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Efficacy of BI 671800, an oral CRTH2 antagonist, in poorly controlled asthma as sole controller and in the presence of inhaled corticosteroid treatment

Ian P. Hall [a, *], Andrew V. Fowler [b], Abhya Gupta [c], Kay Tetzlaff [d], Michael C. Nivens [c], Maria Sarno [b], Helen A. Finnigan [b], Eric D. Bateman [e], E. Rand Sutherland [f]

[a] Division of Respiratory Medicine, University of Nottingham, Nottingham, UK
[b] Clinical Development & Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Ltd., Bracknell, UK
[c] Clinical Development & Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany
[d] Clinical Development & Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany
[e] Department of Medicine, University of Cape Town, Cape Town, South Africa
[f] National Jewish Health, Denver, CO, USA

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ABSTRACT

The prostaglandin D_2 (PGD_2) receptor, CRTH2, plays a role in allergic airway inflammation. The efficacy of BI 671800, a CRTH2 antagonist, was assessed in 2 separate trials in patients with asthma, in either the absence or the presence of inhaled corticosteroid (ICS) therapy. In this study, BI 671800 (50, 200 or 400 mg) and fluticasone propionate (220 μg) all given twice daily (bid) were compared with bid placebo in symptomatic controller-naïve adults with asthma (Trial 1), and BI 671800 400 mg bid compared with montelukast 10 mg once daily (qd), and matching placebo bid, in patients with asthma receiving inhaled fluticasone (88 μg bid) (Trial 2). The primary endpoint in both trials was change from baseline in trough forced expiratory volume in 1 s (FEV_1) percent predicted. After 6 weeks' treatment, adjusted mean treatment differences (SE) for the primary endpoint compared with placebo in Trial 1 were 3.08% (1.65%), 3.59% (1.60%) and 3.98% (1.64%) for BI 671800 50, 200 and 400 mg bid, respectively, and 8.62% (1.68%) for fluticasone 220 μg bid ($p = 0.0311$, $p = 0.0126$, $p = 0.0078$ and $p < 0.0001$, respectively). In Trial 2, adjusted mean FEV_1 (SE) treatment differences compared with placebo were 3.87% (1.49%) for BI 671800 400 mg bid and 2.37% (1.57%) for montelukast ($p = 0.0050$ and $p = 0.0657$, respectively). These findings suggest that BI 671800 is associated with a small improvement in FEV_1 in symptomatic controller-naïve asthma patients, and in patients on ICS.

1. Introduction

Asthma is a chronic inflammatory disease of the airways, marked by symptoms attributable to episodic bronchodilator-responsive airflow limitation and airway hyperresponsiveness [1]. Airway inflammation in asthma involves a complex interaction of inflammatory mediators, often triggered by an allergen-induced immunoglobulin E (IgE)-mediated release by mast cells of mediators such as histamine, proteases, cytokines and eicosanoids, including leukotrienes and prostaglandins.

Prostaglandin D_2 (PGD_2), an arachidonic acid metabolite important to the pathogenesis of asthma, is released by IgE-activated mast cells and other inflammatory cell types, such as

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; AUC, area under the curve; bid, twice daily; CI, confidence interval; CRTH2, chemoattractant receptor homologous molecule on Th2 cells; FAS, full analysis set; $FEF_{25-75\%}$, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; PEF, peak expiratory flow; PGD_2, prostaglandin D_2; qd, once daily; SABA, short-acting β-agonist; Th2, T-helper type 2 [cell]; ULN, upper limit of normal.

* Corresponding author. Faculty Executive Dean's Office, Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK. Tel.: +44 115 823 0019.

E-mail addresses: Ian.Hall@nottingham.ac.uk (I.P. Hall), Andy.Fowler@boehringer-ingelheim.com (A.V. Fowler), Abhya.Gupta@boehringer-ingelheim.com (A. Gupta), Kay.Tetzlaff@boehringer-ingelheim.com (K. Tetzlaff), Chad.Nivens@boehringer-ingelheim.com (M.C. Nivens), Maria.Sarno@boehringer-ingelheim.com (M. Sarno), Helen.Finnigan.ext@boehringer-ingelheim.com (H.A. Finnigan), Eric.Bateman@uct.ac.za (E.D. Bateman), SutherlandE@NJHealth.org (E. Rand Sutherland).

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platelets, alveolar macrophages, T-helper type 2 (Th2) cells and dendritic cells following allergen exposure. The pro-inflammatory effects of PGD_2 occur via interactions with the chemoattractant receptor homologous molecule on Th2 cells (CRTH2), a 7-transmembrane G-protein-coupled receptor selectively expressed on Th2 cells, eosinophils and basophils [2–4]. PGD_2 chemotactic activity recruits circulating eosinophils and basophils from the vascular bed to the site of inflammation in a CRTH2-dependent manner. Furthermore, PGD_2 has an important role in the early phase of CRTH2-dependent Th2-cell recruitment and activation, resulting in the production of cytokines (eg, interleukin (IL)-4, IL-5, IL-9 and IL-13), which, in turn, further stimulate mast cells and eosinophils [5]. Thus, inhibition of CRTH2 may attenuate important inflammatory pathways in asthma, thereby reducing airway inflammation and potentially improving asthma control.

A previous study of the CRTH2 antagonist, OC000459, in corticosteroid-naïve individuals with asthma reported a statistically significant improvement in forced expiratory volume in 1 s (FEV_1) in the per-protocol patient group, but not in the intention-to-treat cohort [6]. A study of a different molecule, a dual DP1 and CRTH2 antagonist, AMG 853, found no improvement in Asthma Control Questionnaire (ACQ) score or FEV_1 [7]. The explanation for these inconsistent results is unclear, but may relate to differences in the efficacy of the agents used, variation in trial design, or differences in receptor selectivity of the 2 compounds.

We hypothesised that inhibition of CRTH2 with BI 671800, a highly specific and potent CRTH2 antagonist [8], would result in improved lung function in adult patients with mild-to-moderate asthma. Here we report the results of 2 clinical trials – 1 in controller-naïve patients with symptomatic asthma (study 1268.17; Trial 1), the other in symptomatic patients taking inhaled corticosteroids (study 1268.16; Trial 2) – and provide evidence that antagonism of CRTH2 can improve lung function in patients with asthma.

2. Methods

2.1. Trial design

We conducted 2 separate clinical trials, both of which were multicentre, multinational, randomised, double-blind and were placebo-controlled, parallel-group, double-dummy designs. Trial 1 examined the efficacy, safety and tolerability of 3 doses of BI 671800 (50, 200 or 400 mg twice daily) and fluticasone propionate 110 μg 2 inhalations twice daily, compared with matching placebo in symptomatic steroid-naïve adults with asthma. Trial 2 compared the efficacy, safety and tolerability of BI 671800 400 mg twice daily and montelukast 10 mg once daily, with matching placebo twice daily in patients with asthma taking inhaled fluticasone (88 μg twice daily).

For both studies, the inclusion criteria were non-smoking (or ex-smoking) patients with asthma, age 18–65 years with documented airflow reversibility, a pre-bronchodilator FEV_1 60–85% predicted, and an ACQ score ≥1.5 at randomisation. For Trial 1, patients were not to have taken an inhaled corticosteroid (ICS) for ≥6 weeks before screening. For Trial 2, patients had to have been on a stable dose of ICS for ≥3 months before screening; following a run-in period of 2–4 weeks, patients were randomised if they were symptomatic despite using inhaled fluticasone propionate (44 μg, 2 inhalations twice daily) during at least the last 2 weeks of the run-in period. A summary of the trial designs is shown in Fig. 1A and B.

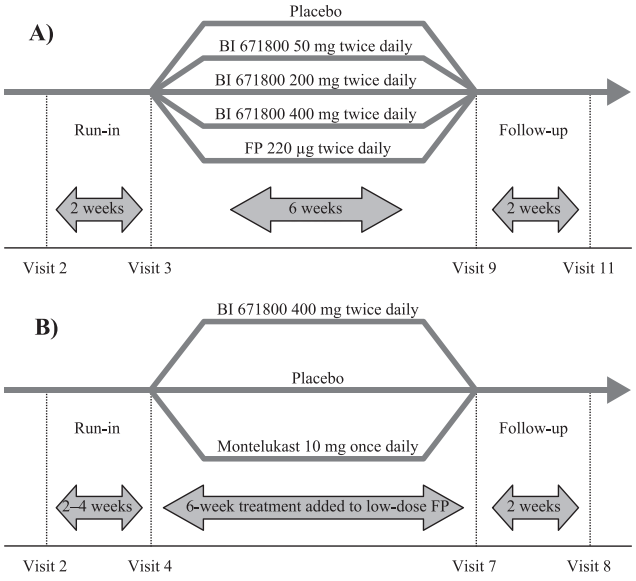

Fig. 1. Design of (A) Trial 1 (1268.17); (B) Trial 2 (1268.16); FP = fluticasone propionate.

2.2. Randomisation and masking

The sponsor generated a randomisation list using a validated system involving a pseudo-random number generator and a supplied seed number. Patients, investigators, and the sponsor remained blinded with regard to the randomised treatment assignments up to database lock, in accordance with the study protocol. After assessment of all inclusion and exclusion criteria, eligible patients were assigned a medication number by an Interactive Voice Response System at the time of randomisation. Respective placebos for BI 671800 and montelukast capsules (Trial 2) and for the fluticasone propionate metered dose inhaler (Trial 1) could not be distinguished by appearance, taste or odour.

2.3. Endpoints

The primary endpoint for both studies was change from baseline in trough FEV_1 percent predicted at 6 weeks. The secondary endpoint was change from baseline in ACQ mean score at 6 weeks. Changes in trough FEV_1 percent predicted and ACQ mean score were analysed in the full analysis set (FAS) using a mixed-effect, repeated-measures model with terms for baseline, treatment, test day, treatment by test day interaction, baseline by test day interaction as fixed effects and patient as a random effect. Other endpoints included FEV_1 percent predicted area under the curve $(AUC)_{0-3h}$, forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC ($FEF_{25-75\%}$), morning and evening peak expiratory flow (PEF), Asthma Quality of Life Questionnaire (AQLQ), short-acting β-agonist (SABA) use, time to first worsening of asthma and time to first exacerbation. In addition to the FAS, a per-protocol sensitivity analysis was performed for each study.

Both studies were approved by the appropriate ethical review committees and were registered with ClinicalTrials.gov (NCT01092148 for Trial 1 and NCT01103349 for Trial 2).

3. Results

In both trials, participant characteristics at baseline were balanced across treatment groups (Tables 1 and 2).

3.1. Efficacy of BI 671800 in patients with asthma not taking an inhaled corticosteroid (Trial 1)

A total of 1045 patients were screened; of these, 656 were screen failures and 389 were randomised: 78 to placebo, 77, 84 and 79 to BI 671800 50, 200 and 400 mg twice daily, respectively, and 71 to fluticasone 220 μg twice daily. A total of 40 participants discontinued the trial prematurely (see Fig. 2A for details). Of the 389 randomised participants, 388 received ≥1 dose of study medication and were included in the treatment set. A further 15 patients had either no baseline or on-treatment trough FEV_1 data, resulting in 373 patients being included in the FAS.

3.2. Effects on lung function (Trial 1)

After 6 weeks of treatment, the adjusted mean treatment differences (SE) compared with placebo for trough FEV_1 were 3.08% (1.65%), 3.59% (1.60%) and 3.98% (1.64%) for 50, 200 and 400 mg twice daily, respectively, and 8.62% (1.68%) for fluticasone 220 μg twice daily (Fig. 3A). Versus placebo, these differences were statistically significant (at the 2.5% level) for all treatment groups with the exception of the 50 mg twice-daily group: (1-sided *p*-values were 0.0311, 0.0126, 0.0078 and $p < 0.0001$, respectively). Compared with fluticasone 220 μg twice daily, the adjusted mean treatment differences (SE) after 6 weeks were −5.54% (1.65%), −5.03% (1.61%) and −4.64% (1.65%) for the 50, 200 and 400 mg twice daily treatment arms, respectively. These differences, in favour of fluticasone, were statistically significant at the 5% significance level (*post hoc* analysis); 2-sided *p*-values were 0.0009, 0.0018 and 0.0050, respectively. The corresponding adjusted mean absolute difference in trough FEV_1 between BI 671800 400 mg and placebo was 134 mL, and 293 mL for fluticasone 220 μg compared with placebo. A *post hoc* subgroup analysis was conducted on groups defined by peripheral blood eosinophil counts. A greater improvement in FEV_1 was noted in patients with an eosinophil count of >350 cells/mm^3 in patients dosed with 200 and 400 mg bid (200 mg bid: increase of 2.85 FEV_1 % predicted vs. baseline for patients with eosinophils >350 cells/mm^3, $n = 30$, compared to 0.64% for patients with <350 cells/mm^3, $n = 51$; 400 mg bid: 4.38% increase vs. baseline for patients with eosinophils >350 cells/mm^3, $n = 17$, compared to 1.35% for patients with <350 cells/mm^3, $n = 54$. Eosinophil data were not available for 6 subjects.

3.3. Effects on asthma control and on exploratory endpoints (Trial 1)

No statistically significant effect (at the 1-sided 2.5% level) of BI 671800 was observed on asthma control (ACQ). In contrast, FP 220 μg twice daily was associated with a statistically significant improvement in ACQ. Some exploratory endpoints demonstrated statistical significant improvements with BI 671800 (at the 1-sided 2.5% level): FEV_1 percent predicted AUC_{0-3h}, trough FEV_1, FEV_1 AUC_{0-3h}, trough FEF and morning PEF (Table 3). Besides the improvement in pulmonary function, the highest dose tested for BI 671800, 400 mg twice daily, also associated prolonged the time to the first asthma worsening compared with placebo (hazard ratio [HR] 0.45, $p = 0.0074$), an efficacy similar to that seen in the fluticasone arm (HR 0.33, $p = 0.0015$).

3.4. Safety and tolerability (Trial 1)

BI 671800 was safe and well tolerated at all doses evaluated. There were no differences in adverse events across treatment groups. Only 2 serious adverse events were reported (1 in the placebo group, 1 in the BI 678100 400-mg dose group). Neither event was considered study drug related. There were more discontinuations due to an adverse event in the placebo group compared with any active treatment group, primarily due to worsening of asthma. A full list of adverse events is reported in Supplementary Table S1. Four patients taking BI 671800 had small elevations of hepatic transaminases that were maximally <6 × ULN (upper limit of normal).

3.5. Efficacy of BI 671800 in patients with asthma taking an inhaled corticosteroid (Trial 2)

A total of 647 patients were screened; of these, 404 were screen failures, and 243 were randomised: 95 to placebo, 81 to BI 671800 400 mg twice daily and 67 to montelukast 10 mg once daily. All continued on inhaled fluticasone 88 μg twice daily. All 243 randomised patients received ≥1 dose of study medication and were included in the treated set. A total of 22 participants discontinued the trial prematurely (see Fig. 2B for details). Thirteen patients had either no baseline or no on-treatment trough FEV_1 data, resulting in only 230 patients being included in the FAS.

Table 1
Baseline characteristics (Trial 1).

Treatment arm	Placebo	BI 671800 50 mg twice daily	BI 671800 200 mg twice daily	BI 671800 400 mg twice daily	FP 220 μg twice daily	Total
n	78	77	83	79	71	388
Age, years	36.4 (13.0)	39.1 (11.5)	35.1 (11.1)	37.5 (12.2)	39.4 (12.2)	37.4 (12.1)
Female, %	47.4	53.2	50.6	54.4	50.7	51.3
BMI	26.4 (4.7)	27.0 (4.6)	25.9 (4.3)	26.5 (4.7)	26.7 (4.6)	26.5 (4.5)
Allergic asthma, *n* (%)	59 (75.6)	58 (75.3)	65 (78.3)	67 (84.8)	56 (78.9)	305 (78.6)
FEV_1, percent predicted	72.7 (6.5)	71.4 (7.3)	73.3 (7.3)	73.6 (6.9)	72.3 (6.9)	72.7 (7.0)
FEV_1, L	2.52 (0.63)	2.41 (0.62)	2.60 (0.65)	2.49 (0.65)	2.42 (0.55)	2.49 (0.62)
FEV_1 at screening, L	2.47 (0.70)	2.32 (0.66)	2.60 (0.68)	2.42 (0.64)	2.36 (0.59)	2.46 (0.65)
FEV_1/FVC ratio, %	68.7 (10.0)	67.1 (10.6)	67.4 (8.5)	68.2 (9.7)	68.1 (8.8)	67.9 (9.5)
Weekly mean SABA use, puffs/day	2.9 (2.7)	3.0 (2.7)	2.7 (2.8)	3.0 (2.7)	2.8 (2.4)	2.9 (2.7)
ACQ score	2.2 (0.6)	2.3 (0.6)	2.3 (0.6)	2.3 (0.5)	2.4 (0.6)	2.3 (0.6)
Weekly mean morning PEF, L/min	378.0 (114.6)	380.8 (124.1)	374.1 (120.9)	381.5 (116.3)	370.0 (118.6)	377.0 (118.4)
No LABA use, *n* (%)	65 (83.3)	65 (84.4)	67 (80.7)	60 (75.9)	56 (78.9)	313 (80.7)

Data expressed as mean (SD) unless otherwise stated; ACQ = Asthma Control Questionnaire; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; FP = fluticasone propionate; FVC = forced vital capacity; LABA = long-acting β_2-agonist; PEF = peak expiratory flow; SABA = short-acting β_2-agonist; SD = standard deviation.

Table 2
Baseline characteristics (Trial 2).

Treatment arm	Placebo	BI 671800 400 mg twice daily	Montelukast 10 mg twice daily	Total
n	95	81	67	243
Age, years	41.4 (12.6)	41.8 (12.7)	41.7 (12.0)	41.6 (12.4)
Female, %	57.9	61.7	62.7	60.5
BMI	26.8 (4.3)	27.6 (4.1)	26.7 (4.1)	27.0 (4.2)
Allergic asthma, *n* (%)	73 (76.8)	67 (82.7)	47 (70.1)	187 (77.0)
FEV_1, percent predicted	72.1 (7.3)	72.6 (7.6)	72.3 (7.2)	72.3 (7.3)
FEV_1, L	2.49 (0.55)	2.49 (0.59)	2.42 (0.61)	2.47 (0.58)
FEV_1 at screening, L	2.35 (0.63)	2.39 (0.70)	2.32 (0.63)	2.36 (0.65)
FEV_1/FVC ratio, %	65.0 (10.8)	65.8 (10.1)	65.5 (8.9)	65.4 (10.0)
Weekly mean SABA use, puffs/day	1.9 (2.1)	1.7 (1.8)	1.8 (1.9)	1.8 (1.9)
ACQ score	2.2 (0.5)	2.1 (0.5)	2.0 (0.5)	2.1 (0.5)
Weekly mean morning PEF, L/min	353.4 (121.8)	363.3 (118.2)	345.7 (115.6)	354.6 (118.6)
No LABA use, *n* (%)	55 (57.9)	49 (60.5)	37 (55.2)	141 (58.0)

Data expressed as mean (SD) unless otherwise stated; ACQ = Asthma Control Questionnaire; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; FP = fluticasone propionate; FVC = forced vital capacity; LABA = long-acting β_2-agonist; PEF = peak expiratory flow; SABA = short-acting β_2-agonist; SD = standard deviation.

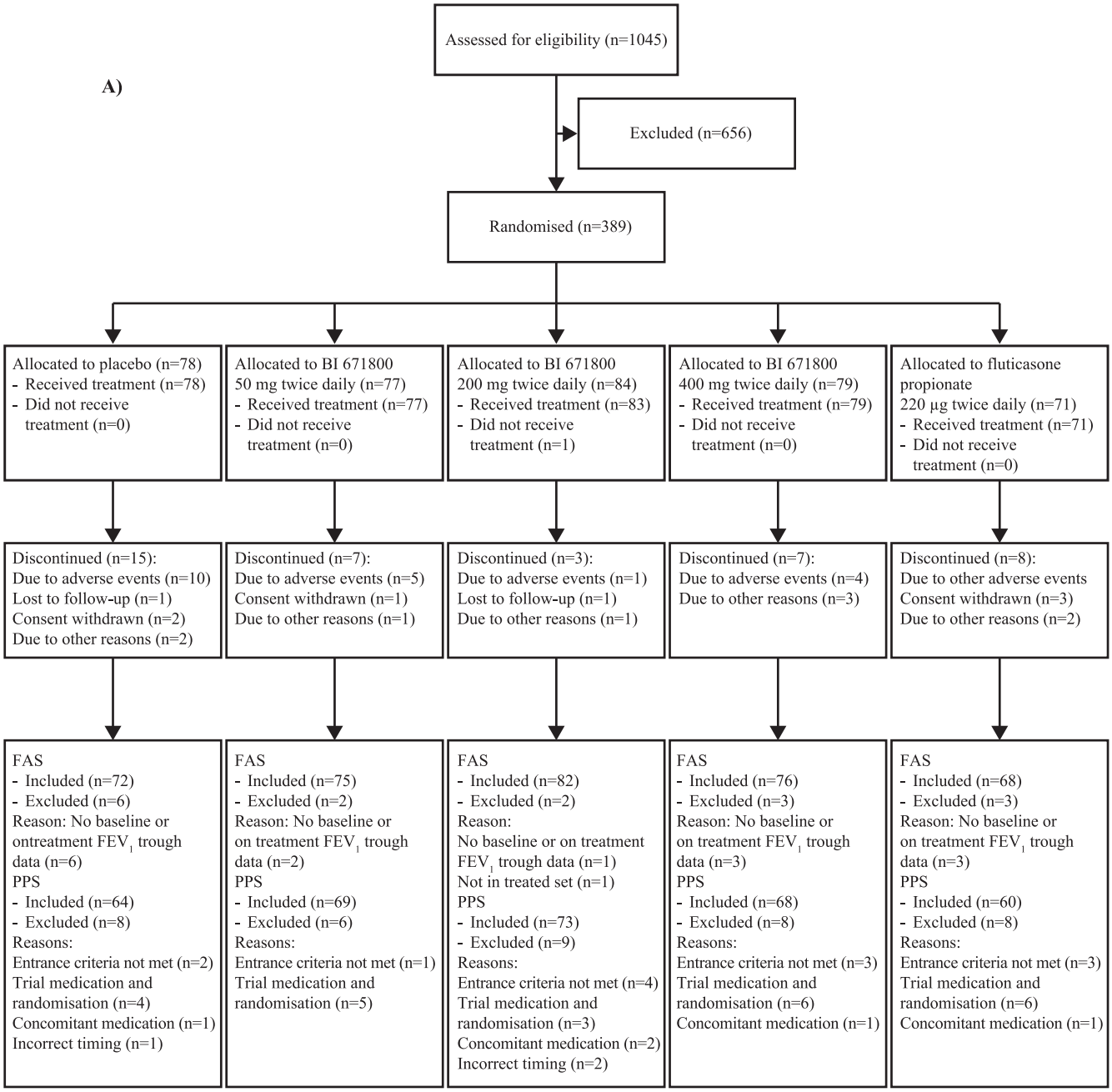

Fig. 2. CONSORT diagrams for Trial 1 (A) and Trial 2 (B). Patients may have >1 reason for exclusion; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 s; PPS = per-protocol set.

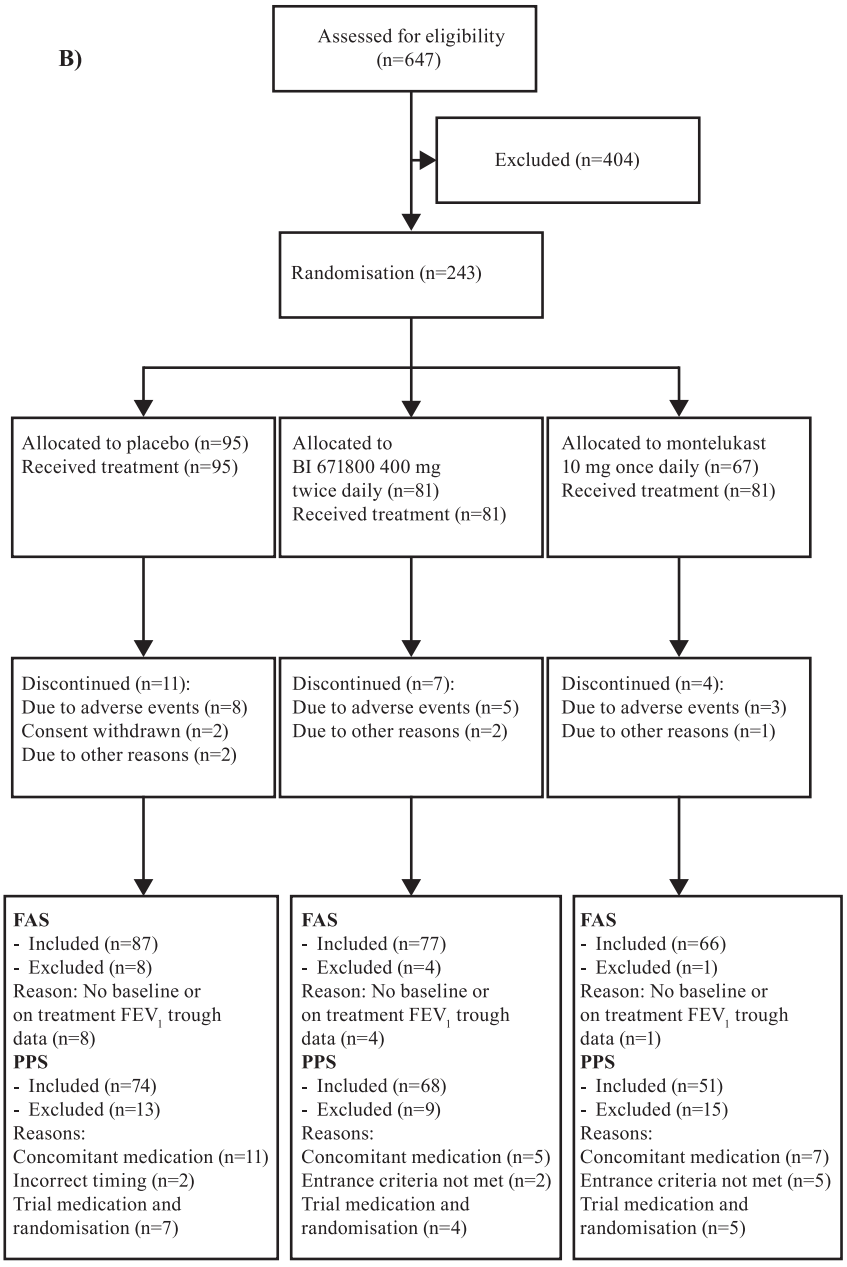

Fig. 2. (*continued*).

3.6. Effects on lung function (Trial 2)

After 6 weeks of treatment, the adjusted mean treatment difference (SE) for change from baseline in trough FEV_1 percent predicted versus placebo was 3.87% (1.49%) for BI 671800 (1-sided *p*-value was 0.0050), but not statistically significant for montelukast (Fig. 3B). Compared with montelukast, the adjusted mean treatment difference (SE) after 6 weeks was 1.50% (1.60%). This difference was not statistically significant ($p = 0.1748$). The corresponding adjusted mean absolute difference in trough FEV_1 between BI 671800 and placebo was 142 mL, and 80 mL for montelukast compared with placebo. In the *post hoc* subgroup analysis of peripheral blood eosinophil counts, an increase in FEV_1 % predicted of 5.06% was observed in the high eosinophil group ($n = 24$) compared to 2.33% in the lower eosinophil group ($n = 50$). Eosinophil data were not available for 3 subjects in this study.

3.7. Effects on asthma control and other endpoints (Trial 2)

The adjusted mean (SE) treatment difference for change from baseline in mean ACQ score versus placebo after 6 weeks of treatment was −0.28 (0.12) for BI 671800 (1-sided *p*-value was 0.0092) but was not statistically significant for montelukast. The in-clinic spirometry assessments, including FEV_1 percent predicted AUC_{0-3h}, trough FEV_1, FEV_1 AUC_{0-3h} and trough FEF, showed BI 671800 400 mg to be statistically significantly superior to placebo at Week 6. These and other endpoint results are presented in Table 4. The effects on asthma worsening for BI 671800 (HR 0.75)

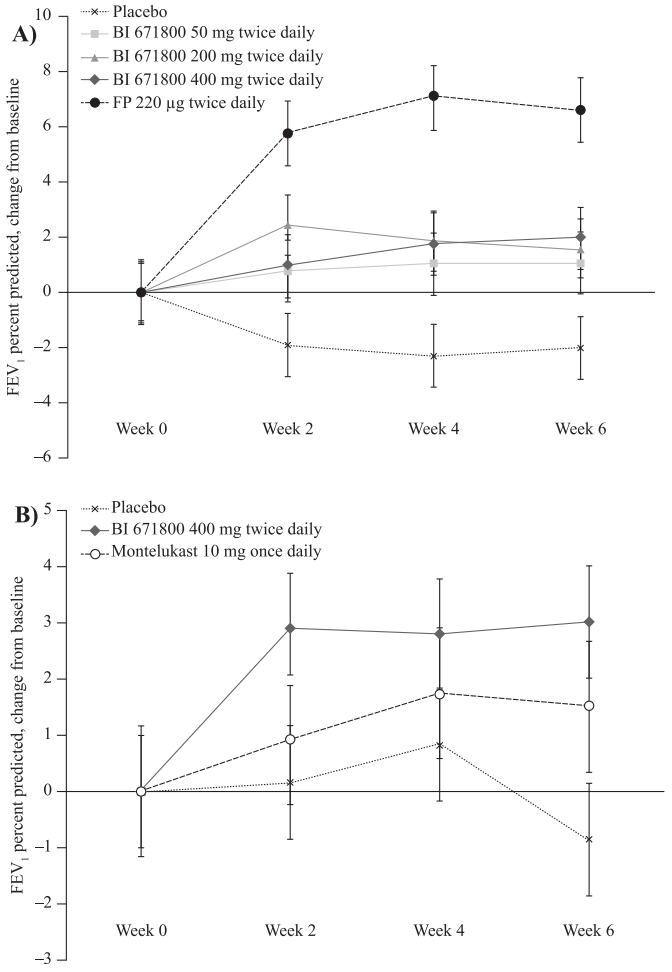

Fig. 3. Adjusted change from baseline in trough FEV_1 percent predicted at 2, 4 and 6 weeks in (A) corticosteroid-naïve patients with uncontrolled asthma treated with different doses of BI 671800, fluticasone propionate or placebo (Trial 1) and (B) patients on inhaled corticosteroids with uncontrolled asthma treated with BI 671800, montelukast or placebo (Trial 2); FEV_1 = forced expiratory volume in 1 s; FP = fluticasone propionate.

and montelukast (HR 1.00) were not statistically significant ($p = 0.2002$ and $p = 0.4940$, respectively).

3.8. Safety and tolerability (Trial 2)

BI 671800 was safe and well tolerated at all doses evaluated. There were no significant differences in adverse events across treatment groups (see Supplementary Table S2). However, 1 serious adverse event of toxic hepatitis (raised liver transaminases, but no change in total bilirubin) was reported in a patient taking BI 671800 and was considered related to the drug. The patient already had raised transaminases during the run-in that had recovered prior to randomisation. Three additional patients taking BI 671800 and 1 patient taking montelukast also had small (maximally <8 × ULN) reversible rises in hepatic transaminase levels.

4. Discussion

Many pro-inflammatory effects of PGD_2 are mediated in the airway through interaction with the CRTH2 receptor expressed on Th2 cells, eosinophils and basophils [2–4]. We present here the results of 2 clinical trials designed to study the efficacy and safety of an oral CRTH2 antagonist, BI 671800, in patients with symptomatic asthma in the presence or absence of ICS therapy. The data presented from study Trial 1 demonstrate that BI 671800, when administered to controller therapy-naïve patients with mild-to-moderate asthma at either 200 or 400 mg twice daily, produces a statistically significant improvement in trough FEV_1 percent predicted compared with placebo (4.0% with the higher dose, equivalent to 134 mL). This response was less than that observed with moderate doses of fluticasone (8.6% improvement in trough FEV_1 percent predicted, equivalent to 293 mL) and was not accompanied by an improvement in asthma control. However, a number of exploratory endpoints also demonstrated improvements: FEV_1 percent predicted AUC_{0-3h}, trough FEV_1, FEV_1 AUC_{0-3h}, trough $FEF_{25-75\%}$, morning PEF and time to asthma worsening.

In Trial 2, add-on therapy with BI 671800 400 mg twice daily in patients taking inhaled fluticasone (88 µg twice daily) also resulted in a statistically significant improvement in trough FEV_1 percent predicted compared with placebo (3.9%, equivalent to 142 mL) – an improvement larger than that demonstrated for montelukast (1.5%, equivalent to 80 mL), although the difference between BI 671800 and montelukast was not statistically significant. This improvement in lung function was accompanied by a modest but statistically significant improvement in mean ACQ score.

Between them, these studies include the largest number of patients with asthma in which the efficacy of CRTH2 antagonists has been assessed. The data presented here provide proof of concept that CRTH2 antagonism can play a beneficial role in the management of asthma, with the effect size for improvement in trough FEV_1 percent predicted being numerically (but not statistically) greater than that seen with the CysLTR1 antagonist montelukast when used in conjunction with ICS therapy. It should be noted that Trial 2 was not powered to investigate the effect of BI 671800 relative to montelukast.

Overall, the improvements in trough FEV_1 percent predicted produced by BI 671800 in Trial 1, although statistically significant, were smaller than those seen with fluticasone. However, the effects of BI 671800 on asthma worsening were similar to those of fluticasone in the controller-naïve population. The observed changes in pulmonary function are also similar to those reported previously with the CysLTR1 antagonist montelukast in corticosteroid-naïve patients with asthma [9]. Side effects were not notably different between treatment groups in our studies, with the exception of a small (and reversible) rise in hepatic transaminases observed in 4 patients in Trial 1 taking BI 671800, and 5 patients in Trial 2, 4 of whom were taking BI 671800. No patient with increases in liver transaminases had a concomitant rise in total bilirubin. One subject in Trial 2 taking BI 671800 developed increases in liver transaminases, described by the investigator as a toxic hepatitis thought to be related to the drug. However, as the affected individual had elevated transaminases at recruitment that recovered during run-in before randomisation, it remains unclear whether the observed hepatitis was causally related to administration of the study drug.

Previously reported studies of the effect of CRTH2 antagonists on asthma control have provided conflicting results. In the study of OC000459 in steroid-naïve patients with asthma, the CRTH2 antagonist achieved a statistically significant improvement in the FEV_1 in the per-protocol analysis compared with placebo (7.66% predicted [95% confidence interval (CI): 0.49–14.82] or 200 mL) but not in the intention-to-treat population (2.44% predicted [95% CI: 4.42–9.31] or 80 mL) [6]. A separate study of OC000459 resulted in attenuation of the late-phase, but not the early-phase, response to allergen challenge following bronchial challenge in sensitive individuals [10]. Studies performed in patients sensitive to grass pollen [11] have also demonstrated that OC000459 can reduce nasal and ocular symptoms. In contrast, the dual DP1 and CRTH2

Table 3
Secondary and exploratory endpoints after 6 weeks of treatment (Trial 1).

Comparison to placebo	BI 671800 50 mg twice daily	BI 671800 200 mg twice daily	BI 671800 400 mg twice daily	FP 220 μg twice daily
ACQ score	0.07 (0.11)	−0.08 (0.11)	−0.06 (0.11)	−0.33 (0.12)
	$p = 0.7413$	$p = 0.2335$	$p = 0.2933$	$p = 0.0021$
FEV_1 percent predicted AUC_{0-3h}, L	2.65 (1.67)	3.54 (1.59)	3.81 (1.64)	7.83 (1.69)
	$p = 0.0564$	$p = 0.0135$	$p = 0.0106$	$p < 0.0001$
FEV_1 trough, L	0.11 (0.06)	0.11 (0.06)	0.13 (0.06)	0.29 (0.06)
	$p = 0.0273$	$p = 0.0242$	$p = 0.0091$	$p < 0.0001$
FEV_1 AUC_{0-3h}, L	0.09 (0.06)	0.10 (0.05)	0.13 (0.06)	0.27 (0.06)
	$p = 0.0566$	$p = 0.0376$	$p = 0.0129$	$p < 0.0001$
FVC trough, L	0.13 (0.06)	0.06 (0.06)	0.02 (0.06)	0.18 (0.06)
	$p = 0.0140$	$p = 0.1336$	$p = 0.3343$	$p = 0.0013$
FEF_{25-75} trough, L/s	0.09 (0.09)	0.11 (0.08)	0.17 (0.09)	0.36 (0.09)
	$p = 0.1560$	$p = 0.0981$	$p = 0.0216$	$p < 0.0001$
Morning PEF, L/min	16.3 (8.1)	11.0 (7.8)	21.5 (8.0)	26.9 (8.2)
	$p = 0.0221$	$p = 0.0803$	$p = 0.0038$	$p = 0.0006$
Evening PEF, L/min	16.8 (7.9)	14.2 (7.6)	14.3 (7.8)	17.7 (8.0)
	$p = 0.0163$	$p = 0.0315$	$p = 0.0340$	$p = 0.0136$
AQLQ score	−0.06 (0.14)	0.07 (0.13)	0.15 (0.13)	0.27 (0.14)
	$p = 0.6571$	$p = 0.3064$	$p = 0.1340$	$p = 0.0254$
Time to first asthma worsening, HR (95% CI)	0.94 (0.54–1.64)	0.69 (0.39–1.24)	0.45 (0.23–0.87)	0.33 (0.23–0.87)
	$p = 0.4153$	$p = 0.1053$	$p = 0.0074$	$p = 0.0015$
Time to first exacerbation, HR (95% CI)	0.23 (0.03–2.06)	0.21 (0.02–1.85)	0.23 (0.03–2.06)	0.25 (0.03–2.26)
	$p = 0.0754$	$p = 0.0592$	$p = 0.0758$	$p = 0.0919$

Data expressed as mean (SE) unless otherwise stated; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; AUC = area under the curve; CI = confidence interval; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in 1 s; FP = fluticasone propionate; FVC = forced vital capacity; HR = hazard ratio; PEF = peak expiratory flow; SE = standard error.

antagonist, AMG 853, failed to improve asthma symptoms or FEV_1 [7], although the potential role of DP1 remains controversial and hence the likely clinical effects of dual inhibition of these receptors is difficult to predict. There has been 1 additional study of BI 671800 in asthma [9]. In a randomised, double-blind, placebo-controlled, incomplete crossover study of 101 asthma patients also taking inhaled fluticasone (88 μg twice daily), 400 mg BI 671800 administered once daily or 200 mg administered twice daily was not associated with improvement in FEV_1 after 4 weeks of administration. However, the dose in that study was only half that given in the current Study 2 (800 mg). The results of the crossover study are difficult to interpret due to the lack of an active control group. Finally, benefit from BI 671800 treatment has also been reported in allergic rhinitis patients: a reduction in nasal and ocular symptoms in a nasal allergen challenge model [12]. Studies 1 and 2 contribute significantly to the body of evidence on this class of drug, and provide further proof of concept for clinical improvement through CRTH2 inhibition.

Table 4
Secondary and exploratory endpoints after 6 weeks of treatment (Trial 2).

Comparison with placebo	BI 671800 400 mg twice daily	Montelukast 10 mg once daily
ACQ score	−0.28 (0.12)	−0.18 (0.12)
	$p = 0.0092$	$p = 0.0732$
FEV_1 percent predicted AUC_{0-3h}	3.75 (1.47)	2.27 (1.55)
	$p = 0.0058$	$p = 0.0715$
FEV_1 trough, L	0.14 (0.05)	0.08 (0.05)
	$p = 0.0026$	$p = 0.0671$
FEV_1 AUC_{0-3h}, L	0.14 (0.05)	0.07 (0.05)
	$p = 0.0028$	$p = 0.0924$
FVC trough, L	0.105 (0.062)	0.002 (0.066)
	$p = 0.0471$	$p = 0.4869$
FEF_{25-75} trough, L/s	0.17 (0.07)	0.17 (0.08)
	$p = 0.0125$	$p = 0.0152$
Morning PEF, L/min	3.76 (6.64)	9.01 (6.97)
	$p = 0.2856$	$p = 0.0985$
Evening PEF, L/min	−0.14 (5.94)	3.42 (6.25)
	$p = 0.5096$	$p = 0.2924$
AQLQ score	0.09 (0.13)	0.09 (0.13)
	$p = 0.2383$	$p = 0.2535$
Time to first asthma worsening, HR (95% CI)	0.75 (0.39–1.46)	1.00 (0.52–1.91)
	$p = 0.2002$	$p = 0.4940$
Time to first exacerbation, HR (95% CI)	0.73 (0.12–4.39)	0.44 (0.05–4.22)
	$p = 0.3668$	$p = 0.2320$

Data expressed as mean (SE) unless otherwise stated; ACQ = Asthma Control Questionnaire; AUC = area under the curve; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HR = hazard ratio; PEF = peak expiratory flow; SE = standard error.

In summary, in our studies of the CRTH2 antagonist BI 671800 in patients with asthma who were either controller-naïve or taking ICS, which are the largest studies of a CRTH2 antagonism in asthma patients to date, modest but statistically significant increases in FEV_1 were observed in controller-naïve patients. These increases were similar to that observed with the leukotriene receptor antagonist, montelukast [9,13], and in subjects taking ICSBI 671800 appeared to produce an additional effect compared with ICS alone. In addition, in *post hoc* sub group analyses, there was a trend towards higher FEV_1 responses in both studies in subjects with an elevated peripheral blood eosinophil count. Thus, PGD_2 inhibition has potential as a treatment for patients with asthma not adequately controlled with ICS alone. Further studies, preferably with the more potent inhibitors of CRTH2 currently under development, are warranted.

Conflicts of interest

IPH received a consultancy fee for his contribution to the design of study 1268.16. ERS's employer (National Jewish Health) received a grant to support his effort related to the trial. EDB has received remuneration for lectures from AstraZeneca, ALK-Abelló, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Takeda, Pfizer and TEVA for consultancy or advisory board membership from Actelion, Almirall, ALK-Abelló, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Elevation Pharma, Forest, GlaxoSmithKline, Hoffmann la Roche, ICON, IMS Consulting Group, Merck, Napp Pharma, Novartis, Pfizer and Takeda. His institution has participated in clinical trials for Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Hoffmann la Roche, GlaxoSmithKline, Genentech, Merck, Novartis, Nycomed and Pfizer. AVF, AG, KT, MCN, MS and HAF are all employees of Boehringer Ingelheim.

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Role of the funding source

Funding was provided by Boehringer Ingelheim. The sponsor participated with the principal investigators in the study design and data interpretation. The decision to submit the paper was made collectively by all authors. The sponsor did not place any restrictions on authors about the statements made in the manuscript. Professor Hall had access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2015.03.003.

References

[1] Global Initiative for Asthma (GINA). Global Strategy for asthma management and prevention. GINA website. Available from: www.ginasthma.org.

[2] Abe H, Takeshita T, Nagata K, Arita T, Endo Y, Fujita T, et al. Molecular cloning, chromosome mapping and characterization of the mouse CRTH2 gene, a putative member of the leukocyte chemoattractant receptor family. Gene 1999;227:71–7.

[3] Nagata K, Hirai H, Tanaka K, Ogawa K, Aso T, Sugamura K, et al. CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast cell-derived factor(s). FEBS Lett. 1999;459:195–9.

[4] Nagata K, Tanaka K, Ogawa K, Kemmotsu K, Imai T, Yoshie O, et al. Selective expression of a novel surface molecule by human Th2 cells in vivo. J. Immunol. 1999;162:1278–86.

[5] Kostenis E, Ulven T. Emerging roles of DP and CRTH2 in allergic inflammation. Trends Mol. Med. 2006;12:148–58.

[6] Barnes N, Pavord I, Chuchalin A, Bell J, Hunter M, Lewis T, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. Clin. Exp. Allergy 2012;42:38–48.

[7] Busse WW, Wenzel SE, Meltzer EO, Kerwin EM, Liu MC, Zhang N, et al. Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients. J. Allergy Clin. Immunol. 2013;131:339–45.

[8] Miller DLCFA. Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid [abstract]. Eur. Respir. J. 2012;40(Suppl. 56). 546S. P12–12347.

[9] Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Piñeiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. Ann. Intern. Med. 1999;130:487–95.

[10] Singh D, Cadden P, Hunter M, Pearce Collins L, Perkins M, Pettipher R, et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. Eur. Respir. J. 2013;41:46–52.

[11] Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Collins LP, Hunter MG, et al. The CRTH2 antagonist OC000459 reduces nasal and ocular symptoms in allergic subjects exposed to grass pollen, a randomised, placebo-controlled, double-blind trial. Allergy 2012;67:1572–9.

[12] Krug NGABP. CRTH2 antagonist, BI 671800 (BI), reduces nasal symptoms and inhibits nasal cytokines and eosinophils in SAR patients exposed to grass pollen in an environmental challenge chamber (ECC) [abstract]. Am. J. Respir. Crit. Care Med 2012;185. A4185.

[13] Barnes N, Wei LX, Reiss TF, Leff JA, Shingo S, Yu C, et al. Analysis of montelukast in mild persistent asthmatic patients with near-normal lung function. Respir. Med. 2001;95:379–86.