

A randomized study of BI 671800, a CRTH2 antagonist, as add-on therapy in poorly controlled asthma

David Miller, M.D.,¹ Chester Wood, M.D.,² Eric Bateman, M.D.,³ Craig LaForce, M.D.,⁴ Jon Blatchford, C.Stat.,⁵ James Hilbert, Ph.D.,² Abhya Gupta, M.D.,⁶ and Andrew Fowler, M.D.⁵

ABSTRACT

Background: Asthma is characterized by a complex interaction of inflammatory mediators. The prostaglandin D₂ receptor, chemoattractant receptor–homologous molecule on Th2 cells (CRTH2), plays a pivotal role in the pathogenesis of allergic airway inflammation.

Objective: To evaluate the efficacy, safety, and pharmacokinetics of BI 671800, a CRTH2 antagonist, when added to inhaled corticosteroid therapy in adult patients with symptomatic asthma.

Methods: In this phase IIa, 12-week, randomized, double-blind, three-period, four-treatment, incomplete block crossover trial, BI 671800 was administered either as a single 400-mg dose in the morning (A.M.) or evening (P.M.), or 200 mg twice daily (A.M. and P.M.) versus placebo, together with fluticasone propionate (44 µg, two inhalations twice daily). The primary end point was the change from baseline in trough forced expiratory volume in 1 second percentage predicted after 4 weeks. The secondary end point was the change in Asthma Control Questionnaire score from baseline.

Results: A total of 108 patients were randomized and treated. After 4 weeks, the adjusted mean ($\pm$ SE) treatment differences for the primary end point versus placebo were $0.08 \pm 0.62\%$, $0.28 \pm 0.61\%$, and $0.67 \pm 0.63\%$ for BI 671800 at 200 mg twice daily, 400 mg A.M., and 400 mg P.M., respectively (not statistically significant). No statistically significant or clinically meaningful differences in the Asthma Control Questionnaire score were observed versus placebo. Each treatment was well tolerated.

Conclusion: BI 671800 at a dose of 400 mg administered for 4 weeks with fluticasone propionate did not provide clinical improvement in patients with asthma; reasons for this are unclear, but it may be due to insufficient inhibition of the CRTH2 receptor at the doses used.

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Asthma is a chronic inflammatory disease, characterized by episodic airway obstruction and increased bronchial responsiveness.^{1,2} Airway inflamma-

tion involves a complex interaction of mediators (such as histamine, proteases, cytokines, and eicosanoids [including leukotrienes and prostaglandins]) that are released from mast cells and often triggered by an immunoglobulin E mediated response to a foreign allergen.^{1,3–7} Prostaglandin D₂ (PGD₂) is an arachidonic acid metabolite important in the pathogenesis of asthma. After allergen exposure, PGD₂ is released by immunoglobulin E activated mast cells and other inflammatory cells, such as T-helper type 2 (Th2) cells, eosinophils, and basophils (Fig. 1), platelets, alveolar macrophages, and dendritic cells.⁸ The proinflammatory effects of PGD₂ occur *via* interactions with the chemoattractant receptor–homologous molecule on Th2 cells (CRTH2), a seven-transmembrane G-protein–coupled receptor selectively expressed on Th2 cells, T-cytotoxic type 2 cells, eosinophils, and basophils.^{9–16}

Chemotactic activity of PGD₂ recruits circulating eosinophils and basophils from the vascular bed to the site of inflammation in a CRTH2-dependent manner. PGD₂ also plays an important role in the early phase of

From the ¹Clinical Research, Clinical Research Network/NEMRA Northeast Medical Research Associates, Inc., North Dartmouth, Massachusetts, ²Clinical Development and Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, ³Department of Medicine, University of Cape Town, Cape Town, South Africa, ⁴Clinical Research, Pediatrics, Allergy and Immunology, Raleigh, North Carolina, ⁵Clinical Development and Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Ltd, Bracknell, United Kingdom, and ⁶Clinical Development and Medical Affairs/Therapeutic Area Respiratory Diseases, Boehringer Ingelheim Pharma GmbH and Co. K.G., Biberach an der Riss, Germany

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J. Blatchford, A. Gupta, and C. Wood are employees of Boehringer Ingelheim. A. Fowler is a former employee of Boehringer Ingelheim, and a current employee of GlaxoSmithKline. J. Hilbert is a former employee of Boehringer Ingelheim, and a current employee of Applied BioMath. E. Bateman has received honoraria for consulting, advisory board membership and lectures, and his institution has received payment for participation in clinical trials from Boehringer Ingelheim. The remaining authors have no conflicts of interest pertaining to this article

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Address correspondence to S. David Miller, M.D., NEMRA Inc., 49 State Road, North Dartmouth, MA 02747

E-mail address: dmiller@nemra-us.com

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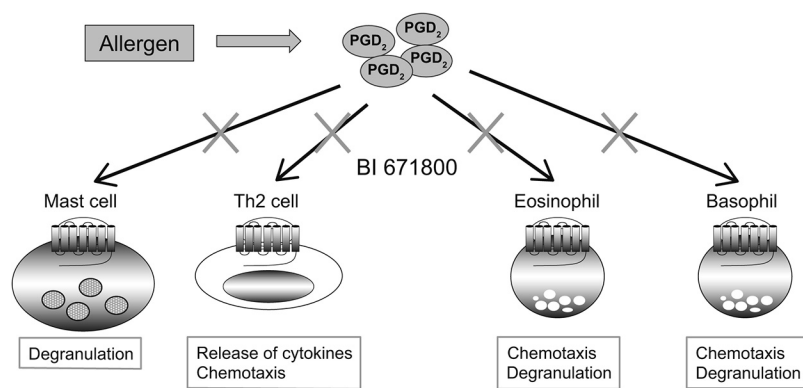


Figure 1. Schematic representation of the antagonism of CRTH2 (expressed on mast cells, T-helper [Th] 2 cells, eosinophils, and basophils) by BI 671800. CRTH2 = Chemotactant receptor-homologous molecule on Th2 cells; PGD₂ = prostaglandin D₂.

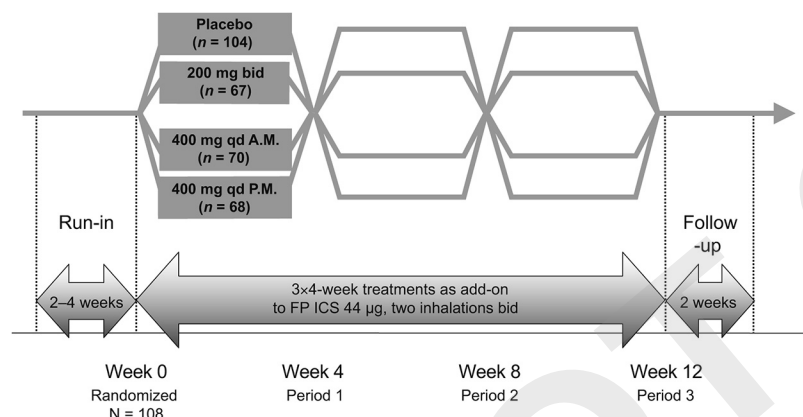


Figure 2. Study design. A.M. = Morning; bid = twice daily; FP = fluticasone propionate; ICS = inhaled corticosteroid; P.M. = evening; qd = once daily.

CRTH2-dependent Th2 cell recruitment and activation, which increases cytokine production (*e.g.*, interleukin [IL] 4, IL-5, and IL-13), which, in turn, stimulates mast cells and eosinophils, and thus augments the allergic inflammatory response.^{11–15} Inflammation in asthma is highly heterogeneous and mediated by a variety of cell types.¹⁷ Thus, despite the broad effects of inhaled steroids, there is a need for new agents with broad anti-inflammatory mechanisms of action, favorable safety profiles, and ease of administration. The role of CRTH2 as a potential therapy for allergic disease has been the focus of considerable research.¹⁸ Because CRTH2 receptors contribute directly to eosinophilic airway inflammation in asthma,^{10,19} CRTH2 antagonists may inhibit the antigen-induced inflammatory response and improve asthma control.

BI 671800 is a highly specific and potent antagonist of CRTH2 (Fig. 1). BI 671800 has been published as compound A.^{18,20} In competitive radioligand binding studies, BI 671800 inhibited the binding of 3H-PGD₂ to CRTH2 and blocked the infiltration of inflammatory cells, including lymphocytes, eosinophils, and neutrophils in a fluorescein isothiocyanate-induced allergic cutaneous inflammation model as well as in a T-cell-driven model of allergic airway inflammation *in vivo*.^{18,20} The objective of the present study was to investigate the efficacy, safety, tolerability, and pharmacokinetics of BI 671800 in combination with an in-

haled corticosteroid (ICS) in patients with symptomatic asthma.

METHODS

Study Design

This 12-week, phase IIa, randomized, double-blind, three-period, four-treatment, incomplete block cross-over-design trial was conducted across 14 centers in the United States. The trial compared the relative efficacy and safety of 400 mg of BI 671800 (as the ethylenediamine salt), given once daily in the morning (A.M.) or evening (P.M.) or as a split twice-daily 200-mg dose, combined with low-dose fluticasone propionate (FP) 44 µg versus placebo, in patients with mild-to-moderate symptomatic asthma. Patients were randomized to 1 of 18 treatment sequences and received placebo in 1 of the 3 consecutive 4-week periods, and two of the three experimental BI 671800 regimens in the remaining periods (Fig. 2 and Supplemental Fig. 1). All of the patients received FP 44 µg (two inhalations twice daily) *via* a metered-dose inhaler during the run-in and treatment periods. FP was inhaled immediately before BI 671800 (or placebo) dosing. Instructions for BI 671800 intake with food are described in the Supplemental Appendix. Permitted and prohibited concomitant medications are also listed in the Supplemental Appendix. The trial was carried

out in accordance with the Declaration of Helsinki (1996), the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice, and applicable regulatory requirements. The protocol was approved by each local institutional review board and an independent ethics committee. ClinicalTrials.gov identifier is NCT01090024. J. Blatchford contributed to the data analysis; J. Hilbert performed the pharmacokinetic analysis; C. Wood, E. Bateman, A. Gupta, A. Fowler, and J. Blatchford assisted with the study design, review, and interpretation of data, and with the preparation of the manuscript. All the authors had equal contributions in terms of reviewing all drafts. All the authors had full access to the data and read and approved the final manuscript.

Patients

Patient inclusion and exclusion criteria are summarized in the Supplemental Appendix. Each patient (or the patient's legally accepted representative) provided written informed consent.

End Points and Assessments

The primary end point was an absolute change from baseline in trough forced expiratory volume in 1 second (FEV₁) percentage predicted after 4 weeks of treatment. Randomized patients were assessed at baseline (week 0) and at the end of each 4-week treatment period (weeks 4, 8, and 12), when supervised pulmonary function testing was conducted up to 3 hours after receiving the dose in the morning and evening. The secondary end point was an Asthma Control Questionnaire (ACQ-7) mean score change from baseline after 4 weeks of treatment. Exploratory end points and pharmacokinetic assessments of BI 671800 for each treatment group (excluding placebo) are described in the Supplemental Appendix (see Supplemental Table 1 for AM2+ e-diary [eResearch Technology, Hoechst, Germany] details). Safety was assessed by the incidence and intensity of adverse events (AEs), treatment-emergent AEs, serious AEs, vital signs (pulse rate and blood pressure), laboratory safety parameters, 12-lead resting electrocardiogram, and physical examination.

Statistical Analyses

The statistical analysis methods are described in the Supplemental Appendix.

RESULTS

Study Population

A total of 221 patients were assessed for eligibility: 113 patients were excluded due to screen failures and 108 were randomized (Fig. 3). More patients were randomized to placebo than to active treatments due to

the incomplete block (three periods, four treatments) crossover design, in which at least one treatment had to be placebo. The majority of the patients were white (82.4%) and 53.7% were women, the mean FEV₁ percentage predicted was 72.8%, the mean ACQ-7 at randomization was 2.1, and the mean age was 41.1 years (Table 1).

Primary and Secondary End Points

Adjusted mean ($\pm$ SE) treatment differences for the primary end point of FEV₁ percentage predicted trough change from baseline after 4 weeks of treatment versus placebo were $0.08 \pm 0.62\%$, $0.28 \pm 0.61\%$, and $0.67 \pm 0.63\%$ for BI 671800 dose of 200 mg twice daily, 400 mg A.M., and 400 mg P.M., respectively. These differences were not statistically significant at the one-sided 2.5% level (Fig. 4 A). When the ICS or ICS plus controller medications were withdrawn at screening, the patients experienced a nominal increase in the mean FEV₁ percentage predicted A.M. trough values during the run-in period through to baseline (70.9 to 72.9%) (Fig. 4 B). At the end of treatment, no statistically significant differences were observed in the FEV₁ percentage predicted A.M. change from baseline with active treatment compared with placebo. For the secondary end point of change from baseline in the mean ACQ-7 score after 4 weeks, the adjusted mean ($\pm$ SE) treatment differences compared with placebo were -0.06 ± 0.06 , -0.09 ± 0.06 , and -0.03 ± 0.06 for the BI 671800 dose of 200 mg twice daily, 400 mg A.M., and 400 mg P.M., respectively. There were no statistically significant differences among the groups at the one-sided 2.5% level (Fig. 5).

Exploratory End Points

There were no clinically relevant differences among the four treatment groups for most of the exploratory end points (Supplemental Table 2).

Exposure

The mean drug plasma-concentration time for the three BI 671800 dosing schedules is shown in Supplemental Fig. 2. The terminal half-life for the 400-mg A.M. dose group was 5.79 hours; this was the only dose group for which the terminal half-life could be calculated. When comparing pharmacokinetic parameters at steady-state (Table 2), the mean maximum drug concentration in plasma and area under the plasma concentration-time curve over the first 12 hours at steady-state were similar between the 200-mg twice-daily dose and the 400-mg once-daily A.M. dose. The 400-mg once-daily P.M. dose generally gave a higher mean maximum drug concentration in plasma and greater area under the plasma concentration-time curve over

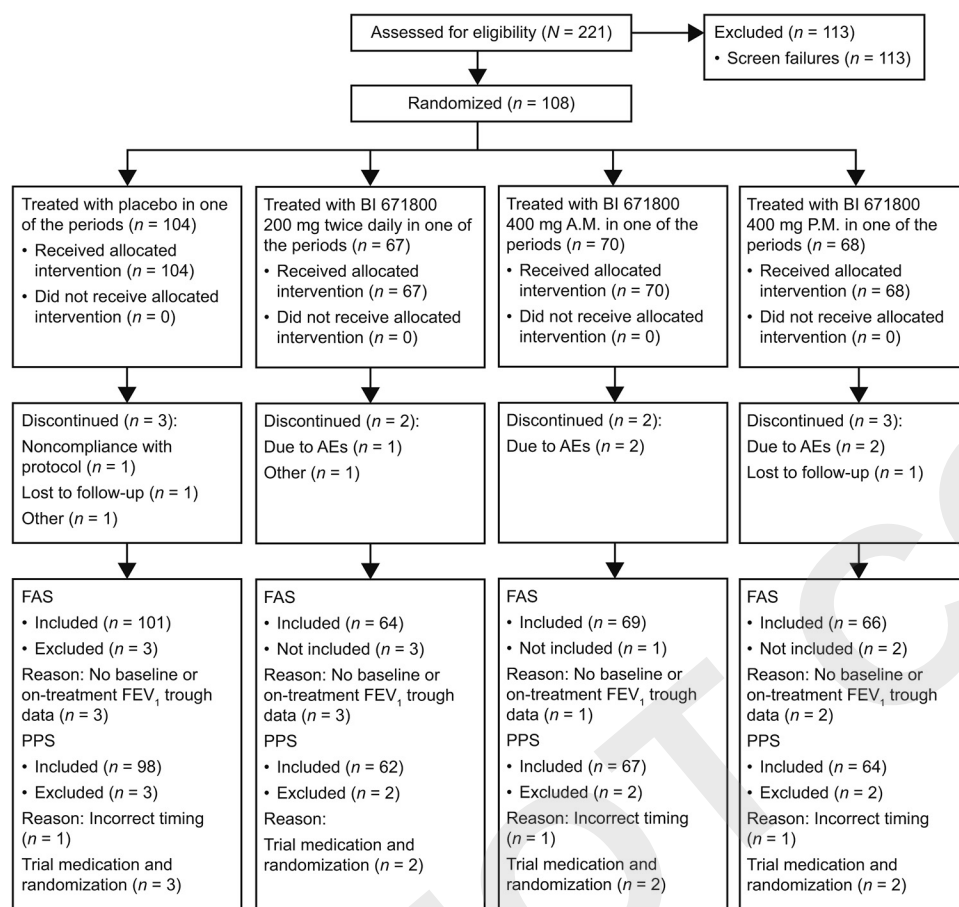


Figure 3. CONSORT diagram illustrating the flow of the patients through the study. The patients may have more than one reason for exclusion. AE = Adverse event; A.M. = morning; FAS = full analysis set; FEV₁ = forced expiratory volume in 1 second; P.M. = evening; PPS = per-protocol set.

the first 12 hours at steady-state exposure than the other regimens.

Safety

The frequency of AEs was similar for the active treatments (28.4, 30.0, and 29.4% of the patients who received BI 671800 at a dose of 200 mg twice daily, 400 mg A.M., and 400 mg P.M., respectively) and placebo (26.0%) (Table 3). The most common treatment-emergent AEs were upper respiratory tract infection and sinusitis, with no clinically relevant differences between treatment groups. There were no deaths or serious AEs. The overall incidence of drug-related AEs was low (2.9 to 6.0%) across the four treatments (Table 3). Five patients experienced 10 treatment-emergent AEs that led to discontinuation from trial medication: increased blood creatinine phosphokinase and increased hepatic enzymes (one patient in the placebo group); nausea (one patient in the BI 671800 at a dose of 200-mg twice-daily treatment group); upper respiratory tract infection and asthma (one patient in the BI 671800 dose 400-mg P.M. treatment group); constipation and nausea (one patient in the BI 671800 dose 400-mg P.M. treatment group); and lethargy, dyspnea, and sensation of heaviness (one patient in the BI 671800 dose 400-mg A.M. treatment group). The AEs of nau-

sea, constipation, and increased hepatic enzymes were considered by the investigator to be drug related. The majority of AEs that led to discontinuation of trial medication (four of five patients) commenced during the first treatment period. There were no clinically meaningful changes in vital signs or in safety laboratory assessments.

DISCUSSION

In this phase IIa trial of 108 patients, treatment with the CRTH2 antagonist, BI 671800, administered either once daily as a single dose of 400 mg in the A.M. or P.M., or 200 mg twice daily for 4 weeks, in conjunction with FP, led to no significant change in lung function or symptoms in patients with mild-to-moderate asthma and with symptoms. The primary end point of change from baseline in the trough FEV₁ percentage predicted did not meet the targeted difference between placebo and BI 671800 (4% predicted). The mean ACQ-7 score improved from baseline with BI 671800, but this was not clinically meaningful or statistically significant versus the placebo group. There were no statistically significant or clinically meaningful effects of BI 671800 on most of the other exploratory end points, consistent with the primary and secondary end-point findings.

Table 1 Baseline patient characteristics at screening

N (%)	108 (100.0)
Age, mean $\pm$ SD, y	41.1 $\pm$ 12.4
Women, no. (%)	58 (53.7)
Smoking status, no. (%)	
Never smoked	82 (75.9)
Ex-smoker	26 (24.1)
Asthma duration, mean $\pm$ SD, y	28.2 $\pm$ 12.9
Allergic asthma, no. (%)	69 (63.9)
BMI, mean $\pm$ SD, kg/m ²	28.8 $\pm$ 4.8
Total serum IgE level, mean $\pm$ SD, kU/L	300.6 $\pm$ 462.2
ECP value, mean $\pm$ SD, μ g/L	28.8 $\pm$ 28.5
FEV ₁ value, mean $\pm$ SD, percentage predicted*	72.8 $\pm$ 7.6
FEV ₁ value at screening, mean $\pm$ SD, L	2.4 $\pm$ 0.6
FEV ₁ reversibility value, mean $\pm$ SD, %	23.3 $\pm$ 12.2
FEV ₁ :FVC ratio, mean $\pm$ SD, %	66.2 $\pm$ 9.0
Weekly PEF A.M. value, mean $\pm$ SD, L/min	412.7 $\pm$ 117.2
Weekly PEF P.M. value, mean $\pm$ SD, L/min	424.1 $\pm$ 117.4
Weekly PEF value variability, mean $\pm$ SD, %	10.5 $\pm$ 8.4
ACQ-7 score*	2.1 $\pm$ 0.5
ACQ-6 score*	1.0 $\pm$ 0.6
SABA use, mean $\pm$ SD, puffs/day*	2.2 $\pm$ 2.2
Concomitant asthma medication use at screening, no. (%)	
LABA+SABA+ICS	56 (51.9)
SABA+ICS	35 (32.4)
LABA+ICS	8 (7.4)
ICS	2 (1.9)
SABA+LTRA+ICS	2 (1.9)
LTRA+ICS	1 (0.9)
LABA+LTRA+ICS	1 (0.9)

SD = Standard deviation; BMI = body mass index; IgE = immunoglobulin E; ECP = eosinophilic cationic protein; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; A.M. = morning; P.M. = evening; ACQ = Asthma Control Questionnaire; SABA = short-acting β_2 -agonist; LABA = long-acting β_2 -agonist; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist.

*At randomization.

Our findings were possibly the result of an incomplete anti-inflammatory action of BI 671800, given that the degree of oxidative stress in the airways may be unchanged by ICS treatment.²¹ Alternatively, the study design may have contributed to the failure to demonstrate a clinical effect of the BI 671800 treatment. There was no active control group to provide design sensitivity. In trials of another CRTH2 antag-

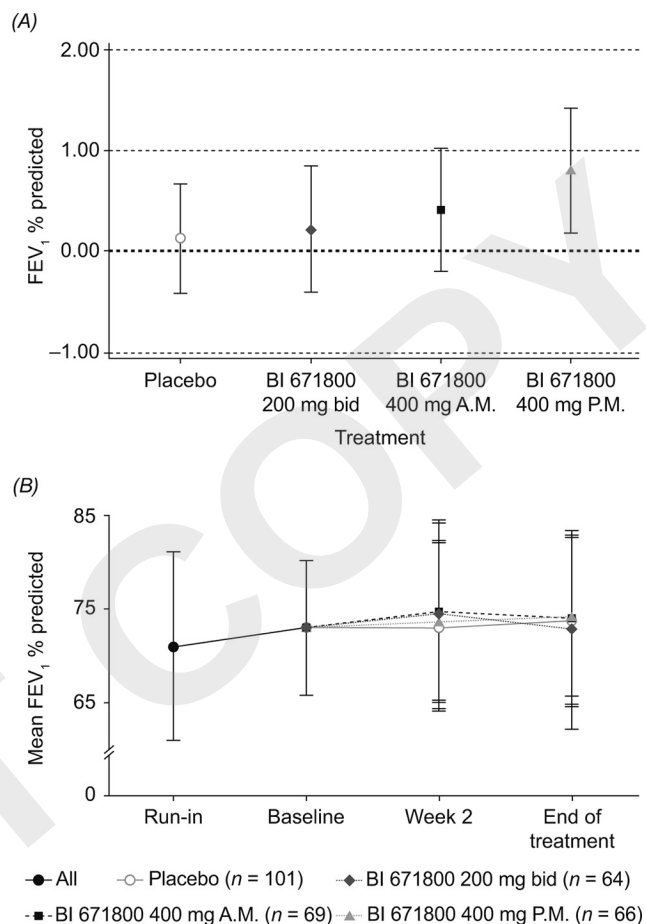


Figure 4. (A) Adjusted mean FEV₁ percentage predicted daily trough change from baseline (error bars = $\pm$ SE) at the end of treatment (full analysis set); (B) Unadjusted FEV₁ percentage predicted A.M. trough over time (error bars = standard deviation) (full analysis set). A.M. = Morning; bid = twice daily; FEV₁ = forced expiratory volume in 1 second; P.M. = evening.

onist, OC000459, in asthma²² and seasonal allergic rhinitis,²³ the possibility of a carryover effect after cross-over was raised but occurred only in the allergic rhinitis study. However, in our study, given the 5–9-hour half-life of BI 671800 (Boehringer Ingelheim, data on file), a pharmacokinetic carryover from the previous 4-week treatment period to the next is unlikely. In addition, there was no apparent difference in pharmacodynamic values (compared with baseline at first randomization) or any change in the patients who received placebo in the second or third treatment periods (*i.e.*, after an initial period of BI 671800 administration).

Another possible reason for the observed lack of efficacy of BI 671800 was the failure to reach sufficient systemic exposure for full inhibition of PGD₂. Inhibition of PGD₂ binding to the CRTH2 receptor can be measured indirectly by determining the degree of the eosinophil shape change *ex vivo*, as demonstrated in a study of patients with allergic rhinitis.²⁴ A phase I

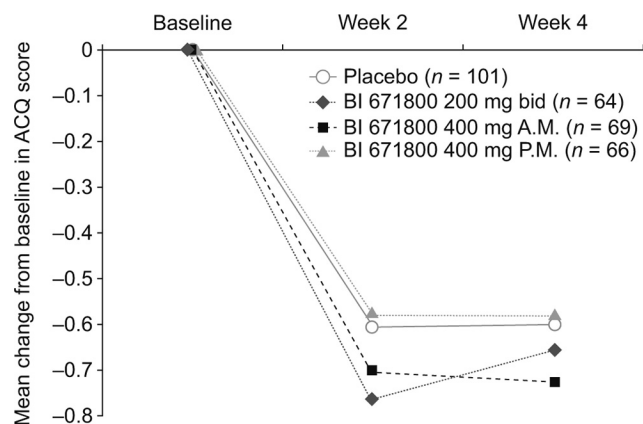


Figure 5. Mean ACQ-7 change from baseline over time (full analysis set). Data in the figure are unadjusted. Baseline is the mean ACQ-7 score obtained at week 0. ACQ-7 = 7-item Asthma Control Questionnaire; A.M. = morning; bid = twice daily; P.M. = evening.

multiple ascending-dose study demonstrated that eosinophil shape change was never completely inhibited by BI 671800, even at the 400-mg twice-daily dose; furthermore, an $E_{\max}$ (maximum observed effect) model estimated the eosinophil shape change half-maximal effective concentration (EC_{50}) as 972 ng/mL. Comparison of the EC_{50} with plasma concentrations of BI 671800 (Boehringer Ingelheim, Biberach, Germany) indicated that plasma concentrations were >972 ng/mL for less than half of the dosing interval for any treatment group, with a mean minimum drug concentration in plasma values well below the EC_{50} value. Thus, greater exposure than provided by the 400-mg maximum daily doses used in the current study may be required for clinical efficacy when BI 671800 is added to a low-dose ICS. In two other studies of BI 671800 in asthma, the 400-mg twice-daily dose showed the greatest efficacy.^{25–27}

The efficacy results of the current study contradict positive data from previous 6-week, randomized, double-blind, placebo-controlled, parallel-group trials. In the first trial, BI 671800 (50, 200, or 400 mg) or matching placebo, and FP 220 μ g were administered twice daily in adults with asthma who were symptomatic controller-naïve.²⁶ In the second, BI 671800 400 mg twice daily was compared with the leukotriene receptor antagonist montelukast 10 mg once daily and matching placebo in patients with asthma who received FP 88 μ g twice daily.^{25,26} In trial 1, the change from baseline in the trough FEV₁ percentage predicted (primary end point) at 6 weeks versus placebo was significantly improved with BI 671800 doses of 50, 200, and 400 mg twice daily (adjusted mean treatment difference 3.08%, one-sided $p = 0.0311$; 3.59%, $p = 0.0126$; and 3.98%, $p = 0.0078$, respectively) and with FP 220 μ g twice daily (8.62%, $p < 0.0001$).^{26,27} In trial 2, the

adjusted mean treatment differences compared with placebo were 3.87% for BI 671800 of dose 400 mg twice daily and 2.37% for montelukast ($p = 0.005$ and $p = 0.0657$, respectively).^{25,26}

These previous results indicated that a total daily dose of BI 671800 of >400 mg was required to achieve an optimal clinical response; however, in trial 1 (performed in patients who were controller-naïve), improvements in lung function versus placebo were observed at the same doses of BI 671800 used in the current study. This raised the possibility that concurrent ICS use may mask or diminish the benefit of BI 671800. In the present study, BI 671800 demonstrated favorable safety and tolerability, and similar incidences of AEs across treatment groups. There were no serious AEs or deaths. Earlier asthma trials^{25–27} also showed BI 671800 to be well tolerated at all doses evaluated.

The mean drug plasma concentration–time profile for BI 671800 after dosing with 200 mg twice daily was similar to the pharmacokinetic profiles reported in a multiple ascending-dose phase I study of BI 671800 (Boehringer Ingelheim) in patients with mild asthma who consumed a standardized high-fat meal between 10 and 20 minutes before each dose. The terminal half-life for the 400-mg A.M. dose group was 5.79 hours, which was in the range reported after multiple dosing in the phase I study, of 4.6–8.8 hours (Boehringer Ingelheim). Because the subjects who had fasted had reduced exposure compared with the subjects who were fed in the controlled phase I study (subjects who were fed had linear kinetics; Boehringer Ingelheim), the differences in pharmacokinetic parameters between A.M. and P.M. dosing of 400 mg of BI 671800 may have reflected differences in the amount and timing of food intake among individual patients. In an earlier phase I, single-dose, food-effect study of BI 671800 in healthy volunteers, a high-fat meal given 30 minutes before dosing increased drug concentrations of BI 671800 by approximately twofold (Boehringer Ingelheim). Although the patients in the present study were instructed to take the medication with food, details of the amount, type, and timing of food intake were not obtained.

Trials of other CRTH2 antagonists demonstrated positive clinical efficacy results in patients with asthma.^{19,28,29} Despite the lack of statistical significance in this study, previous trials indicate that BI 671800 has potential as an asthma therapy. Additional controlled studies of CRTH2 antagonists are needed to clarify their role in asthma management. New agents with more potent inhibition of CRTH2 and greater duration of action may be required to achieve maximum effect and clinical impact.

Table 2 Pharmacokinetic parameters of BI 671800 after BI 671800 treatment*

BI 671800 Treatment	AUC _{0-12,ss} ng/hr/mL		AUC _{0-24,ss} ng/hr/mL	C _{max,ss} ng/mL		C _{min,ss} ng/mL		t _{1/2,ss} hr
	A.M.	P.M.		A.M.	P.M.	A.M.	P.M.	
400-mg once-daily A.M. dosing (n = 27)	17,500 (69)	1910 (91)#	20,400 (67)#	3640 (77)	—	58.4 (75)	—	5.79 (31)
400-mg once-daily P.M. dosing (n = 30)	6400 (98)	26,000 (56)	33,800 (52)	—	5120 (59)	—	152 (75)	N.C.
200-mg twice daily dosing (n = 24)	15,300 (62)	14,200 (60)	30,100 (56)	3140 (62)	2720 (54)	277 (103)	251 (81)	N.C.

AUC_{0-12,ss} = Area under the plasma concentration–time curve from 0 to 12 hours, steady-state; AUC₀₋₂₄ = area under the plasma concentration–time curve from 0 to 24 hours, steady-state; C_{max,ss} = mean maximum drug concentration in plasma, steady-state; C_{min} = mean minimum drug concentration in plasma; t_{1/2,ss} = half-life, steady-state; A.M. = morning; P.M. = evening; N.C. = no comparison.

*Values are expressed as geometric mean (% geometric coefficient of variation).

#n = 26.

Table 3 Frequency of AEs that occurred in ≥2% of patients during any treatment*

System Organ Class Preferred Term	Placebo, no. (%)#	BI 671800		
		200 mg Twice Daily, no. (%)#	400 mg A.M., no. (%)#	400 mg P.M., no. (%)#
Patients	104 (100.0)	67 (100.0)	70 (100.0)	68 (100.0)
Total patients with AEs	27 (26.0)	19 (28.4)	21 (30.0)	20 (29.4)
Total patients with SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total patients with investigator-defined drug-related AEs	5 (4.8)	4 (6.0)	2 (2.9)	3 (4.4)
Patients with AEs that led to discontinuation of drug	1 (1.0)	1 (1.5)	1 (1.4)	2 (2.9)
Gastrointestinal disorders	2 (1.9)	4 (6.0)	2 (2.9)	1 (1.5)
Diarrhea	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Infections and infestations	13 (12.5)	8 (11.9)	6 (8.6)	8 (11.8)
Gastroenteritis viral	1 (1.0)	2 (3.0)	0 (0.0)	0 (0.0)
Sinusitis	2 (1.9)	3 (4.5)	1 (1.4)	0 (0.0)
URTI	4 (3.8)	2 (3.0)	3 (4.3)	5 (7.4)
Musculoskeletal and connective tissue disorders	1 (1.0)	2 (3.0)	5 (7.1)	4 (5.9)
Neck pain	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)
Nervous system disorders	1 (1.0)	2 (3.0)	3 (4.3)	1 (1.5)
Headache	1 (1.0)	2 (3.0)	0 (0.0)	1 (1.5)

AE = Adverse event; A.M. = morning; P.M. = evening; SAE = serious adverse event; URTI = upper respiratory tract infection.

*Medical Dictionary for Regulatory Activities version 13.1 was used for reporting, available at: <http://www.meddra.org/>.

#Percentages were calculated by using the total number of patients per treatment as the denominator.

CONCLUSION

In this 12-week, three-period, incomplete block crossover study, treatment with BI 671800 at dose 400

mg, administered either once daily as a single dose in the A.M. or P.M., or 200 mg twice daily for 4 weeks in conjunction with FP, was safe and well tolerated but

did not provide clinical improvements in patients with mild-to-moderate asthma who had symptoms, which may be due to insufficient inhibition of the CRTH2 receptor and inadequate exposure at the doses tested in combination with a low-dose ICS in this patient population.

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