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

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ABSTRACT
The prostaglandin D2 (PGD2) 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 mg) 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 mg bid) (Trial 2). The primary endpoint in both trials was change from baseline in trough forced expiratory volume in 1 s (FEV1) percent predicted. After 6 weeks’ treatment, adjusted mean treatment differences compared with placebo were 3.87% (1.49%) for BI 671800 50, 200 and 400 mg bid, respectively, and 8.62% (1.68%) for fluticasone 220 mg bid (p = 0.0311, p = 0.0126, p = 0.0078 and p < 0.0001, respectively). In Trial 2, adjusted mean FEV1 (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 FEV1 in symptomatic controller-naïve asthma patients, and in patients on ICS.

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platelets, alveolar macrophages, T-helper type 2 (Th2) cells and dendritic cells following allergen exposure. The pro-inflammatory effects of PGD2 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. PGD2 chemotactic activity recruits circulating eosinophils and basophils from the vascular bed to the site of inflammation in a CRTH2-dependent manner. Furthermore, PGD2 has an important role in the early phase of CRTH2-dependent Th2-cell recruitment and activation, resulting in the production of cytokines (e.g., interleukin (IL)-4, IL-5, IL-9 and IL-13), which, in turn, further stimulate mast cells and eosinophils. 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-naive individuals with asthma reported a statistically significant improvement in forced expiratory volume in 1 s (FEV1) in the per-protocol patient group, but not in the intention-to-treat cohort. A study of a different molecule, a dual DP1 and CRTH2 antagonist, AMG 853, found no improvement in Asthma Control Questionnaire (ACQ) score or FEV1. 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, 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-naive 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-naive 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 FEV1 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.

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 FEV1 percent predicted at 6 weeks. The secondary endpoint was change from baseline in ACQ mean score at 6 weeks. Changes in trough FEV1 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 FEV1 percent predicted area under the curve (AUC0–3h), forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC (FEF25–75%), 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 FEV1 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 FEV1 were 3.08% (1.65%), 3.59% (1.60%) and 3.98% (1.64%) for 50, 200 and 400 mg twice daily, respectively, and were included in the treatment set. A further 15 patients had either no baseline or on-treatment trough FEV1 data, resulting in 373 patients being included in the FAS.

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 statistically significant improvements with BI 671800 (at the 1-sided 2.5% level): FEV1 percent predicted AUC0–3h, trough FEV1, FEV1/AUC0–3h, 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 671800 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 \( < 6 \times \text{ULN} \) (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 FEV1 data, resulting in only 230 patients being included in the FAS.

Table 1
Baseline characteristics (Trial 1).

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Placebo</th>
<th>BI 671800 50 mg twice daily</th>
<th>BI 671800 200 mg twice daily</th>
<th>BI 671800 400 mg twice daily</th>
<th>FP 220 μg twice daily</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>78</td>
<td>77</td>
<td>83</td>
<td>79</td>
<td>71</td>
<td>388</td>
</tr>
<tr>
<td>Age, years</td>
<td>36.4 (13.0)</td>
<td>39.1 (11.5)</td>
<td>35.1 (11.1)</td>
<td>37.5 (12.2)</td>
<td>39.4 (12.2)</td>
<td>37.4 (12.1)</td>
</tr>
<tr>
<td>Female, %</td>
<td>47.4</td>
<td>53.2</td>
<td>50.6</td>
<td>54.4</td>
<td>50.7</td>
<td>51.3</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4 (4.7)</td>
<td>27.0 (4.6)</td>
<td>25.9 (4.3)</td>
<td>26.5 (4.7)</td>
<td>26.7 (4.6)</td>
<td>26.5 (4.5)</td>
</tr>
<tr>
<td>Allergic asthma, n (%)</td>
<td>59 (75.6)</td>
<td>58 (75.3)</td>
<td>65 (78.3)</td>
<td>67 (84.8)</td>
<td>56 (78.9)</td>
<td>503 (78.6)</td>
</tr>
<tr>
<td>FEV1, percent predicted</td>
<td>72.7 (6.5)</td>
<td>71.4 (7.3)</td>
<td>73.3 (7.3)</td>
<td>73.6 (6.9)</td>
<td>72.3 (6.9)</td>
<td>727 (70.0)</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>2.52 (0.63)</td>
<td>2.41 (0.62)</td>
<td>2.60 (0.65)</td>
<td>2.49 (0.65)</td>
<td>2.42 (0.55)</td>
<td>2.49 (0.62)</td>
</tr>
<tr>
<td>FEV1 at screening, L</td>
<td>2.47 (0.70)</td>
<td>2.32 (0.66)</td>
<td>2.60 (0.68)</td>
<td>2.42 (0.64)</td>
<td>2.36 (0.59)</td>
<td>2.46 (0.65)</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %</td>
<td>68.7 (10.0)</td>
<td>67.1 (10.6)</td>
<td>64.7 (8.5)</td>
<td>68.2 (9.7)</td>
<td>68.1 (8.8)</td>
<td>679 (9.5)</td>
</tr>
<tr>
<td>Weekly mean SABA use, puffs/day</td>
<td>2.9 (2.7)</td>
<td>3.0 (2.7)</td>
<td>2.7 (2.8)</td>
<td>3.0 (2.7)</td>
<td>2.8 (2.4)</td>
<td>2.9 (2.7)</td>
</tr>
<tr>
<td>ACQ score</td>
<td>2.2 (0.6)</td>
<td>2.3 (0.6)</td>
<td>2.3 (0.5)</td>
<td>2.3 (0.5)</td>
<td>2.4 (0.6)</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>Weekly mean morning PEF, L/min</td>
<td>378.0 (114.6)</td>
<td>380.8 (124.1)</td>
<td>374.1 (120.9)</td>
<td>381.5 (116.3)</td>
<td>370.0 (118.6)</td>
<td>3770.0 (118.4)</td>
</tr>
<tr>
<td>No LABA use, n (%)</td>
<td>65 (83.3)</td>
<td>65 (84.4)</td>
<td>67 (80.7)</td>
<td>60 (75.9)</td>
<td>56 (78.9)</td>
<td>313 (80.7)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD) unless otherwise stated; ACQ – Asthma Control Questionnaire; BMI – body mass index; FEV1 – forced expiratory volume in 1 s; FP – fluticasone propionate; FVC – forced vital capacity; LABA – long-acting β2-agonist; PEF – peak expiratory flow; SABA – short-acting β2-agonist; SD – standard deviation.
Table 2: Baseline characteristics (Trial 2).

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Placebo</th>
<th>BI 671800 400 mg twice daily</th>
<th>Montelukast 10 mg twice daily</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>95</td>
<td>81</td>
<td>67</td>
<td>243</td>
</tr>
<tr>
<td>Age, years</td>
<td>41.4 (12.6)</td>
<td>41.8 (12.7)</td>
<td>41.7 (12.0)</td>
<td>41.6 (12.4)</td>
</tr>
<tr>
<td>Female, %</td>
<td>57.9</td>
<td>61.7</td>
<td>62.7</td>
<td>60.5</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8 (4.3)</td>
<td>27.6 (4.1)</td>
<td>26.7 (4.1)</td>
<td>27.0 (4.2)</td>
</tr>
<tr>
<td>Allergic asthma, n (%)</td>
<td>73 (76.8)</td>
<td>67 (82.7)</td>
<td>47 (70.1)</td>
<td>187 (77.0)</td>
</tr>
<tr>
<td>FEV₁, percent predicted</td>
<td>72.1 (7.3)</td>
<td>72.6 (7.6)</td>
<td>72.3 (7.2)</td>
<td>72.3 (7.3)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.49 (0.55)</td>
<td>2.49 (0.59)</td>
<td>2.42 (0.61)</td>
<td>2.47 (0.58)</td>
</tr>
<tr>
<td>FEV₁ at screening, L</td>
<td>2.35 (0.63)</td>
<td>2.39 (0.70)</td>
<td>2.32 (0.63)</td>
<td>2.36 (0.65)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, %</td>
<td>65.0 (10.8)</td>
<td>65.8 (10.1)</td>
<td>65.5 (8.9)</td>
<td>65.4 (10.0)</td>
</tr>
<tr>
<td>Weekly mean SABA use, puffs/day</td>
<td>1.9 (2.1)</td>
<td>1.7 (1.8)</td>
<td>1.8 (1.9)</td>
<td>1.8 (1.9)</td>
</tr>
<tr>
<td>ACQ score</td>
<td>2.2 (0.5)</td>
<td>2.1 (0.5)</td>
<td>2.0 (0.5)</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td>Weekly mean morning PEF, L/min</td>
<td>353.4 (121.8)</td>
<td>363.3 (118.2)</td>
<td>345.7 (115.6)</td>
<td>354.6 (118.6)</td>
</tr>
<tr>
<td>No LABA use, n (%)</td>
<td>55 (57.9)</td>
<td>49 (60.5)</td>
<td>37 (55.2)</td>
<td>141 (58.0)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD) unless otherwise stated; ACQ – Asthma Control Questionnaire; BMI – body mass index; FEV₁ – forced expiratory volume in 1 s; FP – fluticasone propionate; FVC – forced vital capacity; LABA – long-acting β₂-agonist; PEF – peak expiratory flow; SABA – short-acting β₂-agonist; SD – standard deviation.

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Fig. 2. CONSORT diagrams for Trial 1 (A) and Trial 2 (B). Patients may have >1 reason for exclusion; FAS – full analysis set; FEV₁ – forced expiratory volume in 1 s; PPS – per-protocol set.
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 FEV₁ 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 FEV₁ 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 FEV₁ % 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 = 0.0092) but was not statistically significant for montelukast. The in-clinic spirometry assessments, including FEV₁ percent predicted AUC₀−₃h, trough FEV₁, FEV₁ AUC₀−₃h 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)
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 $<8 \times$ 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 AU$_{0–3h}$ trough FEV$_1$, FEV$_1$ AU$_{0–3h}$ 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 mg 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% Cl: 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...
antagonist, AMG 853, failed to improve asthma symptoms or FEV1 [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 FEV1 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.

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 FEV1 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 ICS BI 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 FEV1 responses in both studies with an elevated peripheral blood eosinophil count. Thus, PGD2 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, Gentech, Merck, Novartis, Nycomed and Pfizer. AVF, AG, AT, MCN, MS and HAF are all employees of Boehringer Ingelheim.
Acknowledgements

IPH, ERS and EDB contributed to the design of the studies, the evaluation of results and preparation of the manuscript. AF, AG, KT, CN and MS contributed to the design of the studies, the evaluation of results and review/preparation of the manuscript. HF contributed to the data analysis, the evaluation of results and review/preparation of the manuscript. Editorial support was provided by Carol A Richter from PAREXEL, and funded by Boehringer Ingelheim.

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


