

ORIGINAL ARTICLE

Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study

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Summary

Background Bilastine is a new non-sedative H₁ receptor antagonist, indicated for the treatment of allergic rhinitis (AR) (seasonal and perennial).

Objective To assess and compare the efficacy and safety of bilastine 20 mg vs. cetirizine 10 mg and placebo in relieving the symptoms of seasonal allergic rhinitis (SAR).

Methods Overall, 683 SAR patients, aged 12–70 years, were randomized to a double-blind treatment with bilastine 20 mg, cetirizine 10 mg or placebo, once daily for 14 days, in 61 centres across Europe. Patients recorded reflective (over the past 12 h) and instantaneous nasal (obstruction, rhinorrhoea, itching and sneezing) and non-nasal (ocular tearing, redness and itching) symptom scores (NSS and NNSS, respectively) twice daily, according to a pre-determined severity scale to provide reflective and instantaneous total symptom scores (TSS). The primary efficacy measure was the area under curve (AUC) of reflective TSS over 14 days of treatment (TSS-AUC_{0–14 days}). Secondary efficacy measures included mean change from baseline in TSS, NSS and NNSS; discomfort caused by AR; and investigator's clinical global impression of the treatment. Safety was assessed according to adverse events (AEs), laboratory tests and electrocardiograms.

Results The mean TSS-AUC_{0–14 days} (score × day) was reduced in bilastine- and cetirizine-treated groups to a similar and significantly greater extent, compared with placebo (76.5, 72.3 and 100.6, respectively; $P < 0.001$). Similarly, bilastine and cetirizine were comparable and significantly superior to placebo for all secondary outcomes. While all treatments were well tolerated and the AE profiles of bilastine and placebo were similar, significantly fewer patients in the bilastine-treated group experienced somnolence (1.8%; $P < 0.001$) and fatigue (0.4%; $P = 0.02$) than patients in the cetirizine-treated group (7.5% and 4.8%, respectively).

Conclusions Bilastine 20 mg once daily was significantly superior to placebo and comparable to cetirizine 10 mg in relieving symptoms of SAR, although it demonstrated a significantly better AE profile than cetirizine.

Keywords bilastine, cetirizine, H₁ antihistamine, nasal symptoms score, non-nasal symptoms score, seasonal allergic rhinitis, total symptom score

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Introduction

Allergic rhinitis (AR) is a common chronic and socio-economically burdensome disease that affects 10–40% of the population worldwide [1–3], with over 50% of adolescents reporting symptoms of AR in some countries [1]. It has been estimated that AR occurs in over 500 million

people worldwide [1], with studies from the United States indicating around 20–40 million people, including up to 40% children, suffering from AR annually [4]. Despite the large body of evidence, which indicates AR to adversely impact the patients' quality of life (QoL) (including fatigue, headache, diminished cognition, sleep disruption and other systemic symptoms) [3, 5–7] and to possibly lead to

development of comorbid conditions such as acute/chronic sinusitis, otitis media, sleep apnoea, respiratory infections and aggravation of or predisposal to asthma, when not treated adequately [8–11], AR still remains undermanaged and poorly controlled [4, 12].

The demonstration that histamine plays a major role in the manifestation of particularly the symptoms of rhinorrhoea, sneezing and nasal itching [13] has led to the development and recommended use of oral H₁ receptor antagonists (H₁ antihistamines) as first-line pharmacotherapy for AR [1, 4, 14]. The commercially available H₁ antihistamines have generally been shown to be highly effective against nasal itching, sneezing and runny nose [1, 15] and to a lesser extent nasal congestion [16]. Although the majority of the second-generation H₁ antihistamines are generally non-sedating and have a more favourable therapeutic index (benefit-to-risk ratio) than the sedating first-generation H₁ antihistamines [17], some of the second-generation antihistamines have nevertheless been associated with adverse effects such as cardiotoxicity, weight gain and drug–drug interactions [17].

Bilastine is a new H₁ antihistamine, which has been shown to be safe and highly efficacious at a therapeutic dose of 20 mg, in a clinical development programme involving over 600 healthy volunteers and over 4000 AR (seasonal and perennial; SAR and PAR, respectively) or chronic idiopathic urticaria patients worldwide [18]. Moreover, studies in healthy volunteers have demonstrated that doses of bilastine 20–100 mg are devoid of sedative and cardiotoxic effects [19, 20] and do not potentiate significant adverse sedative effects on interaction with alcohol [19]. Similarly, pharmacologic studies have demonstrated bilastine to be a highly selective and potent compound with a rapid onset of action (30–60 min) and a long duration (24 h) of effect [21], anti-inflammatory properties [22, 23], low hepatic metabolism [18] and excretion mostly via the faeces and to a lower extent via the urine [18]. More recently, a randomized, double-blind, placebo-controlled study has demonstrated that a therapeutic dose of bilastine 20 mg once daily was equally well tolerated and significantly more effective than placebo in reducing the symptoms of AR in patients with SAR [24].

The primary objective of this study was to assess and compare the efficacy and safety of once-daily bilastine 20 mg vs. once-daily cetirizine 10 mg or placebo in the treatment of SAR, according to the recommendations of the FDA (Food and Drug Administration) [25] and the new European Guideline (CHMP/EWP/2455/22) [26].

Methods

Patients

Male and female subjects, aged 12–70 years, were enrolled in the study if they had a documented clinical history of

SAR due to a region-specific spring season pollen allergen(s) (including Bermuda grass, rye, sweet grass, blue grass, perennial rye, Timothy grass, birch, Cupressus, oak, olive, Platanus acerifolia, beech, alder, hazelnut, white ash and Salix) for at least 2 years. All subjects were additionally required to exhibit a positive skin prick test (SPT) or a positive specific IgE test (RAST) for at least one seasonal allergen in the past year, and a moderate to moderately severe baseline 12-hour reflective nasal symptom score (NSS; for rhinorrhoea, congestion, itching and sneezing) of ≥ 36 out of a possible total score of 72, assessed on the last 3 days during the screening period, and an instantaneous NSS of ≥ 6 out of a possible total score of 12, assessed on the day of randomization. Similarly, subjects with a positive prick test to perennial allergens (including house dust mite, mould, cat, dog, guinea-pig and rabbit), but without a clinical history of PAR, were also enrolled.

Patients were excluded from the study if they had nasal polyps and a deviation of the nasal septum or significant nasal tract structural malformation or nasal intervention in the previous 6 months; acute or chronic sinusitis; or a history of hypersensitivity to antihistamines, imidazoles or lactose. Patients taking corticosteroids during the last 4 weeks; loratadine or desloratadine during the last 10 days; anti-leukotrienes or ketotifen during the last 2 weeks; macrolides, imidazole, anticholinergics or decongestants during the last 3 days; or immunotherapy within 2 years (unless taking a stable maintenance dose for > 1 month) before entry into the study were also excluded. Similarly, patients with a history of alcohol and drug abuse and those with any clinically significant condition (cardiovascular, neurological, hepatic, renal or malignant diseases) were excluded, as were pregnant or nursing women and patients who had participated in another trial within the previous 3 months.

Study design

This was a randomized, double-blind, parallel-group multicentre study, conducted in 61 centres across seven countries in Europe, between April 2005 and August 2005. The study involved a run-in period lasting from 3 to 28 days, followed by three clinic visits. During the run-in, patients were assessed for eligibility for inclusion in the study based on medical history, physical examination, laboratory tests and severity of their symptoms. Following confirmation of the presence and maintenance, for at least 3 days, of high or very high levels of pollen [as defined according to AAI (NAB) references], eligible patients with reflective NSS scores of ≥ 36 and instantaneous NSS scores of ≥ 6 underwent a physical examination and were randomized to 14 days' treatment with either bilastine 20 mg, cetirizine 10 mg or matched placebo in a 1 : 1 : 1 ratio. Randomization to treatment was performed according to a computer-generated randomization code provided by the study sponsor (FAES

FARMA, S.A., Spain). The patients were supplied with the study medication disguised as identical over-encapsulated tablets in individually coded aluminium blister packs to ensure blinding and instructed to take one tablet an hour before or 2 h after breakfast to avoid any interactions with food, which may affect drug absorption. Diary cards were also provided for the patients to record the severity of their symptoms twice daily (in the morning before taking the study medication and in the evening at bedtime), use of concomitant medication(s), discomfort due to rhinitis and experience of any adverse events (AEs). The patients returned to the clinic after 7 and 14 days, during which they underwent assessments as at the randomization visit, and were additionally assessed for compliance with treatment. At day 14, clinical laboratory tests were performed and the investigators evaluated their global clinical impression of treatment.

This study was conducted in compliance with the Declaration of Helsinki and in accordance with the Local Ethical Committees. The protocol and informed consent form were approved by each Local Ethical Committee, and all participants or legal guardians gave their written informed consent to participate in the study.

Assessment of efficacy

Primary and secondary efficacy measures. The primary efficacy parameter was the area under the curve (AUC) of the reflective total symptoms score (TSS) from day 0 (D0) to day 14 (D14) ($\text{TSS-AUC}_{0-14 \text{ days}}$; expressed as $\text{score} \times \text{day}$ units), based on the patient's evaluation of symptom severity over the past 12 h. The TSS was calculated daily as the sum of four nasal (rhinorrhoea, congestion, itching and sneezing) and three non-nasal (ocular symptoms: tearing, redness and itching) symptom scores (NSS and NNSS, respectively). Secondary efficacy end-points included the AUC of the instantaneous (now) symptom severity score for D0 to D14; AUC of the change from baseline in TSS, NSS and NNSS; mean change from baseline in individual symptoms, TSS, NSS and NNSS; overall assessment of discomfort caused by AR; and investigator's clinical global impression (CGI) of the severity of patients' symptoms.

Evaluation of symptom severity. Patients evaluated the severity of individual nasal and non-nasal symptoms in the morning and in the evening by rating each symptom on a scale of 0–3, where 0 = no symptoms present; 1 = mild symptoms occasionally present but not troublesome; 2 = moderate symptoms frequently present and annoying; and 3 = severe symptoms continuously present and interfering with activities or sleep.

Evaluation of discomfort due to rhinitis. Overall discomfort was assessed at D0, D7 and D14 on a visual analogue scale ranging from 0 to 100 mm, with 0 mm = no discomfort and 100 mm = extreme discomfort.

Investigator's global clinical impression. The investigators' CGI of each patient was recorded at the end of treatment using an efficacy index, based on the degree of therapeutic effect and the intensity of adverse effects ranging from a scale of 1 to 16, with 1 representing vast improvement and no adverse effects, and 16 representing unchanged or worse therapeutic effect and adverse effects outweighing the therapeutic effect.

Evaluation of compliance with treatment. Compliance with treatment was assessed by drug accountability and by asking the patient. Compliance was calculated using the formula $[(\text{tablets dispensed} - \text{tablets returned}) / (\text{date final visit} - \text{date initial visit} + 1)]$.

Assessment of safety

Safety was assessed by means of routine laboratory tests (haematology and biochemistry) and 12-lead electrocardiograms (ECGs) performed at D0 and D14, and the incidence, severity and type of AEs reported by the patients over the course of treatment. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by treatment, system organ class and preferred term.

Statistical analyses

Sample size. Based on a 95% confidence level (α error of 0.05) and a power of 80% (β error of 0.20), the minimum sample size necessary to detect a mean AUC difference of 15% (with a maximum deviation of 50%) between the treatment groups was calculated to be 528 patients (176 per arm). Assuming that about 20% of the subjects might withdraw from the study, the final sample size was calculated to be 660 (220 per arm).

Data management. All data were entered separately in a study-specific database by two independent individuals and analysed by a qualified biostatistician (MDS Pharma Services, Spain), to ensure the accurate handling and statistical analysis of the data as necessary. All efficacy analyses were performed for the intent-to-treat (ITT) patient population, which included all randomized patients who had received at least one treatment dose and who had a baseline assessment and at least one assessment of the primary variable after the baseline visit. Moreover, an analysis of the primary variable was also based on the per-protocol (PP) population, which included all randomized patients who completed the study without major protocol deviations or violations regarding the primary efficacy variable or patients' selection. Safety analyses were performed on the safety population, which included all the randomized patients who had received at least one dose of the study treatment. For missing values, a Last Observation Carried Forward approach was used.

Qualitative variables were summarized with the frequency distribution and quantitative variables with mean, standard deviation (SD) or standard error (SE) and 95% confidence interval (95% CI). An ANOVA model was applied to test the significance of data for the TSS-AUC_{0–14 days}, with 14 days' treatment as the dependent variable and the treatment group as the main factor. An additional approach on the ITT population was used on the absolute individual change vs. baseline values of the TSS, and pair-wise comparisons among the treatment groups for all quantitative efficacy variables were performed using the Tukey–Kramer method. Similar analyses were carried out for the secondary efficacy variables as for the primary efficacy variable and χ^2 or Fisher's exact tests were performed for categorical data. The investigators' CGI, a non-parametric variable, was summarized as the percentage of patients in each category and the Kruskal–Wallis test was used to assess the significance of any treatment differences.

Results

A total of 844 patients were screened, of whom 683 (80.9%) were randomized (Fig. 1). Overall, 681 patients received the study drug and were included in both the ITT and the safety populations. However, three patients failed to score/record data for their symptoms and were there-

fore not included in any analyses for the ITT population. The PP population comprised 551 patients (80.7% of the randomized sample), as 127 patients were additionally excluded due to a variety of reasons. Of these, 62.9% of the patients were excluded for violation of inclusion/exclusion criteria after randomization, 17.4% for deviations in scheduled visits, 11.4% for taking medications not permitted over the course of the trial, 3.0% for non-compliance with treatment, 1.5% for withdrawal of consent and 3.8% for other reasons.

Overall, 16 patients (eight in the placebo group, five in the bilastine group and three in the cetirizine group) were excluded for taking non-permitted medications, of which 90% were other medications normally used for management of rhinitis, including antihistamines, cromoglicate eye drops and intranasal corticosteroids.

The demographic and clinical characteristics of each study group at baseline are presented in Table 1. All groups were similar and showed no significant differences with respect to either demographic or clinical characteristics of the patients before beginning treatment.

Efficacy outcomes

The total mean compliance with treatment was found to be 99.9% for bilastine 20 mg, 100.0% for cetirizine 10 mg

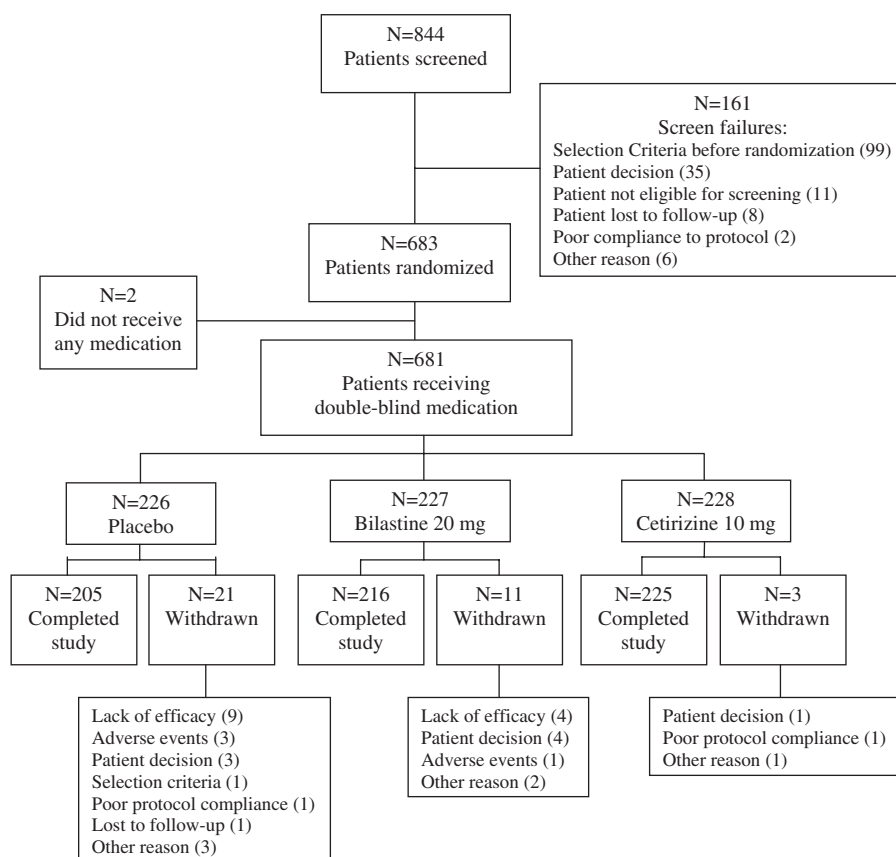


Fig. 1. Patient disposition over the course of study.

Table 1. Patient demographic and clinical characteristics at baseline

Variable	Bilastine 20 mg (N = 226)	Cetirizine 10 mg (N = 227)	Placebo (N = 225)	P value (ANOVA)
Sex (males) [N (%)]	108 (47.8%)	107 (47.1%)	108 (48.0%)	*NS
Age (years) [mean (SD)]	31.16 (11.3)	31.8 (11.1)	30.2 (10.4)	NS
Race (Caucasian) [N (%)]	226 (100.0%)	226 (99.6%)	222 (98.7%)	*NS
BMI (kg/m ²) [mean (SD)]	24.0 (4.5)	24.0 (10.1)	23.6 (4.1)	NS
Heart rate (bpm) [mean (SD)]	72.9 (8.1)	72.5 (8.4)	72.2 (8.4)	NS
Years since diagnosis [mean (SD)]	9.4 (7.4)	9.7 (8.1)	10.4 (8.3)	NS
Subjects with > 3 prick test positive allergens [N (%)]	32 (14.2%)	28 (12.3%)	35 (15.6%)	*NS
TSS [mean (SD)]				
Reflective	11.0 (3.3)	11.1 (3.6)	10.9 (3.8)	NS
Instantaneous	11.2 (3.4)	11.2 (3.7)	11.3 (3.8)	NS
NSS [mean (SD)]				
Reflective	7.5 (1.7)	7.5 (1.9)	7.5 (2.0)	NS
Instantaneous	7.5 (1.9)	7.5 (1.9)	7.6 (2.0)	NS
NNSS [mean (SD)]				
Reflective	3.5 (2.1)	3.6 (2.2)	3.4 (2.3)	NS
Instantaneous	3.7 (2.2)	3.7 (2.2)	3.6 (2.3)	NS
†Overall discomfort score [mean (SD)]	70.8 (12.6)	71.5 (13.0)	71.3 (13.1)	NS

BMI, body mass index; NSS, nasal symptoms score; NNSS, non-nasal symptoms score; TSS, total symptoms score.

*P value based on χ^2 test.

†Overall discomfort associated with rhinitis assessed by visual analogue scale of 0–100 mm.

Table 2. Effect of treatment on TSS in the ITT and PP populations

Variable	Bilastine 20 mg (N = 226)	Cetirizine 10 mg (N = 227)	Placebo (N = 225)	P value (ANOVA)
<i>TSS-AUC_{0–14 days} for ITT population</i>				
Mean (SD)	76.5 (47.9)*	72.3 (46.6)*	100.6 (51.7)	<0.001
95% CI	70.2; 82.8	66.2; 78.4	93.9; 107.5	
<i>Change from baseline in TSS-AUC_{0–14 days} for ITT population</i>				
Mean (SD)	–65.2 (49.0)*	–71.5 (52.3)*	–40.7 (51.6)	<0.001
95% CI	–71.6; –58.7	–78.4; –64.7	–47.4; –33.9	
<i>Change from baseline in TSS for ITT population</i>				
Mean (SD)	–4.76 (3.83)*	–5.32 (4.21)*	–2.88 (4.07)	<0.001
95% CI	–5.26; –4.26	–5.87; –4.77	–3.41; –2.34	
<i>TSS-AUC_{0–14 days} for PP population</i>				
Mean (SD)	80.0 (46.7)*	76.2 (45.9)*	104.1 (47.7)	<0.001
95% CI	73.2; 86.7	69.6; 82.8	97.0; 111.3	

AUC, area under curve; CI, confidence interval; ITT, intent-to-treat; PP, per protocol; SD, standard deviation; TSS, total symptom score.

*P = 0.001 for Bilastine/Cetirizine vs. Placebo.

and 99.8% for placebo, with no statistically significant differences among the treatment groups.

Assessment of the effect of treatment on the AUC for TSS over the 14-day treatment period (TSS-AUC_{0–14 days}), the primary efficacy measure for the ITT-population, demonstrated that both bilastine 20 mg and cetirizine 10 mg significantly reduced the TSS-AUC_{0–14 days}, compared with placebo ($P < 0.001$) (Table 2). A comparison of the TSS-AUC_{0–14 days} for bilastine and cetirizine demonstrated that these were not significantly different ($P = 0.63$). Analysis of data from the PP population demonstrated results similar to those for the ITT population,

with bilastine and cetirizine being significantly more effective than placebo in attenuating the TSS-AUC_{0–14 days} (Table 2).

Assessment of the change from baseline in the TSS-AUC_{0–14 days} also demonstrated significantly greater decreases for bilastine- and cetirizine-treated groups than for the placebo-treated group ($P < 0.001$) (Table 2). The change from baseline in TSS-AUC_{0–14 days} was not significantly different between bilastine 20 mg- and cetirizine 10 mg-treated groups.

Similarly, assessment of the change from baseline in TSS at the end of treatment demonstrated bilastine and

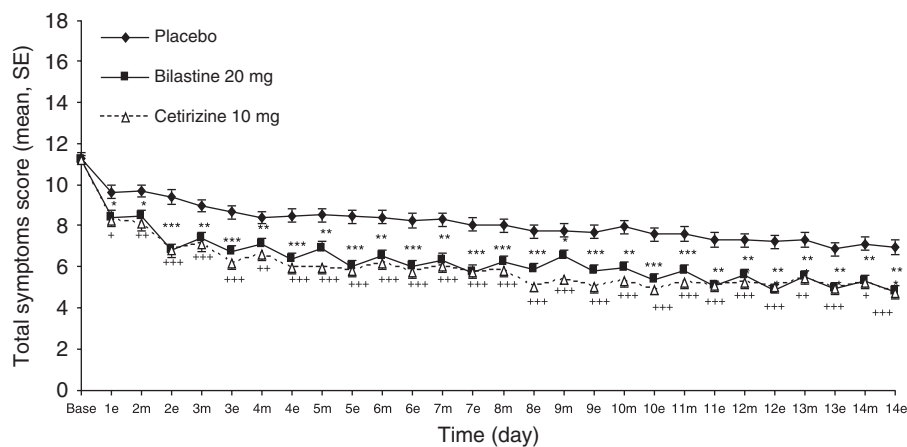


Fig. 2. Evolution of morning (m) and evening (e) instantaneous total symptoms score, according to the patients' diary in the intent-to-treat population; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (bilastine vs. placebo); + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ (cetirizine vs. placebo).

Table 3. Effect of treatment on change from baseline in individual symptoms scores after 7 and 14 days, in the intent-to-treat population

	Mean (SD)			
	Bilastine 20 mg (<i>N</i> = 226)	Cetirizine 10 mg (<i>N</i> = 227)	Placebo (<i>N</i> = 225)	<i>P</i> value (ANOVA)
% Change in sneezing				
Day 7	−52.4 (50.3)*	−55.0 (49.0)*	−33.6 (59.1)	<0.001
Day 14	−64.3 (44.4)*	−63.7 (43.8)*	−41.0 (62.4)	<0.001
% Change in runny nose				
Day 7	−44.5 (42.0)*	−46.9 (47.8)*	−26.1 (49.3)	<0.001
Day 14	−57.4 (41.6)*	−58.4 (43.7)*	−38.3 (53.2)	<0.001
% Change in nasal itching				
Day 7	−51.0 (46.3)*	−54.8 (47.0)*	−31.2 (49.6)	<0.001
Day 14	−59.5 (41.7)*	−61.9 (43.7)*	−42.3 (53.5)	<0.001
% Change in nasal congestion				
Day 7	−43.8 (42.1)*	−40.2 (48.5)*	−25.9 (48.6)	<0.001
Day 14	−48.5 (39.0)*	−50.6 (43.9)*	−35.3 (53.6)	<0.001
% Change in ocular itching				
Day 7	−49.6 (51.2)*	−48.5 (57.5)*	−24.4 (63.1)	<0.001
Day 14	−64.4 (46.6)*	−59.1 (54.1)*	−41.2 (57.8)	<0.001
% Change in tearing				
Day 7	−57.2 (53.6)*	−60.3 (53.4)*	−34.7 (62.9)	<0.001
Day 14	−70.9 (46.6)*	−67.0 (50.6)*	−51.0 (54.3)	0.002
% Change in ocular redness				
Day 7	−60.0 (51.4)*	−53.4 (53.4)*	−33.6 (61.1)	<0.001
Day 14	−65.2 (50.8)	−65.3 (50.9)	−56.3 (51.2)	NS

* $P < 0.001$ for Bilastine/Cetirizine vs. Placebo.

cetirizine to decrease the TSS to a significantly greater degree than placebo (Table 2). Overall, the baseline TSS was decreased by 44.7% (= 1.7-fold; $P < 0.001$ vs. placebo) in bilastine-treated patients and 49.1% (= 1.85-fold; $P < 0.001$ vs. placebo) in cetirizine-treated patients, compared with a decrease of 26.6% in placebo-treated patients.

Figure 2 shows the evolution of the instantaneous TSS over a period of 14 days' treatment. Both bilastine and cetirizine progressively improved the symptoms of AR to a significantly greater extent than placebo over the entire treatment period ($P < 0.001$; ANOVA). Furthermore, differences between bilastine/cetirizine vs. placebo were

significant from day 1 onward over the entire treatment period (Fig. 2). There was no significant difference between the active treatments.

Assessment of patient-rated mean (SD) morning and evening instantaneous TSS indicated that these were not significantly different for bilastine [morning = 76.55 (43.44) and evening = 75.09 (48.39), mean difference = −1.46 (95% CI: −3.70; 0.79; $P = 0.20$)], nor cetirizine [morning = 70.89 (44.32) and evening = 72.02 (48.07), mean difference = 1.12 (95% CI: −0.93; 3.17; $P = 0.28$)]. In contrast, the patient-rated mean (SD) morning and evening instantaneous TSS were significantly different in placebo-treated patients

Table 4. Effect of treatment on nasal and non-nasal symptom scores, overall rhinitis discomfort score and the investigators' clinical global impression at treatment day 14 in the intent-to-treat population

	Bilastine 20 mg (N = 226) Mean (SD)	Cetirizine 10 mg (N = 227) Mean (SD)	Placebo (N = 225) Mean (SD)	P value (ANOVA)
<i>NSS-AUC_{0-14 days}</i>				
Patient-rated reflective	54.71 (30.3) [†]	50.12 (28.4) [†]	69.65 (31.4)	< 0.001
Patient-rated instantaneous	55.73 (29.4) [†]	51.01 (29.1) [†]	71.00 (31.9)	< 0.001
<i>Change from baseline in NSS</i>				
Mean (SD)	-3.11 (2.29) [†]	-3.56 (2.48) [†]	-1.97 (2.48)	< 0.001
95% CI	-3.41; -2.81	-3.89; -3.24	-2.29; -1.64	
<i>NNSS-AUC_{0-14 days}</i>				
Patient-rated reflective	21.79 (21.8) [†]	22.19 (22.5) [†]	31.02 (24.7)	< 0.001
Patient-rated instantaneous	23.46 (21.7) [†]	23.73 (22.8) [†]	32.89 (25.9)	< 0.001
<i>Change from baseline in NNSS</i>				
Mean (SD)	-1.65 (1.89) [†]	-1.76 (2.03) [†]	-0.91 (1.90)	< 0.001
95% CI	-1.89; -1.40	-2.02; -1.49	-1.16; -0.66	
<i>Overall discomfort associated with rhinitis</i>				
(% change)	-54.6 (33.8) [†]	-54.6 (34.7) [†]	-35.5 (39.1)	< 0.001
Investigators' CGI	5.0 (3.9) [‡]	4.7 (3.6) [‡]	7.2 (4.5)	< 0.001*

AUC, area under curve; CGI, clinical global impression; NSS, nasal symptom score; NNSS, non-nasal symptom score; SD, standard deviation.

*P value based on Kruskal-Wallis test.

[†]P < 0.001 for Bilastine/Cetirizine vs. Placebo.

[‡]P < 0.05 for Bilastine/Cetirizine vs. Placebo.

[morning = 96.54 (49.53) and evening = 102.81 (54.90); mean difference = 6.27 (95% CI: 4.08; 8.46; $P < 0.001$)).

Analysis of the effect of treatment on individual symptoms demonstrated that scores for sneezing, rhinorrhoea, nasal itching, nasal congestion, ocular itching, tearing and ocular redness were all decreased to a significantly greater degree from baseline in bilastine- and cetirizine-treated patients than in placebo-treated patients ($P < 0.001$ for all symptoms) after treatment for 7 days, and apart from ocular redness, after treatment for 14 days. (Table 3).

The effects of treatment on total NSS and NNSS, discomfort due to AR and the investigators' CGI are shown in Table 4. Global differences among the three groups were observed in favour of the active treatments in the AUC for reflective and instantaneous NSS and NNSS at day 14 ($P < 0.001$), although there were no significant differences between the reflective and instantaneous scores. Assessment of the change from baseline also demonstrated NSS and NNSS to be decreased to a significantly greater degree after treatment with bilastine (42.4% and 49.8%, respectively) and cetirizine (48.2% and 51.0%, respectively), than after treatment with placebo (26.9% and 27.6%, respectively; $P < 0.001$ for all comparisons vs. bilastine/cetirizine) (Table 4).

Similarly, statistically significant differences were found among the three groups for discomfort and the investigators' CGI ratings at D14 ($P < 0.001$) (Table 4). Moreover, pair-wise comparisons indicated that treatment with both bilastine and cetirizine was significantly more effective than treatment with placebo in improving both nasal and non-nasal symptoms, discomfort due to AR and

Table 5. Incidence of treatment-emergent AEs reported over 2 weeks

	Bilastine 20 mg (N = 227) N (%)	Cetirizine 10 mg (N = 228) N (%)	Placebo (N = 226) N (%)	P value (χ^2 test)
<i>Patients reporting ≥ 1 AE</i>	56 (24.7%)*	82 (36.0%)	67 (29.6%)	0.03
<i>Incidence $\geq 2\%$ in any treatment group</i>				
Headache	24 (10.6%)	19 (8.3%)	31 (13.7%)	NS
Somnolence	4 (1.8%)	17 (7.5%) [†]	5 (2.2%)**	< 0.001
Fatigue	1 (0.4%)	11 (4.8%) [†]	7 (3.1%)*	0.02
Dyspnoea	2 (0.9%)	5 (2.2)	2 (0.9)	NS
<i>Drug-related AEs</i>	33 (14.5%)	56 (24.6%) [†]	44 (19.5%)	0.03
<i>Withdrawals due to AEs</i>	1 (< 1%)	0 (0%)	3 (1.3%)	NS
<i>Serious AEs</i>	0	0	0	NS

AE, adverse event.

* $P < 0.05$ for Bilastine vs. placebo

** $P \leq 0.01$ for Cetirizine vs. Placebo.

[†] $P \leq 0.01$ for Bilastine vs. Cetirizine.

the investigators' CGI. However, the efficacy of bilastine was not significantly different from the efficacy of cetirizine, with respect to any of these outcomes.

Safety assessment

Overall, 24–36.0% patients in any treatment group experienced at least one AE; however, the incidence of AEs was significantly lower in the bilastine 20 mg-treated group than in the cetirizine 10 mg-treated group (Table 5). The most common AEs (incidence $\geq 2\%$) were

headache, somnolence, fatigue and dyspnoea, with significantly fewer patients in the bilastine-treated group experiencing somnolence (1.8%; $P < 0.001$) and fatigue (0.4%; $P = 0.02$), than patients in the cetirizine-treated group (7.5% and 4.8%, respectively) (Table 5). Similarly, the incidence of total drug-related AEs was significantly lower in the bilastine-treated group (14.5%; $P = 0.03$) than in the cetirizine-treated group (24.5%) (Table 5). Neither serious AEs nor death were reported during the study, and there were no clinically significant changes from baseline values in any laboratory tests (haematological or liver/kidney function tests), ECGs, heart rate or systolic and diastolic blood pressure in any treatment group.

Discussion

This study compared the efficacy and tolerability of bilastine 20 mg once daily for 2 weeks with that of cetirizine 10 mg or placebo once daily in symptomatic SAR patients, at the height of the pollen season. Overall, bilastine 20 mg had an efficacy profile that was similar to that of cetirizine 10 mg, and significantly better than that of placebo, as indicated by significantly greater changes in NSS and NNSS over the course of the study and by the end of treatment, as well as significantly greater improvements in discomfort associated with AR symptoms and the investigators' CGI. Comparison of the safety profiles of the study drugs, however, indicated bilastine 20 mg to be equally safe and well tolerated as placebo, and significantly better tolerated than cetirizine, as indicated by significantly lower incidences of total AEs, somnolence, fatigue and drug-related AEs, compared with cetirizine.

The current recommendation for clinical trials assessing the efficacy and safety of H_1 -antihistamines is to investigate AR patients identified as suffering from either 'persistent' or 'intermittent' symptoms classified according to the ARIA classification [1]. In the present study, patients defined according to the traditional classification of SAR were investigated because the study was conceived and implemented before rigorous validation, standardization and general adoption of the ARIA classification among clinicians and physicians treating patients with AR. However, evidence from epidemiological studies suggests that about 40–45% of patients previously classified as SAR or PAR actually have persistent or intermittent symptoms, respectively [27], and the demonstration that patients in the present study were sensitized to a variety of perennial allergens suggests that bilastine is also likely to be effective in patients classified according to the ARIA classification.

The findings of the present study are, nevertheless, in accordance with the findings of another study, which compared the efficacy of bilastine 20 mg vs. the efficacy of desloratadine 5 mg or placebo once daily for 14 days in symptomatic SAR patients [24]. Using a similar study

design, Bachert *et al.* [24] demonstrated that bilastine 20 mg reduced the AUC of TSS to a significantly greater degree from baseline compared with placebo, but not compared with desloratadine 5 mg, over a period of 14 days. Additionally, bilastine and desloratadine were equally and significantly more effective than placebo in improving the NSS, NNSS and rhinitis-associated discomfort scores. Although the effect of bilastine was not investigated on the QoL of patients in the present study, Bachert *et al.* [24] demonstrated that bilastine and desloratadine also significantly improved the QoL of patients with SAR assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), compared with placebo. The authors demonstrated that the total RQLQ score and all individual RQLQ domains scores, except for the nasal symptoms, sleep and emotional domains, were reduced to significantly greater levels from baseline in the bilastine-treated group than in the placebo-treated group, with no significant differences between the active treatment groups [24].

However, assessment of safety also demonstrated bilastine to be equally safe and as well tolerated as placebo, with headache, somnolence and fatigue being the three most common AEs reported by $\geq 2\%$ of patients in any treatment group [24]. Furthermore, there were no serious AEs or adverse vital signs, ECGs or laboratory results in these patient groups.

Similarly, the findings of this study are also in accordance with several phase II studies, which have demonstrated a clinical dose of bilastine 20 mg to provide significant relief of both seasonal and perennial symptoms of AR [18], compared with placebo. The finding for the good safety profile of bilastine demonstrated in the present study is also in accordance with the findings from other phase I and phase II studies, which have not demonstrated any evidence of either drug accumulation at doses of bilastine 5–100 mg or evidence of modified psychomotor performance, sedation or cardiotoxicity at doses of bilastine 20–80 mg [18–20]. Indeed, a thorough examination of the effects of bilastine on the QT/QTc interval, as recommended by the ICH E14 guideline, has recently suggested that bilastine does not lead to any significant vascular repolarization at up to five times the recommended therapeutic dose of bilastine 20 mg [20].

Our findings for the efficacy of cetirizine are also in accordance with the findings of several well-controlled studies documenting the efficacy and tolerability of this agent in patients with SAR. In one large, randomized, double-blind, placebo-controlled study, Murray *et al.* [28] evaluated the efficacy and safety of 2-weeks' treatment with cetirizine 10 mg OD, and its impact on the QoL and self-reported work/school-related productivity and activity impairment (WPAI) in 865 adult patients with SAR. The authors demonstrated that cetirizine resulted in significantly greater mean reduction (28.9%) in the total

symptom severity complex (TSSC) score compared with placebo (12.7%; $P < 0.001$). Cetirizine also led to significantly greater improvements in the overall RQLQ and individual domain scores compared with placebo by the end of treatment, and decreased WPAI to a significantly greater degree from baseline than in placebo-treated patients ($P < 0.001$). Similarly, Noonan et al. [29] investigated the efficacy, safety and QoL of 2-weeks' treatment with cetirizine 10 mg OD in another cohort of 403 adult patients with SAR. These authors demonstrated that cetirizine-treated patients experienced significantly greater symptom relief and improvements in overall health-related quality of life (HRQL) and in each of the seven domains of the RQLQ than the placebo-treated patients, with significant correlations between symptomatic relief and overall HRQL ($r = 0.49\text{--}0.68$, $P < 0.01$). Furthermore, more patients were satisfied with the treatment in the cetirizine group (65%) than in the placebo group (44%) [29]. The incidence of treatment-related side-effects was also similar in the cetirizine- and placebo-treated groups, with somnolence and fatigue being the most frequently reported adverse effects [28, 29].

In summary, the results of this study show that bilastine 20 mg once daily for 2 weeks was significantly more effective than placebo and similar in efficacy to cetirizine 10 mg once daily in the symptomatic treatment of SAR. The finding that bilastine significantly attenuates nasal congestion and ocular symptoms of AR suggests that this agent may have significant benefits, not commonly observed with some of the other antihistamines used in the management of symptoms of AR. Although cetirizine was also found to be efficacious in this regard, the demonstration that significantly fewer patients treated with bilastine experienced lower incidences of overall and drug-related AEs, particularly somnolence and fatigue, compared with cetirizine but not placebo is of particular consequence. This suggests that bilastine may have a more favourable safety profile, and therefore possibly a better therapeutic index, compared with cetirizine.

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