Efficacy of the oral chemoattractant receptor homologous molecule on T_H2 cells antagonist BI 671800 in patients with seasonal allergic rhinitis

Norbert Krug, MD,[a] Abhya Gupta, MD,[b] Philipp Badorrek, MD,[a] Ruediger Koenen, MD,[b] Meike Mueller, PhD,[a] Anna Pivovarova, MSc,[b] James Hilbert, PhD,[c] Kristiane Wetzel, PhD,[b] Jens M. Hohlfeld, MD,[a] and Chester Wood, MD[c]

Hannover and Biberach, Germany, and Ridgefield, Conn

Background: The inflammatory response in patients with seasonal allergic rhinitis (SAR) is partly mediated by the prostaglandin D_2 receptor chemoattractant receptor homologous molecule on T_H2 cells (CRTH2).

Objective: We sought to investigate the efficacy and safety of the oral CRTH2 antagonist BI 671800 (50, 200, and 400 mg twice daily), fluticasone propionate nasal spray (200 μg once daily), or oral montelukast (10 mg once daily) administered for 2 weeks in patients with SAR.

Methods: In this randomized, double-blind, placebo-controlled, partial-crossover study, participants aged 18 to 65 years with a positive skin prick test to *Dactylis glomerata* pollen were exposed to out-of-season allergen in the environmental challenge chamber for 6 hours. The primary efficacy variable was the total nasal symptom score assessed as the area under the curve $(AUC)_{0\text{-}6h}$.

Results: In total, 146 patients (63.7% male; mean age, 36.1 years) were randomized. The adjusted mean total nasal symptom score $AUC_{0\text{-}6h}$ was significantly reduced versus placebo with 200 mg of BI 671800 (absolute difference, −0.85; percentage difference, −17%; $P = .0026$), montelukast (absolute difference, −0.74; percentage difference, −15%; $P = .0115$), and fluticasone propionate (absolute difference, −1.64; percentage difference, −33%; $P < .0001$). Compared with placebo, BI 671800 significantly reduced nasal eosinophil values ($P < .05$ for all doses), significantly inhibited nasal inflammatory cytokine levels (IL-4 and eotaxin, $P < .05$; 200 mg twice daily), and induced a dose-related reduction in *ex vivo* prostaglandin D_2–mediated eosinophil shape change.

Conclusion: Two hundred milligrams of BI 671800 twice daily demonstrated efficacy in treating SAR symptoms induced by environmental challenge chamber allergen exposure and had a favorable safety profile. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Chemoattractant receptor homologous molecule on T_H2 cells, BI 671800, environmental challenge chamber, prostaglandin D_2, seasonal allergic rhinitis, inflammation*

Allergic rhinitis (AR) is a common IgE-mediated disease whereby inhaled allergens cause a type 1 hypersensitivity reaction.[1] Inflammation in patients with AR is heterogeneous because it is derived from a variety of cell types, and therapies targeting a single mediator are often not sufficient to resolve all the different symptoms or underlying inflammation.[1,2] There is a need for agents with pharmacologically broad anti-inflammatory mechanisms, ease of administration, and a favorable safety profile.

Prostaglandin D_2 (PGD_2), an arachidonic acid metabolite, is a key mediator in inflammation after allergen exposure and is released by IgE-activated mast cells and other inflammatory cell types.[3,4] PGD_2 might help in recruiting and activating T_H2 lymphocytes and eosinophils[4] and therefore plays an important role in AR. Increased PGD_2 levels have been found in the alveolar lavage fluid of patients with respiratory allergy after antigen challenge,[5] and nasal challenge with PGD_2 induces a greater degree of nasal congestion than that induced by histamine.[6] The proinflammatory effects of PGD_2 occur through interactions with the chemoattractant receptor homologous molecule on T_H2 cells (CRTH2), a 7-transmembrane type G protein–coupled receptor selectively expressed on T_H2 cells, T cytotoxic type 2 cells, eosinophils, and basophils.[3] CRTH2 activation triggers intracellular calcium mobilization, as well as the release of chemokines and inflammatory mediators, leading to an increasingly recognized role in the initiation and perpetuation of allergic diseases.[7] The activation of CRTH2 has recently been discovered to function as a survival signal for T_H2 lymphocytes, a process involving the phosphatidylinositol 3-kinase pathway.[8] This suggests that CRTH2 antagonists might not only inhibit the

From [a]the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Hannover; [b]Boehringer Ingelheim, Biberach; and [c]Boehringer Ingelheim Pharmaceuticals, Ridgefield.

Supported by Boehringer Ingelheim.

Disclosure of potential conflict of interest: N. Krug has received support for travel from Boehringer Ingelheim; has consultancy arrangements with Bayer, Boehringer Ingelheim, Chiesi, Novartis, MedImmune, and Sterna Biologics; has received one or more grants from or has one or more grants pending with Allergopharma, Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Leti Pharma, Novartis, Nycomed, Parexel, Pfizer, and Sterna Biologics; and has received one or more payments for lecturing from or is on the speakers' bureau for AstraZeneca, GlaxoSmithKline, Chiesi, and Novartis. A. Gupta, J. Hilbert, R. Koenen, A. Pivovarova, K. Wetzel, and C. Wood are employed by Boehringer Ingelheim. P. Badorrek has been supported by one or more grants from Boehringer Ingelheim. M. Mueller has been supported by one or more grants from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Novartis, Sterna Biologics, DRK BLutspendedienst Springe, and Pulmatrix. J. M. Hohlfeld has consultancy arrangements with Boehringer Ingelheim, Nycomed, and Roche; has received one or more grants from or has one or more grants pending with Allergopharma, Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Leti Pharma, Novartis, Nycomed, Parexel, Pfizer, Pulmatrix, Sterna Biologicals, Sun Pharma, Trimel Biopharma, and Bionorica; and has received one or more payments for lecturing from or is on the speakers' bureau for Novartis and Nycomed.

Received for publication December 7, 2012; revised October 3, 2013; accepted for publication October 14, 2013.

Corresponding author: Norbert Krug, MD, Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Nikolai-Fuchs-Str 1, Hannover 30625, Germany. E-mail: norbert.krug@item.fraunhofer.de.

0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2013.10.013

Abbreviations used
AE: Adverse event
AR: Allergic rhinitis
AUC: Area under the curve
CRTH2: Chemoattractant receptor homologous molecule on T_H2 cells
ECC: Environmental challenge chamber
ESC: Eosinophil shape change
FP: Fluticasone propionate
FSC: Forward scatter
MMRM: Mixed-model repeated measure
PGD_2: Prostaglandin D_2
SAR: Seasonal allergic rhinitis
TNSS: Total nasal symptom score

recruitment and activation of T_H2 cells but also accelerate apoptosis and clearance of these cells from inflamed tissue, thereby promoting the resolution of the underlying inflammation in AR.[4,7]

Preclinical data show that CRTH2 receptor antagonism reduces underlying inflammation in AR animal models.[9,10] Furthermore, patients with AR demonstrate higher PGD_2 and CRTH2 gene and protein expression than healthy control subjects,[11,12] and alleles of certain CRTH2 single nucleotide polymorphisms are associated with a higher degree of bronchial hyperresponsiveness.[13] Studies in human subjects have shown that a selective CRTH2 antagonist is effective at reducing eosinophil counts in asthmatic patients compared with placebo,[14] and a recent study demonstrated a reduction in nasal and ocular allergic symptoms by pretreatment with the CRTH2 antagonist OC000459 in patients with AR exposed to grass pollen in an allergen challenge chamber.[15] BI 671800 is a highly specific and potent antagonist of the PGD_2 receptor CRTH2, with half-maximal inhibitory concentration values ranging from 1.7 nmol/L in a competitive binding assay to 7.1 nmol/L in cell migration assays. BI 671800 is active in a number of animal models of asthma and allergic dermatitis; in human subjects it inhibits PGD_2-stimulated eosinophil shape change (ESC), a marker of eosinophil activation that is dependent on CRTH2 (data on file).

The objective of the current study was to investigate the clinical efficacy, safety, and tolerability of 3 twice-daily doses (50, 200, and 400 mg) of BI 671800, as well as the active comparators montelukast (10 mg) and nasal fluticasone propionate (FP; 200 μg), both administered once daily in the morning, in an environmental challenge chamber (ECC) in patients with seasonal allergic rhinitis (SAR).

METHODS

Study design

This was a phase IIa, single-center, randomized, double-blind, placebo-controlled, triple-dummy, 2-way, partial-crossover study conducted at the Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany (Clinical Trial Identifier: NCT01007721). Adults with SAR were repeatedly exposed to grass pollen *(Dactylis glomerata)* in the ECC, an accepted model of allergen exposure during the out-of-season period.[16] Each patient received a BI 671800 capsule (active or placebo twice daily) plus an encapsulated montelukast tablet (active or placebo once daily) plus FP nasal spray (active or placebo once daily). In this partial crossover design it was planned that 5 groups of 30 patients would each receive 1 of the 5 active treatments in 1 of the 2 study periods and placebo only in the other period (n = 150 in total).

After the initial screening visit and a baseline period, including a test for responsiveness to *D glomerata* at visit 2 by means of a 2-hour ECC exposure test, patients were randomized to a treatment sequence (see the Methods section in this article's Online Repository at www.jacionline.org) in which they would receive 1 of the 5 active treatments for 2 weeks and placebo for 2 weeks; they were then exposed on the last day of each treatment period to 4000 grains/m^3 *D glomerata* in the ECC for 6 hours and evaluated for treatment efficacy with a 2- to 4-week washout between-treatment periods (study design, see Fig E1 in this article's Online Repository at www.jacionline.org). The trial was carried out in compliance with international and local regulatory requirements. The protocol was approved by the competent local authorities.

Patients

Male and female patients aged 18 to 65 years with a history of SAR and a positive skin prick test response to *D glomerata* within the previous 12 months were screened for entry into the trial. To be randomized to study treatment, patients were required to have a total nasal symptom score (TNSS) of 2 or less before allergen exposure at the baseline visit and a TNSS of greater than 5 at least once during the 2-hour baseline ECC after allergen exposure. Full inclusion and exclusion criteria and details of permitted/prohibited prior or concomitant medications are outlined in the Methods section in this article's Online Repository. Before participation in the trial, written informed consent was obtained from each patient.

Assessments

Nasal symptoms. TNSSs, including symptoms for rhinorrhea, nasal congestion, sneezing, and nasal itching, were evaluated as the primary efficacy variable. Each patient recorded scores for each of these symptoms by severity (0, none; 1, mild; 2, moderate; and 3, severe) before and every 20 minutes during their time in the ECC.[16] The TNSS was calculated by adding the scores of the 4 symptoms and the area under the curve (AUC) from 0 to 6 hours that represented the primary efficacy end point. Secondary end points included TNSSs over different periods (0-1, 1-2, 2-3, 3-4, 4-5, and 5-6 hours and 0-2, 2-4, and 4-6 hours) during allergen exposure and nasal subscores assessed as the AUC of values.

Nasal secretions and airflow. Nasal secretions (as the total difference of paper tissue weight[17]) and nasal flow (rhinomanometry) were measured every 120 minutes during the challenge, as described by Krug et al.[16] Nasal lavage samples were obtained, as previously described,[17] at the end of each 6-hour allergen challenge in the ECC.

Analysis of inflammatory cells. The absolute numbers (counts) and proportions (percentages) of macrophages, neutrophils, lymphocytes, monocytes, eosinophils, and epithelial cells in nasal lavage fluid were measured at the end of the allergen challenge.

Analysis of inflammatory cytokines. Assessment of cytokines (the soluble inflammatory biomarkers IL-4, IL-5, IL-13, and eotaxin) from nasal fluid samples was done with a validated multiplex immunoassay (as described in the Methods section in this article's Online Repository).

ESC. The ability of BI 671800 to block *ex vivo* ESC induced by the interaction of PGD_2 with the CTRH2 receptor was quantified as described in the Methods section in this article's Online Repository. Fig E3 (in this article's Online Repository at www.jacionline.org) shows the gating strategy for identification of eosinophils and determination of ESC.

Safety. Safety was assessed as the incidence and intensity of adverse events (AEs), vital signs (pulse rate and blood pressure), laboratory safety parameters, 12-lead resting electrocardiograms, lung function (FEV_1), and physical examination. Rescue medication use was also recorded.

Statistical analyses

All statistical analyses were prespecified, with the exception of the additional supportive mixed-effects analysis of nasal secretions and biomarkers. The placebo control group consisted of all placebo crossover periods from all treatment sequences. Three hypotheses for testing superiority

of the 3 doses of BI 671800 versus placebo were defined; a stepwise hierarchical procedure was used to control type 1 error. No adjustment for multiplicity was performed. The 1-sided hypotheses ($\alpha = .025$) were to be tested based on adjusted mean TNSS $AUC_{0\text{-}6h}$ values from a mixed-model repeated measurement (MMRM), with the sources of variation of treatment and period as fixed effects and patient as a random effect. The SAS/STAT MIXED procedure (SAS Institute, Cary, NC) was used.

A sample size of 120 randomized patients was chosen to allow detection of a 0.9 effect size at a power of 80% (between-person SD of 1.5 and within-person correlation of 0.2).[18] A total sample size of 150 randomized patients (30 patients per active treatment group) was planned to allow for 20% patient dropout.

Nasal secretion was analyzed in a descriptive manner and with MMRM. The nasal airflow rate was presented as the $AUC_{0\text{-}6h}$ and assessed with MMRM. Inflammatory biomarkers (eosinophil counts, eotaxin, IL-4, IL-5, and IL-13) determined after 6 hours in the ECC were log_{10}-transformed and analyzed with an MMRM. ESCs were evaluated as the change over time per treatment period in a descriptive manner. The analyses of AEs were descriptive. On the rare occasions when ECC data were missing at random, missing data points were linearly interpolated (see the Methods section in this article's Online Repository).

RESULTS

Study population

A total of 146 participants (63.7% male; 97.9% white; mean age, 36.1 years) were randomized into the treatment phases and received study medication. All were allergic to pollen. Historically, most patients experienced the AR symptoms of itching eyes (77.4%), rhinorrhea (71.9%), nasal congestion (54.8%), and sneezing (50.0%) during their grass pollen season. Baseline characteristics of the total population are shown in Table I and in the Online Results Repository. Patient disposition is shown in Fig E2 in this article's Online Repository at www.jacionline.org.

TABLE I. Baseline characteristics (treated set)

	Total
Patients (no.)	146
Male (%)	63.7
White race (%)	97.9
Age (y), mean (SD)	36.1 (10.1)
Weight (kg), mean (SD)	78.6 (14.6)
Seasonal nasal symptoms, no. (%)	
Rhinorrhea	105 (71.9)
Nasal congestion	80 (54.8)
Sneezing	73 (50.0)
Nasal itching	60 (41.1)
SAR medications, no. (%)	
Oral antihistamines	118 (80.8)
Nasal antihistamines	51 (34.9)
Nasal steroids	20 (13.7)
Oral leukotriene antagonists	1 (0.7)

Nasal symptoms

All the study treatments showed a numerically lower adjusted mean TNSS $AUC_{0\text{-}6h}$ than placebo after 2 weeks of treatment with study medications (Fig 1). For the 200-mg twice-daily BI 671800 treatment group, the montelukast group, and the FP group, a statistically significant difference in adjusted mean TNSS $AUC_{0\text{-}6h}$ values was seen versus placebo (200-mg twice-daily BI 671800: absolute difference, −0.85; 95% CI, −1.40 to −0.3; percentage difference, −17%; $P = .0026$; montelukast: absolute, −0.74; 95% CI, −1.31 to −1.17; percentage, −15%; $P = .0115$; FP: absolute, −1.64; 95% CI, −2.18 to −1.11; percentage, −33%; $P < .0001$; Table II).

For the 200-mg twice-daily BI 671800 treatment group, a statistically significant difference in adjusted mean TNSS AUC versus placebo was observed for all time periods (TNSS $AUC_{0\text{-}2h}$, $P = .0090$; $AUC_{2\text{-}4h}$, $P = .0035$; $AUC_{4\text{-}6h}$, $P = .0065$) apart from 0 to 1 hour (−0.44; $P = .0798$). This was also seen for the FP treatment group (TNSS $AUC_{0\text{-}1h}$, $P = .0007$; $P < .0001$ for all other intervals) but not for the other treatment groups.

The individual nasal symptom $AUC_{0\text{-}6h}$ scores are presented in Table E1 in this article's Online Repository at www.jacionline.org. BI 671800, 200 mg twice daily, was effective at reducing rhinorrhea, itching, and sneezing when compared with placebo. In patients receiving FP, all individual symptoms were reduced, whereas in patients receiving montelukast only congestion and rhinorrhea improved.

Nasal secretion and nasal airflow

Nasal secretion compared with placebo was also numerically reduced (by 54.6% with FP, 24.5% with 200 mg of BI 671800 twice daily, 22.9% with 400 mg of BI 671800 twice daily, 13.8% with montelukast, and 11.5% with 50 mg of BI 671800 twice daily), although only FP showed a statistically significant decrease (see Table E2 in this article's Online Repository at www.jacionline.org).

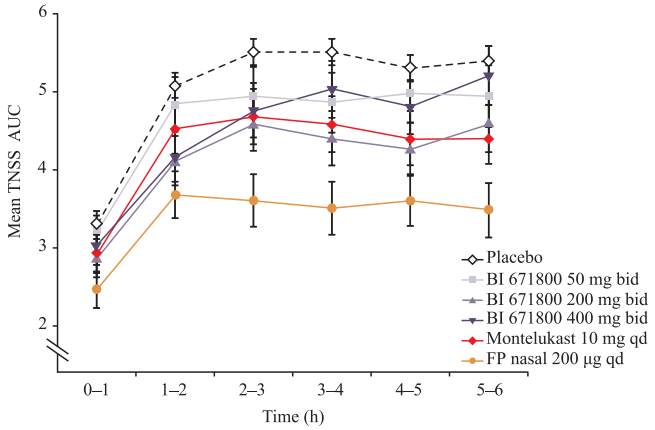

FIG 1. Adjusted means (SEs) for hourly TNSS AUC values. *bid*, Twice daily; *qd*, once daily.

Nasal flow rate versus that seen in the placebo group over 0 to 6 hours was statistically significantly increased only with FP (difference for $AUC_{0\text{-}6h}$ 52.62 mL/s; $P = .0381$); the effect for montelukast was +25.89 mL/s (8% increase, $P = .3381$) and the effect for 200 mg of BI 671800 was +13.00 mL/s (4% increase, $P = .6083$).

Nasal eosinophil values and cytokine levels

After 6 hours in the ECC, there was a significant decrease in both the absolute counts and percentages of nasal eosinophils with active study treatments compared with placebo but no changes in values for the other inflammatory cell types. The decrease was not dose related for BI 671800 (Fig 2, *A*).

BI 671800 exerted a statistically significant inhibitory effect on levels of the inflammatory cytokines IL-4 and eotaxin in nasal fluid when administered at 200 mg twice daily ($P < .05$); when looking at IL-5 and IL-13, there was a trend for significance in reductions in cytokine concentration with 200 mg twice daily

TABLE II. Comparison* of TNSS $AUC_{0\text{-}6h}$ values for the different study treatment groups

Treatment	n	TNSS $AUC_{0\text{-}6h}$ adjusted mean (SE)	Comparison vs placebo		
			Adjusted mean of difference (SE)	95% CI	*P* value
Placebo	123	5.02 (0.148)			
BI 671800, 50 mg bid	22	4.62 (0.309)	−0.40 (0.306)	−1.01 to 0.20	.1917
BI 671800, 200 mg bid	27	4.16 (0.281)	−0.85 (0.279)	−1.40 to −0.30	.0026
BI 671800, 400 mg bid	25	4.50 (0.293)	−0.51 (0.293)	−1.09 to 0.06	.0810
Montelukast, 10 mg qd	25	4.28 (0.292)	−0.74 (0.290)	−1.31 to −0.17	.0115
FP, 200 μg qd	29	3.37 (0.273)	−1.64 (0.271)	−2.18 to −1.11	<.0001

bid, Twice daily; *qd*, once daily.
*Mixed-effect model.

(Fig 2, *B*: IL-13, $P = .0597$; and Fig 2, *C*; IL-5, $P = .0543$). FP reduced IL-4, IL-5, IL-13, and eotaxin levels significantly in nasal secretions. Treatment with the other doses of BI 671800 or montelukast did not affect the cytokine concentration.

PGD_2-induced ESC

ESC was notably inhibited by BI 671800 at all doses, with the median ESC decreasing in a dose-related manner (Fig 3). The changes in mean ESC minimum observed effect values from placebo were −52.4% for the 50-mg twice-daily dose, −75.5% for the 200-mg twice-daily dose, and −89.1% for 400-mg twice-daily dose of BI 671800; values for the corresponding placebos did not deviate greatly from 10% to 15% shape change over the time patients were in the ECC. As expected, FP and montelukast did not inhibit shape change because these compounds do not inhibit PGD_2 binding to CRTH2.[2]

Safety

BI 671800 was well tolerated at all doses studied, and no serious AEs occurred during the trial. Consistent with known AEs reported during allergen exposure in an ECC, the most common AE was headache, and the most common drug-related AEs were headache and epistaxis (see Table E3 in this article's Online Repository at www.jacionline.org). These AEs were seen in patients treated with BI 671800 and the active comparators and during placebo dosing. No findings relating to treatment with BI 671800 were observed in the clinical laboratory, during measurement of vital signs, in electrocardiographic data, or during monitoring of lung function during and after the time in the ECC.

DISCUSSION

Classical trials for SAR are conducted during the pollen season; however, variability in pollen levels can have a negative effect on the sensitivity of the study. In our study participants were subjected to allergen provocation in an ECC unit out of the pollen season. The conditions in this specifically designed room ensure a validated, highly controlled, and standardized allergen exposure, which is ideal for dose-finding studies and investigations into new AR therapies.[16,19,20]

Overall, the trial showed that 200 mg of BI 671800 twice daily was effective in reducing total and individual symptoms and nasal AR symptoms (rhinorrhea, sneezing, and nasal itching score) in an ECC model, achieving a significant and clinically relevant reduction in TNSSs from 0 to 6 hours. However, BI 671800 did not significantly reduce nasal secretions or affect nasal flow rate. Clinical efficacy was not proved for the 50-mg twice-daily and 400-mg twice-daily doses, although this trial was not designed or powered to assess a formal dose response for BI 671800. The absence of greater activity at the highest investigational dose studied has been noted in other AR studies considering nasal steroids[21,22] and might represent variability because of lack of power to assess the dose response or a plateau of the effect at higher doses. Although a false-positive finding with 200 mg of BI 671800 twice daily cannot be excluded, it is less likely because significant changes were detected in symptom scores and in biomarkers in parallel in this dose group only. Despite the partial crossover design of the study, no carryover effect was observed in this study or in 2 phase II asthma studies with the same compounds in which a treatment effect was observed.[23,24] This is different from what has been reported by the CRTH2 antagonists OC000459 in asthmatic patients[25] and those with SAR,[15] in whom a carryover effect was noted.

Several studies have demonstrated significant expression of various cytokines and chemokines in inflammatory cells at the sites of nasal allergic inflammation in nasal antigen challenge models[26,27] and during a natural allergy season.[28] In particular, the cytokines IL-4, IL-5, and IL-13 might be critical to the allergic response by contributing to eosinophilia, airway hyperreactivity, IgE production, involvement in late-phase allergic responses, and mucus overproduction.[28,29] A reduction in concentrations of the nasal cytokines IL-4 and eotaxin and a trend for reduction of IL-5 and IL-13 concentrations was also observed in patients receiving 200 mg of BI 671800 twice daily. As expected, BI 671800 administration resulted in a dose-related inhibition of *ex vivo* PGD_2-induced ESC. However, PGD_2-induced ESC might be considered a marker derived from a CRTH2 receptor target engagement assay rather than a biomarker for efficacy.

The effects of the nasal corticosteroid FP and the oral leukotriene receptor antagonist montelukast were also studied to gauge and compare the magnitude and effects of BI 671800 versus recommended treatments for SAR. All analyses were exploratory in nature because the trial was not powered for comparison with active treatments. The magnitude of the effect of 200 mg of BI 671800 twice daily on the primary end point of the TNSS was between that observed for FP and montelukast.

A major strength of the study is that both clinical end points and biomarkers were included as end points. Clinical efficacy (shown for 200 mg of BI 671800 twice daily and the steroid

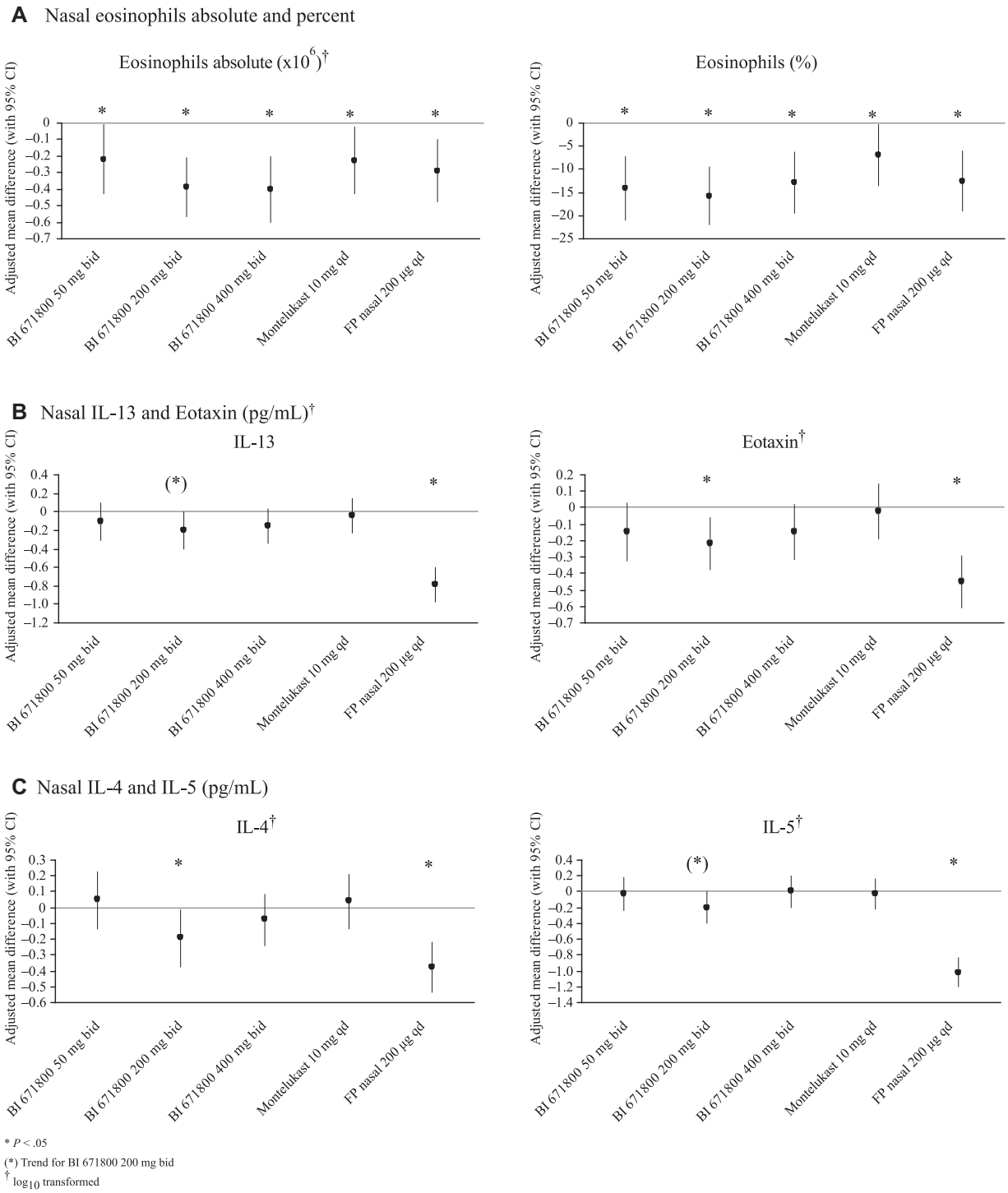

FIG 2. Nasal eosinophil and cytokine values after 6 hours in the ECC. **A,** Absolute and percent nasal eosinophils count. **B,** Nasal IL-13 and eotaxin values. **C,** Nasal IL-4 and IL-5 values. *bid*, Twice daily; *qd*, once daily.

FP) was clearly reflected in the reduction in nasal cytokine levels. No adjustment for multiplicity was performed or planned in this trial. Further research through an appropriately powered trial is needed to confirm the differential effects of CRTH2 inhibition versus currently available therapies in patients with SAR.

The oral CRTH2 antagonist BI 671800 at a dose of 200 mg twice daily demonstrated efficacy when treating nasal AR symptoms induced by allergen exposure in the ECC, particularly in terms of rhinorrhea, nasal itching, and sneezing. BI 671800 was well tolerated, with no clinically meaningful drug-related AEs.

We thank Anja Casper for her important contribution as a clinical trial coordinator. Editorial and writing assistance was provided by Elena Garonna, PhD, of PAREXEL, which was funded by Boehringer Ingelheim.

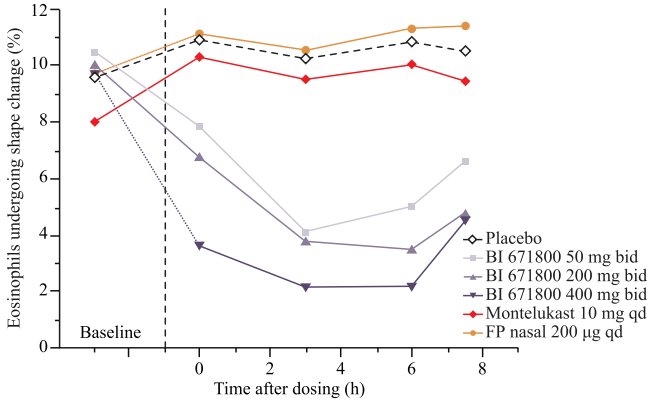

FIG 3. ESC median percentage change over time. *bid*, Twice daily; *qd*, once daily.

Clinical implications: The oral CRTH2 antagonist BI 671800 at 200 mg twice daily demonstrated efficacy as a treatment for SAR with a favorable safety profile.

REFERENCES

1. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. Proc Am Thorac Soc 2011;8:106-14.
2. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. Int Immunopharmacol 2011;11:1646-62.
3. Kostenis E, Ulven T. Emerging roles of DP and CRTH2 in allergic inflammation. Trends Mol Med 2006;12:148-58.
4. Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. Nat Rev Drug Discov 2007;6:313-25.
5. Murray JJ, Tonnel AB, Brash AR, Roberts LJ, Gosset P, Workman R, et al. Release of prostaglandin D2 into human airways during acute antigen challenge. N Engl J Med 1986;315:800-4.
6. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. J Allergy Clin Immunol 1990;86:924-35.
7. Pettipher R, Whittaker M. Update on the development of antagonists of chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). From lead optimization to clinical proof-of-concept in asthma and allergic rhinitis. J Med Chem 2012;55:2915-31.
8. Xue L, Barrow A, Pettipher R. Novel function of CRTH2 in preventing apoptosis of human Th2 cells through activation of the phosphatidylinositol 3-kinase pathway. J Immunol 2009;182:7580-6.
9. Stearns BA, Baccei C, Bain G, Broadhead A, Clark RC, Coate H, et al. Novel tricyclic antagonists of the prostaglandin D2 receptor DP2 with efficacy in a murine model of allergic rhinitis. Bioorg Med Chem Lett 2009;19:4647-51.
10. Lukacs NW, Berlin AA, Franz-Bacon K, Sasik R, Sprague LJ, Ly TW, et al. CRTH2 antagonism significantly ameliorates airway hyperreactivity and downregulates inflammation-induced genes in a mouse model of airway inflammation. Am J Physiol Lung Cell Mol Physiol 2008;295:L767-79.
11. Okano M, Fujiwara T, Sugata Y, Gotoh D, Masaoka Y, Sogo M, et al. Presence and characterization of prostaglandin D2-related molecules in nasal mucosa of patients with allergic rhinitis. Am J Rhinol 2006;20:342-8.
12. Nantel F, Fong C, Lamontagne S, Wright DH, Giaid A, Desrosiers M, et al. Expression of prostaglandin D synthase and the prostaglandin D2 receptors DP and CRTH2 in human nasal mucosa. Prostaglandins Other Lipid Mediat 2004; 73:87-101.
13. Cameron L, Depner M, Kormann M, Klopp N, Illig T, von ME, et al. Genetic variation in CRTh2 influences development of allergic phenotypes. Allergy 2009;64:1478-85.
14. 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.
15. 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.
16. Krug N, Hohlfeld JM, Larbig M, Buckendahl A, Badorrek P, Geldmacher H, et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. Clin Exp Allergy 2003;33:1667-74.
17. Nicholson GC, Kariyawasam HH, Tan AJ, Hohlfeld JM, Quinn D, Walker C, et al. The effects of an anti-IL-13 mAb on cytokine levels and nasal symptoms following nasal allergen challenge. J Allergy Clin Immunol 2011;128:800-7.
18. Badorrek P, Dick M, Schauerte A, Hecker H, Murdoch R, Luettig B, et al. A combination of cetirizine and pseudoephedrine has therapeutic benefits when compared to single drug treatment in allergic rhinitis. Int J Clin Pharmacol Ther 2009;47:71-7.
19. Badorrek P, Dick M, Hecker H, Schaumann F, Sousa AR, Murdoch R, et al. Anti-allergic drug testing in an environmental challenge chamber is suitable both in and out of the relevant pollen season. Ann Allergy Asthma Immunol 2011;106:336-41.
20. Hohlfeld JM, Holland-Letz T, Larbig M, Lavae-Mokhtari M, Wierenga E, Kapsenberg M, et al. Diagnostic value of outcome measures following allergen exposure in an environmental challenge chamber compared with natural conditions. Clin Exp Allergy 2010;40:998-1006.
21. Meltzer EO, Orgel HA, Bronsky EA, Furukawa CT, Grossman J, LaForce CF, et al. A dose-ranging study of fluticasone propionate aqueous nasal spray for seasonal allergic rhinitis assessed by symptoms, rhinomanometry, and nasal cytology. J Allergy Clin Immunol 1990;86:221-30.
22. Ratner PH, Wingertzahn MA, van Bavel JH, Hampel F, Darken PF, Hellbardt S, et al. Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2006;97:657-63.
23. Sutherland R, Tetzlaff K, Nivens C, Tsukayama A, Guerreros RM, Bateman E, et al. Efficacy and safety of BI 671800, an oral CRTH2 antagonist in controller naïve patients with poorly-controlled asthma. Eur Respir J 2012;40(Suppl 56): 546S.
24. Hall I, Sarno M, Disse B, Atis S, Bateman E, Finnigan H, et al. Efficacy and safety of BI 671800, an oral CRTH2 antagonist, as add on therapy in poorly controlled asthma patients prescribed an inhaled corticosteroid. Eur Respir J 2012;40(Suppl 56):312S.
25. Singh D, Cadden P, Hunter M, Pearce CL, 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.
26. Erin EM, Leaker BR, Zacharasiewicz AS, Higgins LA, Williams TJ, Boyce MJ, et al. Single dose topical corticosteroid inhibits IL-5 and IL-13 in nasal lavage following grass pollen challenge. Allergy 2005;60:1524-9.
27. Serrano CD, Valero A, Bartra J, Roca-Ferrer J, Munoz-Cano R, Sanchez-Lopez J, et al. Nasal and bronchial inflammation after nasal allergen challenge: assessment using noninvasive methods. J Investig Allergol Clin Immunol 2012;22:351-6.
28. Bachert C, van Kempen M, Van Cauwenberge P. Regulation of proinflammatory cytokines in seasonal allergic rhinitis. Int Arch Allergy Immunol 1999;118:375-9.
29. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol 2010;10:838-48.

METHODS

Study design

This 2-way partial crossover study incorporated a balanced and incomplete block design. Patients each received 1 of the 5 active treatments (A, B, C, D, or E) in the first or second treatment periods and placebo (F) in the other treatment period. Eligible patients were randomized to 1 of 10 possible treatment sequences (ie, AF, FA, BF, FB, CF, FC, DF, FD, EF, FE) based on the triple-dummy design:

- *A (active treatment with 50 mg of BI 671800 twice daily)*: 2 capsules of 25 mg of BI 671800 plus 2 capsules of BI 671800 placebo (twice daily in the morning and evening) plus 1 overencapsulated montelukast placebo tablet (once daily in the morning) plus FP placebo nasal spray (2 puffs to each nostril once daily in the morning);
- *B (active treatment with 200 mg of BI 671800 twice daily)*: 2 capsules of 100 mg of BI 671800 plus 2 capsules of BI 671800 placebo (twice daily in the morning and evening) plus 1 overencapsulated montelukast placebo tablet (once daily in the morning) plus FP placebo nasal spray (2 puffs to each nostril once daily in the morning);
- *C (active treatment with 400 mg of BI 671800 twice daily)*: 4 capsules of 100 mg of BI 671800 (twice daily in the morning and evening) plus 1 overencapsulated montelukast placebo tablet (once daily in the morning) plus FP nasal spray placebo (2 puffs to each nostril once daily in the morning);
- *D (active treatment with 10 mg of montelukast once daily)*: 1 overencapsulated 10-mg montelukast tablet (once daily in the morning) plus 4 capsules of BI 671800 placebo (twice daily in the morning and evening) plus FP placebo nasal spray (2 puffs to each nostril once daily in the morning);
- *E (active treatment with 200 μg of FP once daily)*: 200 μg of FP nasal spray (2 puffs of 50 μg to each nostril once daily in the morning) plus 4 capsules of BI 671800 placebo (twice daily in the morning and evening) plus 1 overencapsulated montelukast placebo tablet (once daily in the morning); and
- *F (placebo)*: 4 capsules of BI 671800 placebo (twice daily in the morning and evening) plus 1 overencapsulated montelukast placebo tablet (once daily in the morning) plus FP placebo nasal spray (2 puffs to each nostril once daily in the morning).

Analysis was based on a comparison of 30 patients each receiving active treatment versus 150 patients receiving placebo.

Treatment assignment was conducted in a double-blind fashion, with eligible patients randomly assigned to a treatment sequence by allocation of medication numbers. The study medication administered to individual patients was blinded to the patient, the investigator, the trial team, and the sponsor. Each patient received a BI 671800 capsule (active or placebo twice daily) plus an encapsulated montelukast tablet (active or placebo once daily) plus an FP nasal spray (active or placebo once daily), as described above. The randomization list was generated by using a validated system, involving a pseudorandom number generator with a supplied seed number so that the resulting sequence of treatments was reproducible and nonpredictable. Randomization was conducted in blocks to achieve balanced allocation. Efficacy analyses were performed for all randomized patients in the treated set who provided postdosing efficacy data; the treated set consisted of all patients who were dispensed study medication and documented as having taken at least 1 dose of investigational treatment.

Patients

Other than the inclusion criteria already mentioned in the main text, patients were required to be nonsmokers or exsmokers with a cigarette smoking history of 10 or fewer pack years and smoking cessation for at least 1 year before enrollment; be able to comply with the study protocol requirements, medication restrictions, and procedures, including portable lung function device and rescue medication use; have a body mass index of 18 kg/m^2 or greater and 35 kg/m^2 or less and a negative breath alcohol test result; and have negative urine cotinine and drug test results at screening (visit 1). The patient's postbronchodilator FEV_1 was to be 80% or greater of their personal best to undergo each allergen exposure in the environmental challenge chamber.

Patients were excluded if they had any pulmonary disease other than AR or mild intermittent asthma managed by taking short-acting β-adrenergic agents alone, other medical conditions (eg, cardiac, gastrointestinal, hepatic, renal, metabolic, dermatologic, neurologic, hematologic, oncologic, and psychiatric conditions or patients who had undergone resection, radiation therapy, or chemotherapy for malignancy within the previous 5 years), other nasal and sinus diseases or conditions (ie, nasal polyps and frequent nose bleeds), respiratory tract infection, or asthma exacerbation in the 4 weeks before visit 1 (or during the screening and baseline periods). Additionally, patients who fulfilled any of the following exclusion criteria were not eligible for randomization into the treatment phase of the trial: patients at risk of prolonged QT-interval effects, pregnant or nursing women, women of childbearing potential who were not using an effective method of birth control, or patients with previous participation in this study (receipt of a randomized treatment) or active participation in a current interventional study, clinically relevant abnormal baseline hematology, blood chemistry, or urinalysis at screening. Patients were not to be randomized if they had aspartate aminotransferase or alanine aminotransferase levels of greater than 2 times the upper limit of normal at screening, significant alcohol or drug abuse within the past 2 years, or a known hypersensitivity to any component of the investigational treatment, FP nasal spray, montelukast, or salbutamol metered-dose inhaler components.

Medications thought to interact or attenuate study drugs were not permitted. Rescue medication (salbutamol) was allowed and recorded (by participants) throughout the study. The protocol also excluded patients taking cytochrome P4502C8 or cytochrome P4502C9 substrates because of the potential for BI 671800 to have adverse hepatic effects and to inhibit cytochrome P4502C8 and cytochrome P4502C9 activity, raising safety concerns. The cytochrome P4502C9 substrates included but were not restricted to amiodarone, amodiaquine, paclitaxel, rosiglitazone, pioglitazone, repaglinide, warfarin, tolbutamide, phenytoin, losartan, and acencoumarol. Patients were also excluded if they had been treated with immunomodulatory therapy, biological agent–based antagonist therapy (in the previous 6 months), a systemic corticosteroid (in the previous 3 months), or topical steroids or had received a change in prescription medications (within the previous 4 weeks). Other prohibited medications were long-acting β_2-agonist agents, methylxanthines, leukotriene modifiers, antihistamines, oral decongestants, antirhinitis therapies (ie, decongestants, herbal agents, and anticholinergic agents), hay fever medication, tricyclic antidepressants, aspirin, and any nonsteroidal anti-inflammatory drug (only paracetamol was to be used for occasional pain relief) or oral β_2-agonists within the previous 2 weeks or a short-acting bronchodilator within the 6 hours before baseline pulmonary function testing.

Analysis of cytokines in nasal fluid

Briefly, pledget filter papers were transferred into a SpinX-vial (Sigma-Aldrich, St Louis, Mo) and 500 μL of assay buffer (Beadlyte Cytokine Assay Buffer; Millipore, Temecula, Calif) was pipetted into the membrane insert. The vials were then centrifuged for 5 minutes at 4°C and 16,000*g*. The membrane insert and dry filter paper were discarded, and the assay buffer in the SpinX-vial was vortexed for 5 seconds. Samples were placed in aliquots, shock-frozen in liquid nitrogen, and stored at −70°C until shipment to the analytic facility in which cytokine assays were conducted. The electrochemiluminescence response of standards for each interleukin were fitted to a 4-parameter logistic equation to quantitate the analyte concentrations. The detection range of the assay was 2.44 to 3750 pg/mL for IL-4 and IL-13, 1.22 to 3750 pg/mL for IL-5, and 2.44 to 625 pg/mL for eotaxin.

ESC

The ESC in whole blood, as induced by stimulation with PGD_2, was measured in comparison with native eosinophils. Change in forward scatter (FSC) was measured by using flow cytometry in duplicate samples. Venous blood (minimum of 1.5 mL) was collected in a sodium citrate safety vacutainer tube and kept at room temperature under agitation for a maximum of 4 hours until preparation of the sample. Two samples (750 μL) were transferred into

each of 2 polypropylene tubes, and 7.5% dextran solution (225 μL) was added into each tube and mixed by means of pipetting. The samples were incubated for 15 minutes at room temperature, and the erythrocyte-depleted interphase (approximately 200-300 μL) was collected.

Isolated cells (100 μL per sample) were transferred into polypropylene flow cytometric tubes (Beckman Coulter, Fullerton, Calif) and incubated for 5 to 10 minutes. Ice-cold 500 nmol/L PGD_2 diluted in Mg- and Ca-free D-PBS (10 μL) or ice-cold D-PBS (10 μL) was added.

Cells were mixed and incubated at room temperature for 5 minutes. The reaction was stopped by adding ice-cold BD Cytofix buffer (250 μL) diluted 1:4 in D-PBS, and 140 μL of ice-cold D-PBS was added to a final sample volume of 500 μL.

The cells were measured with a Beckman Coulter FC500 flow cytometer within 2 hours after fixation. The flow cytometer was set to the linear mode for FSC and side scatter, and a sensitive FL2 log mode setting was used. The collection angle for FSC was set on 8° to enlarge the detectable shift in FSC induced by the ESC. Fig E3 shows the gating strategy for identification of eosinophils and determination of ESC. For calculation of ESC, the means of the duplicates were determined, and the mean value of PBS-treated samples was subtracted from the mean value of PGD_2-treated samples.

Laboratory safety parameters

Clinical laboratory testing was to be conducted for all patients at the screening visit (visit 1) and repeated at visits 3, 4, 5, 6; at the end of the trial, at visit 7, or at the withdrawal visit if the patient did not complete all study visits; or when deemed necessary. Blood was to be drawn with the patient fasted for the previous 8 hours. Hematology, blood chemistry, and urinalysis were conducted by a central laboratory. Hematologic assessment parameters included the following: hemoglobin, hematocrit, red blood cell count, white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), total eosinophil count, and platelet count. Blood chemistry assessment parameters included alkaline phosphatase, C-reactive protein, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatine kinase, creatine kinase-MB isoenzyme, gamma glutamyltransferase, total bilirubin, potassium, sodium, glucose, calcium, inorganic phosphate, uric acid, urea nitrogen, creatinine, total protein, albumin, total IgE, ECP, and C-telopeptide of type 1 collagen (CTX-1, a collagen I breakdown product measured at visits 3, 6, and 7). HIV and hepatitis C and B screening tests were conducted for all patients; patients with a positive result were not to be enrolled into the trial. Urinalysis assessment parameters included specific gravity, pH, glucose, protein, and microhematuria.

Handling of missing data

Every effort was made to ensure the collection of complete data for each assessment time point on each test day. However, missing TNSSs and individual subscore and nasal flow data were linearly interpolated when time points both before and after were available (by using the predose value if necessary). If there were no subsequent nonmissing values, the last observation carried forward was to be used. Postdosing data missing because of an AE or the need for rescue medication were replaced by the least favorable prior measurement/score for the test day (including the predose value). If all data from a visit were missing at random (ie, the patient withdrew for another reason or a visit was missed but the patient had not withdrawn), the likelihood-based MMRM was used to handle missing data. Tissue weight, ESC, or biomarker data or AEs were not imputed, if missing.

Changes in conduct of trial/analyses

The mixed-effects model planned for the primary analysis was adapted to enable assessment of the average difference between placebo and a given active treatment across visit times rather than the effect at a particular visit. For TNSSs and symptom subscores, individual values obtained at 20 minutes, 40 minutes, and 1 hour after dosing were defined as additional end points. Analyses in addition to those prespecified were also carried out and included detailed pharmacodynamic analysis of biomarker data.

RESULTS

Study population: Concomitant medications

The most common concomitant therapies were an analgesic (paracetamol) and contraceptives. No notable differences in concomitant medication use were apparent when comparing treatment groups.

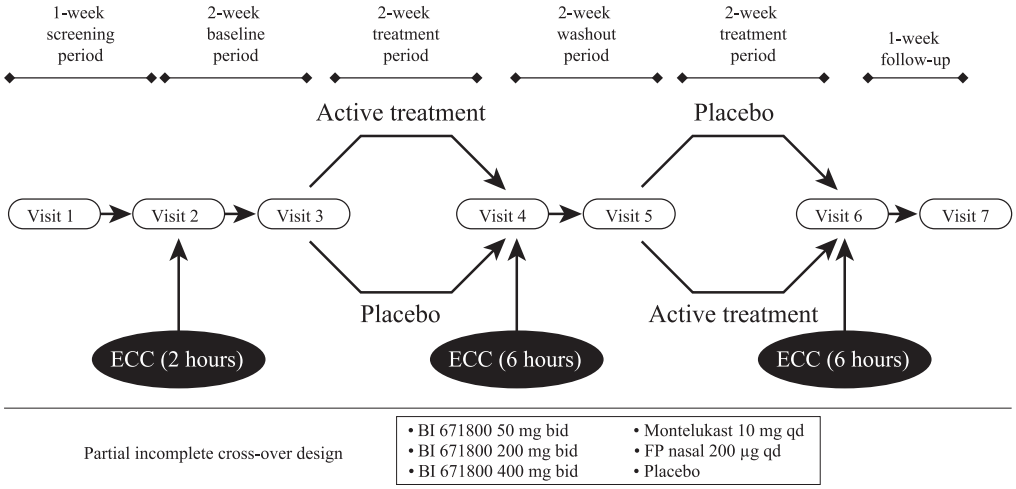

FIG E1. Study design. *bid*, Twice daily; *qd*, once daily.

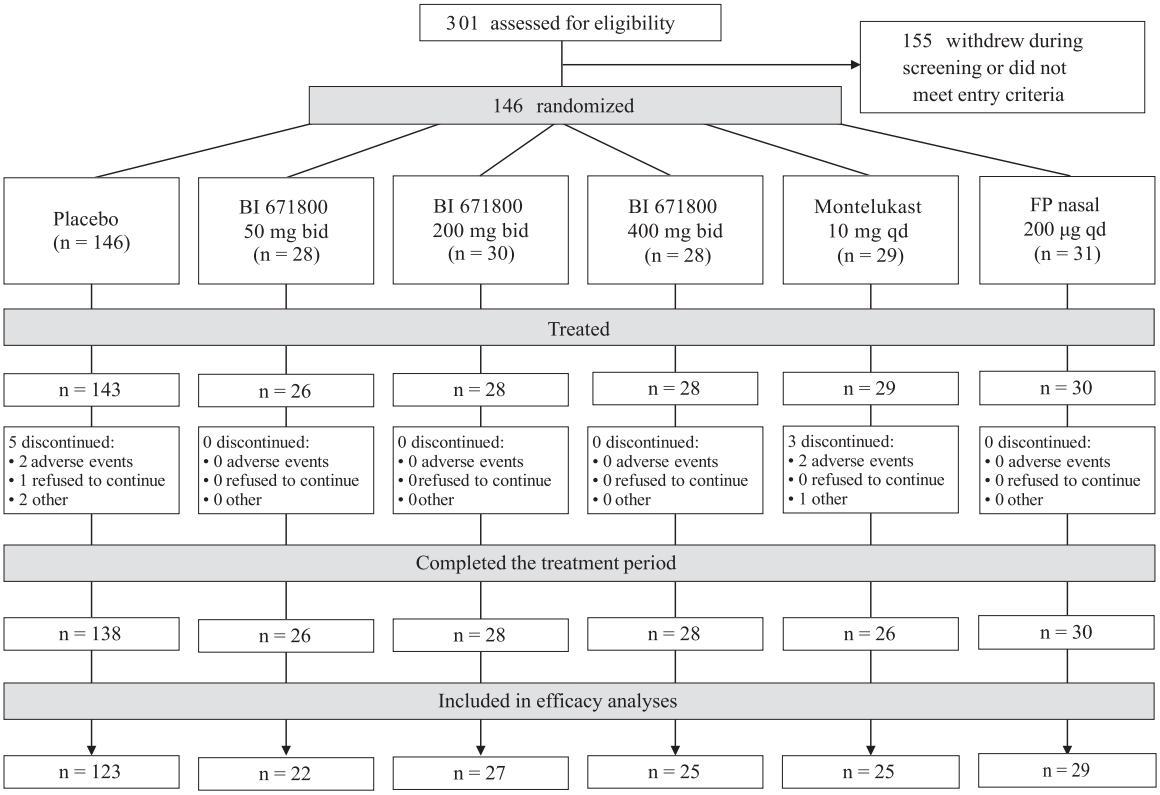

FIG E2. CONSORT diagram illustrating the flow of patients through the study. *bid*, Twice daily; *qd*, once daily.

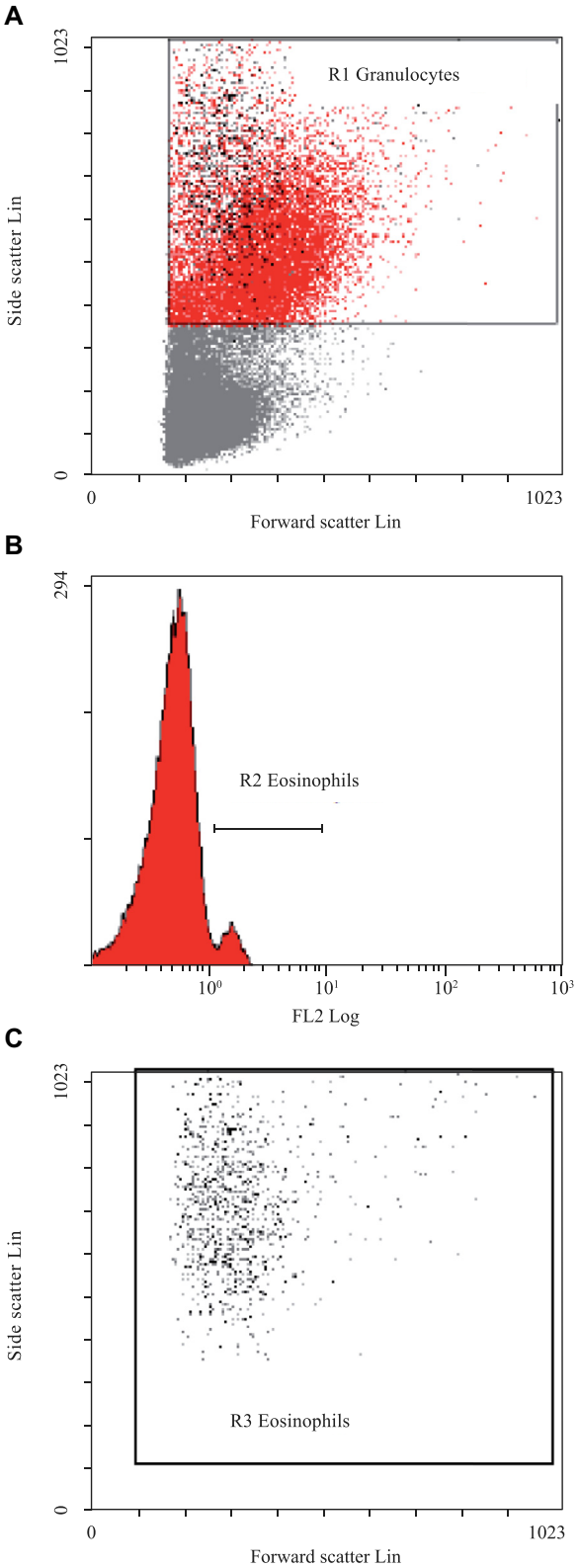

FIG E3. Gating strategy for identification of eosinophils and ESC determination. **A,** *Dot blot* showing FSC versus side scatter was used to set a region (R1) around the granulocytes excluding low FSC and side scatter events. **B,** The resulting histogram showing the FL2 channel was used to gate the high autofluorescent population representing the eosinophils, and a marker was set above these cells (R2). **C,** This cell population was displayed in a FSC/side scatter dot blot gated on R1 and R2. From this cell population, 500 to 1000 events were recorded, and the mean FSC value of this cell population in R3 representing eosinophils was determined.

TABLE E1. Comparison* of individual nasal symptom scores $AUC_{0\text{-}6h}$ for the different study treatment groups

			Comparison vs placebo		
	No.	**$AUC_{0\text{-}6h}$ adjusted mean (SE)**	**Adjusted mean of difference (SE)**	**95% CI**	***P* value**
Congestion					
Placebo	123	1.62 (0.053)			
BI 671800, 50 mg bid	22	1.57 (0.109)	−0.05 (0.108)	−0.26 to 0.17	.6627
BI 671800, 200 mg bid	27	148 (0.099)	−0.14 (0.098)	−0.33 to 0.06	.1604
BI 671800, 400 mg bid	25	1.60 (0.103)	−0.02 (0.103)	−0.22 to 0.19	.8634
Montelukast, 10 mg qd	25	1.34 (0.103)	−0.28 (0.102)	−0.48 to −0.08	.0065
FP, 200 μg qd	29	1.23 (0.096)	−0.39 (0.095)	−0.58 to −0.20	.0001
Rhinorrhea					
Placebo	123	1.39 (0.044)			
BI 671800, 50 mg bid	22	1.29 (0.094)	−0.11 (0.093)	−0.29 to 0.08	.2592
BI 671800, 200 mg bid	27	1.11 (0.085)	−0.29 (0.085)	−0.45 to −0.12	.0010
BI 671800, 400 mg bid	25	1.22 (0.089)	−0.17 (0.089)	−0.35 to 0.00	.0543
Montelukast, 10 mg qd	25	1.20 (0.088)	−0.19 (0.088)	−0.37 to −0.02	.0305
FP, 200 μg qd	29	0.89 (0.083)	−0.50 (0.083)	−0.67 to −0.34	<.0001
Itching					
Placebo	123	1.08 (0.045)			
BI 671800, 50 mg bid	22	0.96 (0.094)	−0.12 (0.093)	−0.30 to 0.07	.2146
BI 671800, 200 mg bid	27	0.84 (0.086)	−0.24 (0.085)	−0.41 to −0.07	.0057
BI 671800, 400 mg bid	25	0.87 (0.089)	−0.20 (0.089)	−0.38 to −0.03	.0235
Montelukast, 10 mg qd	25	0.94 (0.089)	−0.14 (0.088)	−0.31 to 0.03	.1131
FP, 200 μg qd	29	0.70 (0.083)	−0.38 (0.083)	−0.54 to −0.21	<.0001
Sneezing					
Placebo	123	0.93 (0.045)			
BI 671800, 50 mg bid	22	0.79 (0.092)	−0.13 (0.091)	−0.31 to 0.05	.1509
BI 671800, 200 mg bid	27	0.74 (0.084)	−0.19 (0.083)	−0.35 to −0.03	.0232
BI 671800, 400 mg bid	25	0.81 (0.087)	−0.12 (0.087)	−0.29 to 0.05	.1730
Montelukast, 10 mg qd	25	0.80 (0.087)	−0.13 (0.086)	−0.30 to 0.04	.1420
FP, 200 μg qd	29	0.55 (0.081)	−0.37 (0.081)	−0.53 to −0.21	<.0001

bid, Twice daily; *qd*, once daily.
*Mixed-effects model.

TABLE E2. Comparison* of total nasal secretion weights over 6 hours

			Comparison vs placebo		
Treatment	**No.**	**Adjusted mean (SE)**	**Adjusted mean of difference (SE)**	**95% CI**	***P* value**
Placebo	121	29.24 (1.706)			
BI 671800, 50 mg bid	22	24.13 (3.129)	−5.10 (2.936)	−10.91 to 0.70	.0842
BI 671800, 200 mg bid	26	25.07 (2.907)	−4.17 (2.694)	−9.49 to 1.16	.1243
BI 671800, 400 mg bid	24	26.83 (3.030)	−2.41 (2.849)	−8.04 to 3.23	.3998
Montelukast, 10 mg qd	24	25.13 (3.049)	−4.10 (2.886)	−9.81 to 1.60	.1571
FP, 200 μg qd	28	10.36 (2.845)	−18.9 (2.658)	−24.13 to −13.62	<.0001

bid, Twice daily; *qd*, once daily.
*Mixed-effects model.

TABLE E3. Summary of common AEs occurring at greater than 2% in any treatment group (treated patients)

Event	Placebo (n = 143), no. (%)	BI 671800, 50 mg bid (n = 26), no. (%)	BI 671800, 200 mg bid (n = 28), no. (%)	BI 671800, 400 mg bid (n = 28), no. (%)	Montelukast, 10 mg qd, (n = 29), no. (%)	FP, 200 μg qd (n = 30), no. (%)
Patients with any AE	54 (37.8)	9 (34.6)	10 (35.7)	9 (32.1)	14 (48.3)	13 (43.3)
Patients with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with AEs leading to discontinuation	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)
Patients with drug-related AEs*	9 (6.3)	2 (7.7)	5 (17.9)	0 (0.0)	2 (6.9)	8 (26.7)
AE >2% in any treatment group (preferred term)						
Headache	18 (12.6)	0 (0.0)	4 (14.3)	3 (10.7)	7 (24.1)	7 (23.3)
Epistaxis	4 (2.8)	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	3 (10.0)
Nasopharyngitis	13 (9.1)	2 (7.7)	0 (0.0)	2 (7.1)	2 (6.9)	3 (10.0)
Lip swelling	0 (0.0)	0 (0.0)	2 (7.1)	1 (3.6)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	4 (2.8)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Vomiting	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)

bid, Twice daily; *qd*, once daily.
*In the opinion of the investigator.