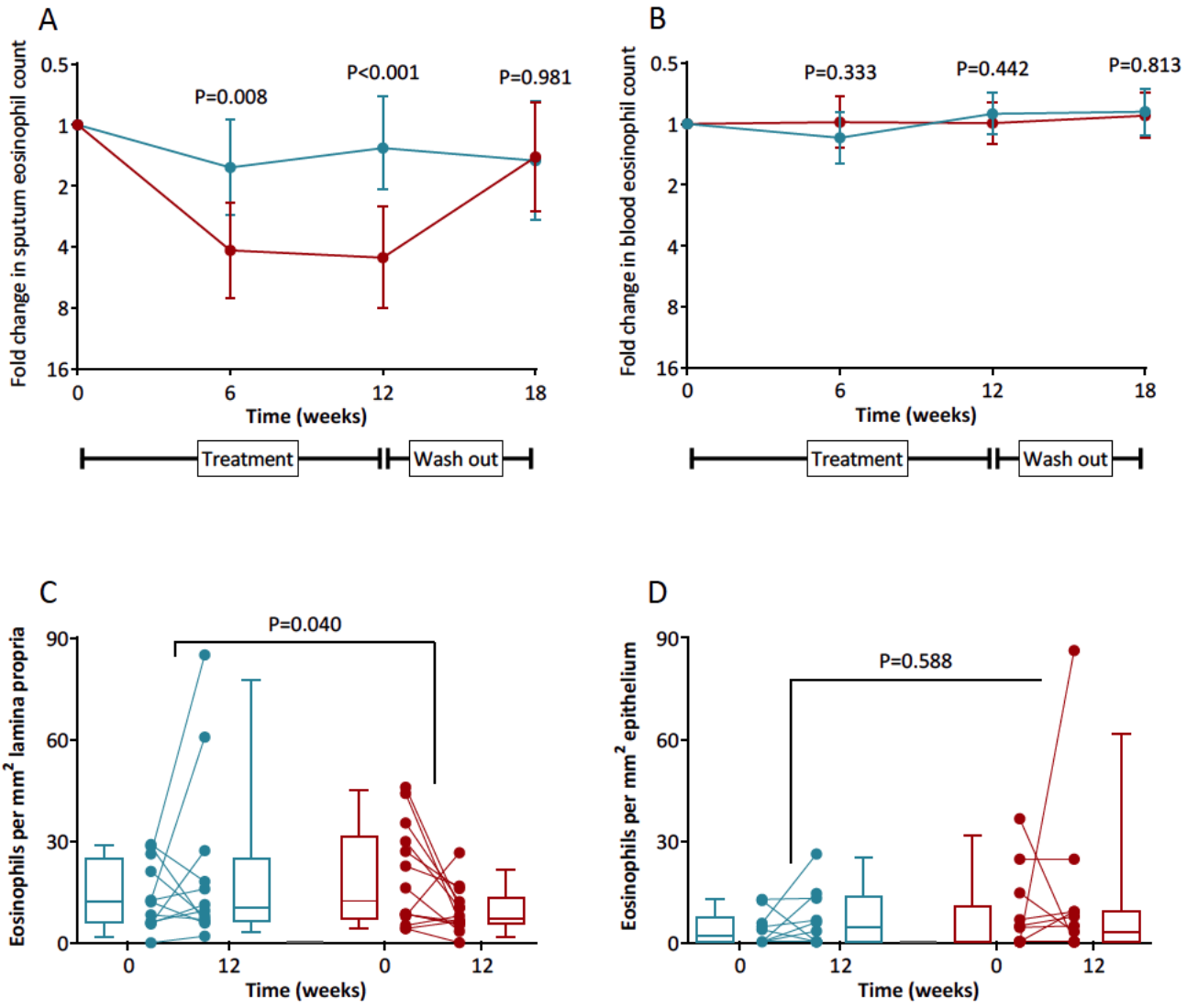
A
Fold change in sputum eosinophil count
0.5
1
2
4
8
16
P=0.008
P<0.001
P=0.981
0
6
12
18
Time (weeks)
Treatment
Wash out
B
Fold change in blood eosinophil count
P=0.333
P=0.442
P=0.813
C
Eosinophils per mm2 lamina propria
90
60
30
0
P=0.040
Time (weeks)
D
Eosinophils per mm2 epithelium
P=0.588

Figure 3

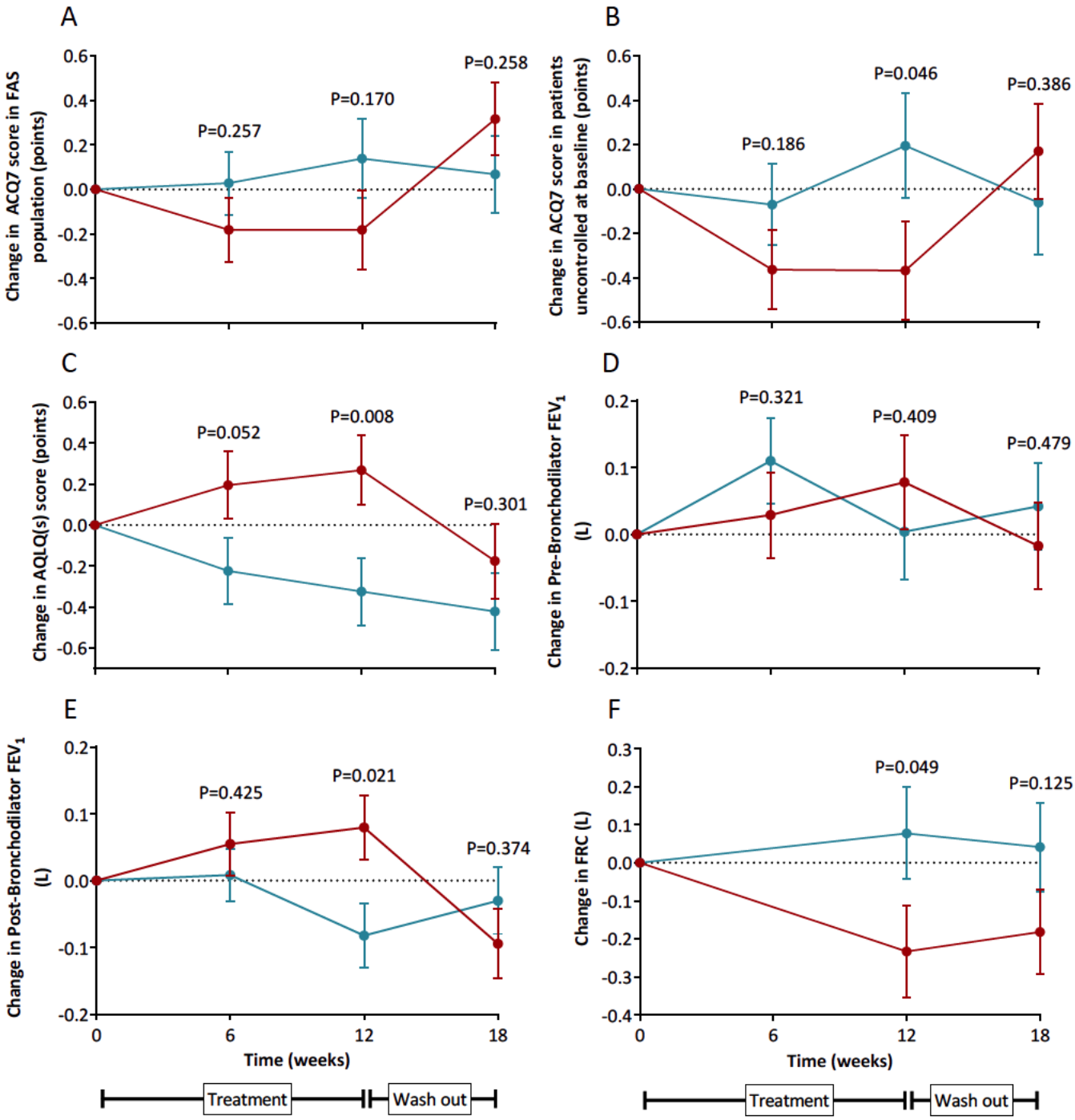
A
Change in ACQ7 score in FAS population (points)
P=0.257
P=0.170
P=0.258
B
Change in ACQ7 score in patients uncontrolled at baseline (points)
P=0.186
P=0.046
P=0.386
C
Change in AQLQ(s) score (points)
P=0.052
P=0.008
P=0.301
D
Change in Pre-Bronchodilator FEV1 (L)
P=0.321
P=0.409
P=0.479
E
Change in Post-Bronchodilator FEV1 (L)
P=0.425
P=0.021
P=0.374
F
Change in FRC (L)
P=0.049
P=0.125
0
6
12
18
Time (weeks)
Treatment
Wash out

Figure 4

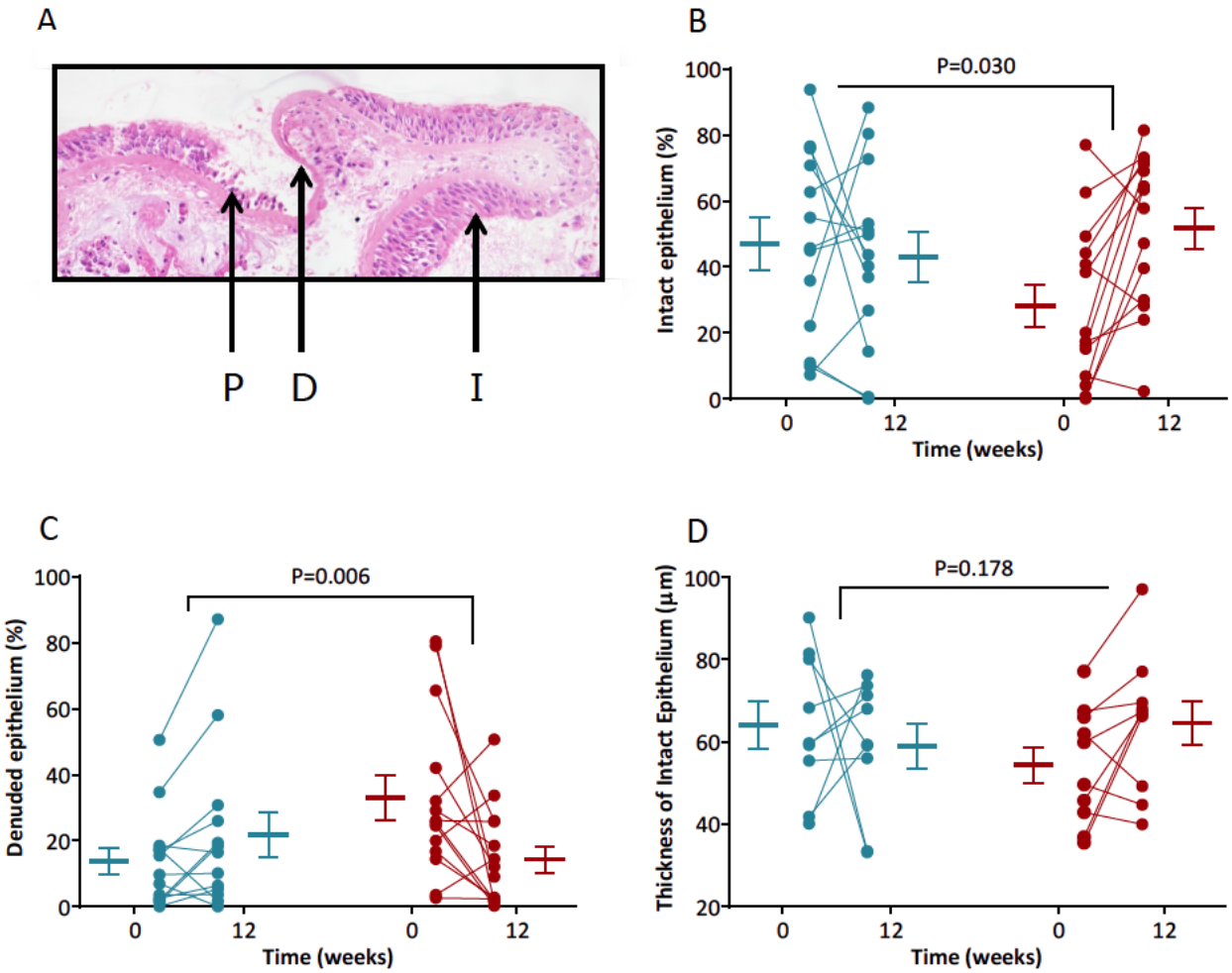
A
P
D
I
B
P=0.030
Intact epithelium (%)
Time (weeks)
C
P=0.006
Denuded epithelium (%)
Time (weeks)
D
P=0.178
Thickness of Intact Epithelium (µm)
Time (weeks)

Figure Legends

Figure 1: Summary of study protocol and participant flow

Panel A shows the timings of study visits and treatment allocations. Panel B shows the number of patients who attended screening, were randomised, and completed each of the study visits.

Figure 2: Comparison of eosinophilic inflammation outcomes between the study groups

Panels A and B show fold-changes in sputum and blood eosinophil counts respectively at each study visit compared to the baseline visit, in the placebo (blue) and fevipiprant (orange) groups. P values refer to differences between the study groups with respect to change from the baseline visit. Panels C and D show lamina propria and epithelial eosinophil numbers respectively at the baseline and post-treatment visits, in the placebo (blue) and fevipiprant (orange) groups. Box and whisker plots show the median, 25^{th} and 75^{th} percentiles as a box, and the 10^{th} and 90^{th} percentiles as whiskers. P values refer to differences between the study groups with respect to change from the baseline visit to the post-treatment visit.

Figure 3: Comparison of patient-reported and lung function outcome measures between the study groups

Changes compared to the baseline visit are shown in the placebo (blue) and fevipiprant (orange) groups with respect to Asthma Control Questionnaire score (ACQ7) in the Full Analysis Set (FAS, Panel A), ACQ7 in the subgroup with a baseline value ≥ 1·5 (Panel B), standardised Asthma Quality of Life Questionnaire score (AQLQ(S), Panel C), forced expiratory volume in one second (FEV_1) performed before the administration of a bronchodilator (Panel D), FEV_1 performed after the administration of a bronchodilator (Panel

E), and functional residual capacity (FRC, Panel F). P values refer to differences between the study groups with respect to change from the baseline visit to the post-treatment visit.

Figure 4: Comparison of epithelial damage outcome measures between the study groups

Panel A shows a photomicrograph of a bronchial biopsy specimen demonstrating the appearance of intact epithelium (I), partially denuded epithelium (P) and denuded epithelium (D). Panels B-D show percentage of epithelium that is intact, percentage of epithelium that is denuded and thickness of intact epithelium respectively at the baseline and post-treatment visits, in the placebo (blue) and fevipiprant (orange) groups. Error bars indicate the mean plus or minus the standard error of the mean. P values refer to differences between the study groups with respect to change from the baseline visit to the post-treatment visit.