

## Original article

## Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients

**Background:** Bilastine is a novel, nonsedating H<sub>1</sub>-antihistamine developed for symptomatic treatment of Allergic Rhinitis and Chronic Idiopathic Urticaria. The objective of this study was to compare the efficacy and safety of bilastine 20 mg vs placebo and desloratadine 5 mg in subjects with seasonal allergic rhinitis (SAR).

**Methods:** This randomized, double blind, placebo-controlled, parallel-group multicentre study evaluated the effect of 2 weeks' treatment with bilastine 20 mg, desloratadine 5 mg or matched placebo once daily, in 12–70 years old symptomatic SAR patients. All subjects assessed the severity of nasal (obstruction, rhinorrhoea, itching, and sneezing) and nonnasal (ocular itching, tearing, ocular redness, itching of ears and/or palate) symptoms on a predetermined scale to provide a total symptom score (TSS), composed of nasal and nonnasal symptom scores (NSS and NNSS, respectively). The primary efficacy measure was the area under the curve (AUC) for the TSS over the entire treatment period.

**Results:** Bilastine 20 mg significantly reduced the AUC of TSS to a greater degree from baseline compared to placebo (98.4 with bilastine vs 118.4 with placebo;  $P < 0.001$ ), but not compared to desloratadine 5 mg (100.5). Bilastine 20 mg was not different from desloratadine 5 mg but significantly more effective than placebo in improving the NSS, NNSS, and rhinitis-associated discomfort scores ( $P < 0.05$ ), and rhinoconjunctivitis quality of life questionnaire total ( $P < 0.005$ ) and four out of seven individual domain ( $P < 0.05$ ) scores. The incidence of treatment emergent adverse events was similar for bilastine (20.6%), desloratadine (19.8%), and placebo (18.8%).

**Conclusion:** Bilastine 20 mg once daily was efficacious, safe and not different from desloratadine 5 mg once daily in the treatment of SAR symptoms.

**C. Bachert<sup>1</sup>, P. Kuna<sup>2</sup>, F. Sanquer<sup>3</sup>, P. Ivan<sup>4</sup>, V. Dimitrov<sup>5</sup>, M. M. Gorina<sup>6</sup>, P. van de Heyning<sup>7</sup>, A. Loureiro<sup>8</sup>, The Bilastine International Working Group**

<sup>1</sup>Department of Oto-Rhino-Laryngology, Ghent University Hospital, Ghent, Belgium; <sup>2</sup>Klinika Pulmonologii i Alergologii, Lodz, Poland; <sup>3</sup>Cabinet d'Allergologie et Immunologie Clinique, Quimper, France; <sup>4</sup>Emergency Clinical Hospital 'Sf. Spiridon', Braila, Romania; <sup>5</sup>Alexandrovska MHAT Hospital, Sofia, Bulgaria; <sup>6</sup>Hospital de la Cruz Roja, Barcelona, Spain; <sup>7</sup>University Hospital of Antwerpen-Edegem, Antwerpen-Edegem, Belgium; <sup>8</sup>Hospitais Universidade Coimbra, Coimbra, Portugal

**Key words:** bilastine; desloratadine; H<sub>1</sub>-antihistamine; quality of life; seasonal allergic rhinitis; total symptom score.

Prof. Claus Bachert  
Department of Oto-Rhino-Laryngology  
Ghent University Hospital  
De Pintelaan 185  
9000 Ghent  
Belgium

Accepted for publication 1 May 2008

Allergic rhinitis (AR) is a highly prevalent and disabling inflammatory disease affecting about 10–40% of the global population (1). Estimates suggest that AR affects about 23% to 30% of the population in Europe (2, 3), whereas data from the US indicate that about 20–40 million people (10–30% of adults and up to 40% of children) are affected each year (4). However, it is likely that the prevalence of AR is actually higher because the disease is often underdiagnosed or unconfirmed by allergy testing in about 45–50% of AR patients in the general population (2, 5). Although AR is not a life threatening condition, it is a major cause of suffering, leading to severe impairments in the quality of life (QOL) of affected individuals (6) and substantially impacting the health and economic burden of individual and society alike (6, 7).

AR is characterized by bothersome symptoms including rhinorrhoea, nasal congestion/obstruction, sneezing and nasal itch; often accompanied by allergic

conjunctivitis, itching and ocular redness, lacrimation, and itching of the ears and/or palate; which lead to loss of sleep and fatigue, headache, irritability and diminished attention/cognition (8, 9). Furthermore, AR is often associated with comorbidities, and when not treated adequately may lead to the development or worsening of comorbidities; including acute/chronic sinusitis, recurrent nasal polyposis, otitis media, sleep apnoea, respiratory infections and aggravation of or predisposal to asthma (6, 10–12). In view of the prominent role of histamine in the pathophysiology of AR (13), several national and international treatment guidelines have recommended that oral H<sub>1</sub>-antihistamines should be regarded as the mainstay of pharmacotherapy and employed as first-line treatment for the symptoms of AR (1, 4, 14–16).

Bilastine is a novel histamine H<sub>1</sub> receptor antagonist developed for the treatment of symptoms of seasonal and perennial allergic rhinitis (SAR and PAR, respectively) and

chronic idiopathic urticaria (CIU). Pharmacologic studies have demonstrated that bilastine is highly selective for H<sub>1</sub>-receptors (17) and possesses both antihistaminic and anti-inflammatory properties *in vitro* and *in vivo* (17, 18). Indeed, comparison with cetirizine and fexofenadine has demonstrated that bilastine possessed antihistaminic and antiallergic properties, which were of comparable potency to cetirizine and superior to fexofenadine (18). Studies in healthy volunteers further indicated that bilastine had a rapid onset (30–60 min) and long duration (24 h) of action (19), did not undergo any hepatic metabolism (20), and was excreted mainly in the faeces (21). Similarly, other studies demonstrated that a therapeutic dose of bilastine 20 mg did not potentiate any CNS or cardiotoxic effects of alcohol (22). The safety and efficacy of bilastine has also been established in several Phase I studies involving over 600 healthy volunteers and several Phase II and Phase III studies involving over 4000 SAR, PAR or CIU patients worldwide (21). The aim of the present study was to compare the efficacy and safety of a single daily dose of 20 mg bilastine in patients with SAR vs placebo and desloratadine 5 mg, a treatment option commonly employed for this condition.

## Methods

### Patients

Male and female patients, aged 12–70 years, with a documented history of SAR for at least 2 years and a positive skin prick test (wheal  $\geq 3$  mm larger than the diluent control) to at least one seasonal allergen specific to their geographical location [including a variety of common grass pollen (Bermuda, Rye, Sweet grass, Blue grass, Perennial rye, and Timothy grass) and tree pollen (birch, Cupressus, oak, olive, Platanus acerifolia, beech, alder, hazelnut, white ash and Salix)] were enrolled in the study. Patients with a positive prick test to perennial allergens (including house dust mite, mould, cat, dog, Guinea pig, and rabbit), but without any symptoms of PAR were also enrolled. All patients were additionally required to have a minimum reflective nasal symptom (NSS) score of  $\geq 36$  as sum of the six assessments in the last 3 days of the screening period. Patients were essentially medication free at enrolment; with patients with hypersensitivity to H<sub>1</sub> antihistamines or benzimidazoles and those taking specific H<sub>1</sub> or H<sub>2</sub> antihistamines within 3 days to 6 weeks; systemic or intranasal corticosteroids within 4 weeks; and intranasal and systemic decongestants within 3 days of randomization to treatment were excluded from the study. Similarly, patients who had received immunotherapy (unless on a stable dose within the prior month, and none within 24 h before any study visit) or any CNS acting agents (including antidepressants, sedatives, anxiolytics, hypnotics, opioids or neuroleptics) at any time were also excluded. Patients who had undergone nasal surgery in the previous 6 months and patients with nasal polyps, significant deviation of the nasal septum, acute or chronic sinusitis, any clinically significant condition (cardiovascular, neurological, hepatic, renal or malignant diseases), a history of alcohol abuse, and pregnant or lactating women were also excluded.

### Study design

This was a randomized, double blind, placebo-controlled, parallel-group multicentre study, conducted in eight countries across Europe

(Belgium, Bulgaria, France, Germany, Poland, Portugal, Romania and Spain), between April 2003 and August 2003. The study involved four visits, during which patients provided informed written consent and medical history; demographic characteristics and vital signs were assessed at the first visit (screening; week –1). Patients were provided with diary cards to record and rate the severity of nasal and nonnasal symptoms twice daily over the past 12 h, according to predefined scales. Patients returned to the clinic 1 week later, and those with NSS  $\geq 36$  in the last 3 days of the run-in period were randomized to receive either placebo, bilastine 20 mg, or desloratadine 5 mg, according to a computer generated randomization list provided by the study sponsor (FAES FARMA S.A., Spain). The study treatments were provided as encapsulated preparations of similar appearance, for blinding and oral administration once a day in the morning under fasting conditions (1–2 h before breakfast) for 14 days. All eligible patients completed the rhinoconjunctivitis quality of life questionnaire (RQLQ) and were provided with new diary cards for recording and rating the severity of both nasal and nonnasal symptoms as before. The patients returned to the clinic on two subsequent visits after 1 and 2 weeks of treatment, during which they were assessed as at the randomization visit, and compliance with study medication and usage of any concomitant medication was noted. The incidence and type of any adverse events (AEs) experienced over the course of the study was also noted at each visit.

The study was approved by the Ethic Committees of all centres involved in the study and performed in accordance with the ICH Good Clinical Practice regulations and the principles of the Declaration of Helsinki.

### Evaluation of efficacy

Efficacy was evaluated according to several outcome measures. The main efficacy outcome was defined by the area under the curve (AUC) for the total symptom score (TSS), which was composed of nasal and nonnasal symptom scores (NSS and NNSS, respectively) recorded by the patient from baseline (day 0) to the end of treatment (day 14). Secondary outcome measures included assessment of NSS and NNSS, QOL assessed by the RQLQ, overall assessment of discomfort due to rhinitis, and the investigators' global clinical impression (CGI).

*Assessment of symptom scores.* Patients evaluated the severity of both nasal (congestion, rhinorrhoea, sneezing, and itch) and nonnasal (ocular itching, burning, redness, sensation of foreign body in eye, tearing, and itching of ears and/or palate) symptoms over the previous 12 h using a 4-point scale of 0–3; with 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 work or sleep.

*Quality of life.* The QOL was assessed at randomization visit and at the end of treatment using the validated self-administered RQLQ (23, 24). The RQLQ evaluates the effect of symptoms and treatment on the patient's physical, social and emotional well-being, based on seven domains (activity limitations, emotional function, eye symptoms, nonhay fever symptoms, nasal symptoms, practical problems and sleep problems). The patients score each item on a seven-point scale ranging from 0 (i.e. not troubled/none of the time) to 6 (i.e. extremely troubled/all the time), and a high score is taken as an indication of poor QOL.

*Discomfort due to rhinitis.* Discomfort due to rhinitis was rated at randomization visit and after treatment for 1 week and 2 weeks of

treatment on a 0–100 mm visual analogue scale (VAS), ranging from 0 = no discomfort to 100 = extreme discomfort.

*Investigator's global clinical impression.* Investigators provided a global clinical impression (CGI) for each patient at the end of the study, according to a clinical index, ranging from a scale of 1 (marked improvement without AEs) to 16 (no change or worse therapeutic effect with AEs exceeding therapeutic effect), based on the degree of therapeutic effect and the intensity of adverse effects.

*Compliance with treatment.* Patients' compliance with treatment was calculated as the mean of tablets counted on treatment days 7 and 14, using the following formula:

$$[(\text{tablets dispensed} - \text{tablets returned}) / (\text{date of final visit} - \text{date of initial visit}) + 1].$$

### Evaluation of safety

Safety and tolerability of the study treatments were evaluated based on the AE profile (incidence and type of AE) reported for each treatment by the patients. Vital signs, a 12 lead ECG and results of standard blood tests performed at entry and at the end of the study were additionally considered for evaluation of drug safety and tolerability.

### Statistical analyses

The study sample was calculated based on a 15% difference in the main outcome between groups, considering a maximal deviation (50%) of the study sample, a 80% of power and a 5% two-sided level of significance; 660 patients (220 per arm) were included after estimating 20% withdrawals from the study. The ITT population included all randomized patients receiving at least one dose of treatment and from whom a baseline assessment and at least one assessment after the baseline visit were available.

The homogeneity of data was confirmed by an ANCOVA model generated with the total symptoms score of rhinitis as the covariable. An ANOVA model or a nonparametric approach was used to compare the AUC of symptoms score between groups. Rhinoconjunctivitis quality of life questionnaire scores between baseline and the end of treatment were analysed using an ANOVA model or a Kruskal–Wallis test as appropriate. Comparisons between treatment groups were estimated with a 95% confidence interval. Proportions of treatment emergent adverse events (TEAE) were analysed by means of a chi-square test.

## Results

### Patient disposition and baseline characteristics

Figure 1 shows the disposition of patients. Overall, 849 patients were screened and 721 patients (84.8%) randomized to receive bilastine 20 mg (233 patients), desloratadine 5 mg (242 patients) or placebo (245 patients). Of the 128 patients excluded, 104 patients (81.3%) failed to meet the inclusion criteria, nine patients (7%) withdrew consent to participate in the study, and the remaining 15 patients (11.7%) were excluded for various reasons.

Following randomization 41 patients (22 (9%) in the placebo group, 10 (4.2%) in the bilastine 20 mg group, and 9 (3.7%) in the desloratadine 5 mg group) did not complete

the study, primarily due to the lack of efficacy of treatment in each of the three treatment groups. One patient in the bilastine group, two in the desloratadine group and five in the placebo group discontinued due to an AE.

Demographic and baseline clinical characteristics of the patients randomized to treatment indicated that the three treatment groups were similar (Table 1).

### Efficacy measures

Patients' compliance with study treatment was similar in all treatment groups (100%, 99.4%, and 99.6% for placebo, bilastine and desloratadine, respectively).

*Effect of treatment on symptom scores.* Bilastine 20 mg progressively improved the symptoms of allergic rhinitis from baseline levels over a period of 2 weeks (Fig. 2). The AUC of TSS, the primary outcome measure, was decreased to a significantly greater extent in the bilastine 20 mg-treated group compared with placebo-treated group ( $P < 0.001$ ) (Table 2). Assessment of change from baseline in TSS at days 7 and 14 also indicated significantly greater improvements in the symptoms of rhinitis after 7 and 14 days of treatment with bilastine 20 mg compared with placebo ( $P < 0.001$  and  $< 0.002$ , respectively) (Table 2). Desloratadine 5 mg-induced decreases in AUC of TSS and change from baseline in TSS at days 7 and 14 were also significantly greater compared with placebo ( $P < 0.001$  to  $< 0.002$ ), but these were not significantly different compared with bilastine 20 mg (Table 2).

NSS and NNSS also improved progressively over the treatment period in all treatment groups. Assessment of the significance of differences between the treatment groups demonstrated bilastine 20 mg to improve both NSS and NNSS to significantly greater extent than placebo, as indicated by greater decreases in both the AUC of NSS and NNSS and change from baseline in NSS and NNSS at days 7 and 14 (Table 2). Desloratadine 5 mg also improved NSS and NNSS to a significantly greater degree than placebo, but not compared with bilastine 20 mg (Table 2).

*Effect of treatment on QOL.* Bilastine 20 mg improved the QOL of patients, as measured by the RQLQ. The total RQLQ score was significantly reduced from baseline by a value of 1.6 (1.2; 1.8–1.4) in the bilastine 20 mg-treated group compared with a value of 1.3 (1.3; 1.5–1.1) (SD; 95% IC) in the placebo-treated group ( $P < 0.005$ ) (Table 3). Comparison of the effect of bilastine 20 mg with desloratadine 5 mg demonstrated both agents were equally effective in improving the QOL of patients in this study cohort [mean (SD); 1.6 (1.2)] (Table 3). Bilastine 20 mg was also found to be significantly more effective than placebo in improving the scores for all individual RQLQ domains, except for the nasal symptoms, sleep and emotional domains. Similarly, desloratadine 5 mg

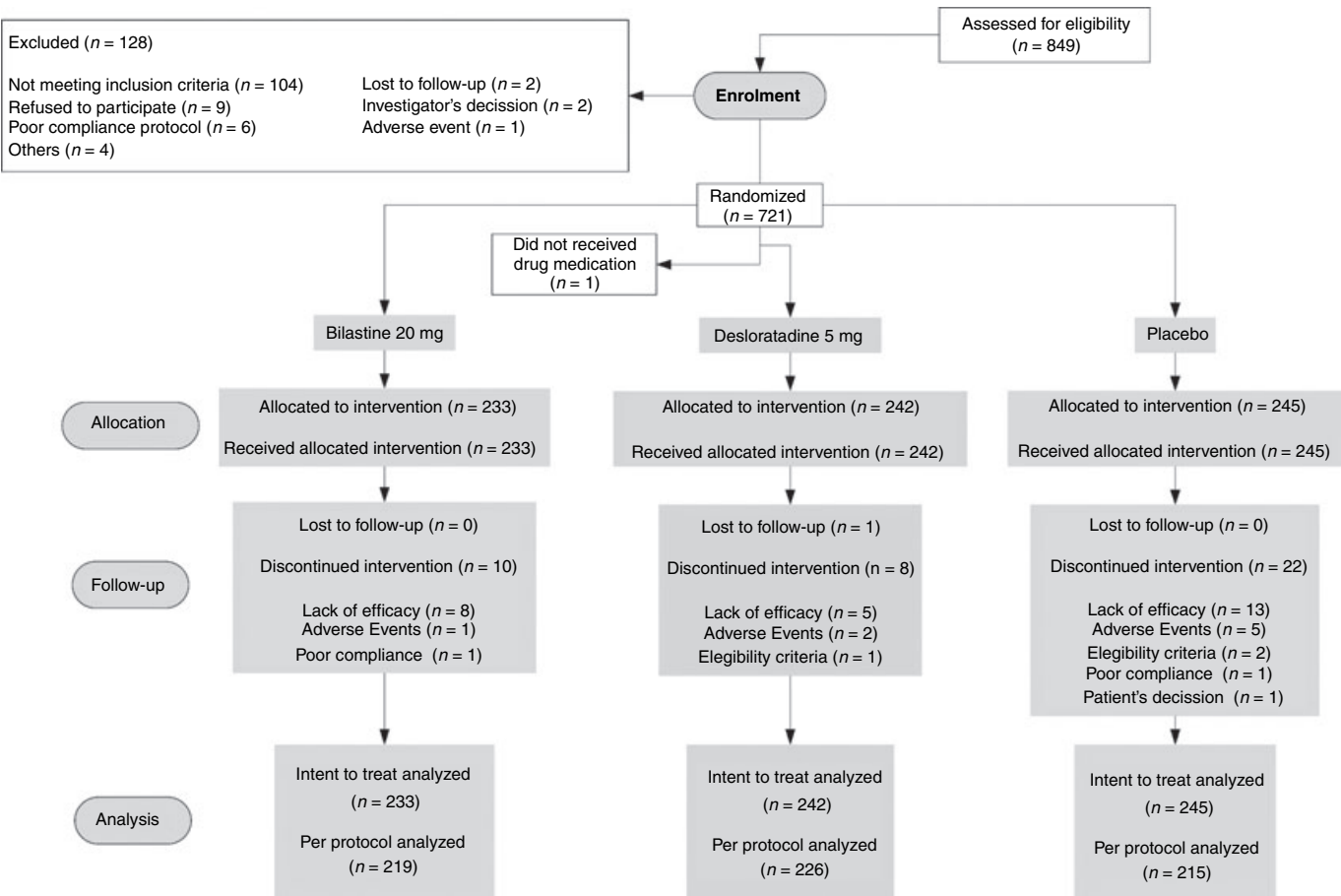


Figure 1. Patient disposition.

Table 1. Patient demographic and clinical characteristics at baseline

| Variable                                             | Placebo (n = 245) | Bilastine 20 mg (n = 233) | Desloratadine, 5 mg (n = 242) | P-value (test)         |
|------------------------------------------------------|-------------------|---------------------------|-------------------------------|------------------------|
| Gender (males)                                       | 118 (48.2%)       | 121 (51.9%)               | 126 (52.1%)                   | 0.621 (chi-square)     |
| Ethnic (Caucasian)                                   | 241 (98.4%)       | 231 (99.1%)               | 240 (99.2%)                   | 1.000 (chi-square)     |
| Age (years)                                          | 30.6 (10.6)       | 30.6 (11.0)               | 29.8 (10.6)                   | 0.661 (ANOVA)          |
| BMI (kg/m <sup>2</sup> )                             | 23.6 (4.3)        | 23.6 (3.9)                | 23.6 (4.3)                    | 0.975 (ANOVA)          |
| Years since diagnosis, median (inter-quartile range) | 7.0 (4–13)        | 7.0 (4–14)                | 7.0 (4–13)                    | 0.459 (Kruskal–Wallis) |
| Allergens at prick test (% with > 3)                 | 64 (26.4%)        | 63 (27.0%)                | 63 (26.1%)                    | 0.975 (chi-square)     |
| TSS at day 0                                         | 12.8 (4.1)        | 12.9 (3.9)                | 13.0 (4.0)                    | 0.862 (ANOVA)          |
| NSS at day 0                                         | 7.4 (2.2)         | 7.5 (2.1)                 | 7.7 (2.1)                     | 0.284 (ANOVA)          |
| NNSS at day 0                                        | 5.4 (2.5)         | 5.4 (2.3)                 | 5.3 (2.4)                     | 0.865 (ANOVA)          |
| *VAS score <sub>[0 to 100]</sub>                     | 69.2 (15.6)       | 69.4 (15.1)               | 69.8 (16.9)                   | 0.913 (ANOVA)          |

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

\*Visual analogue scale for discomfort associated with rhinitis [results expressed as mean (SE)].

did not show any significant improvements in scores for nasal symptoms and emotional domains, compared with placebo.

*Effect of treatment on discomfort associated with rhinitis.* Bilastine 20 mg led to significantly greater decreases from baseline in mean rhinitis discomfort scores at day 7 ( $-38.8\% \pm 33.5\%$ ) and day 14

( $-49.2\% \pm 36.7\%$ ), compared with placebo ( $-28.0\% \pm 34.6\%$  ( $P < 0.001$ ) and  $-37.6\% \pm 40.6\%$  ( $P < 0.001$ ), at days 7 and 14, respectively). Similarly, desloratadine 5 mg led to significantly greater decreases from baseline in mean rhinitis discomfort scores of  $-39.1\% \pm 34.9\%$  ( $P < 0.001$ ) and  $-48.7\% \pm 37.5\%$  ( $P < 0.001$ ) at days 7 and 14, respectively, compared with placebo, but not compared to bilastine 20 mg.

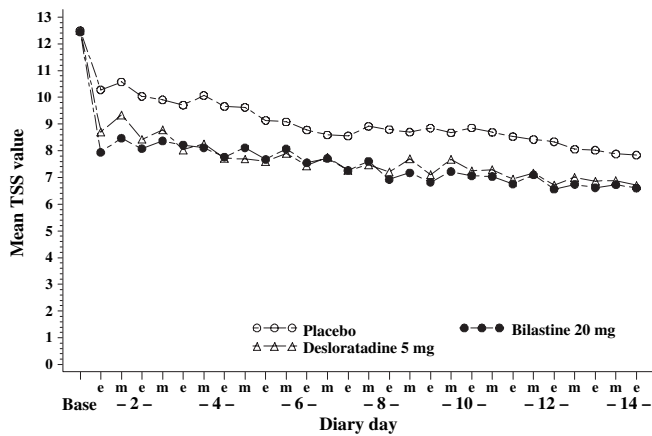


Figure 2. Effect of treatment on mean TSS, recorded twice daily as reflective 12-h scores in the evening (e) and morning (m).

**Investigators' CGI.** The investigators' mean  $\pm$  SD scores for CGI were found to be  $6.8 \pm 4.6$ ,  $5.8 \pm 4.3$  and  $5.5 \pm 3.8$  for placebo-, bilastine 20 mg- and desloratadine 5 mg-treated groups, respectively; with a lower score indicating a better outcome.

#### Safety evaluation

A total of 207 patients reported at least one AE. Overall, the safety profile of bilastine 20 mg and desloratadine 5 mg were comparable to placebo; with headache somnolence and fatigue being the three most common AEs reported by  $\geq 2\%$  of patients in any treatment group (Table 4). No serious AEs were reported and there were no relevant differences among the treatment groups for vital signs, ECG or laboratory results.

#### Discussion

The aim of this study was to determine the efficacy and tolerability of bilastine 20 mg once daily for 2 weeks, compared to placebo and desloratadine 5 mg, in the treatment of symptomatic SAR. Our study demonstrated that bilastine 20 mg significantly improved both nasal and nonnasal symptoms of SAR, compared with placebo. However, the  $>35\%$  improvement from baseline in nasal symptoms noted after 14 days with placebo is surprising, considering that baseline demographic and clinical characteristics of this group were similar in all respects

Table 2. Effect of treatment on rhinitis symptom scores

| Parameter                        | Placebo (n = 245)          | Bilastine 20 mg (n = 233) | Desloratadine 5 mg (n = 242) | P-value (ANOVA) |
|----------------------------------|----------------------------|---------------------------|------------------------------|-----------------|
|                                  | Mean (SE) [95% CI]         | Mean (SE) [95% CI]        | Mean (SE) [95% CI]           |                 |
| Total symptoms score (TSS)       |                            |                           |                              |                 |
| AUC <sub>TSS</sub>               | 118.4 (62.7) [110.5–126.3] | 98.4 (58.1) [90.9–105.9]  | 100.5 (54.6) [93.6–107.4]    | < 0.001         |
| % Change from baseline at day 7  | –28.3 (47.4)               | –41.7 (36.4)              | –42.9 (35.1)                 | < 0.001         |
| % Change from baseline at day 14 | –37.4 (47.0)               | –48.9 (38.6)              | –49.5 (38.8)                 | 0.002           |
| Nasal symptoms score (NSS)       |                            |                           |                              |                 |
| AUC <sub>NSS</sub>               | 71.6 (32.9) [67.4–75.7]    | 62.6 (32.8) [58.3–66.8]   | 63.8 (29.7) [60.1–67.6]      | 0.004           |
| % Change from baseline at day 7  | –26.4 (50.2)               | –41.1 (38.6)              | –45.0 (35.5)                 | < 0.001         |
| % Change from baseline at day 14 | –38.4 (46.6)               | –48.3 (38.6)              | –51.9 (39.0)                 | < 0.001         |
| Non-nasal symptoms score (NNSS)  |                            |                           |                              |                 |
| AUC <sub>NNSS</sub>              | 47.2 (35.6)                | 36.5 (29.8)               | 37.2 (30.8)                  | < 0.001         |
| % Change from baseline at day 7  | –24.2 (78.4)               | –39.6 (47.9)              | –36.8 (54.5)                 | 0.019           |
| % Change from baseline at day 14 | –29.6 (69.2)               | –47.1 (56.7)              | –43.7 (49.0)                 | 0.003           |

AUC, area under the curve.

Table 3. Effect of treatment on rhinoconjunctivitis quality of life questionnaire scores

| RQLQ domains           | Placebo (n = 245) | Bilastine 20 mg (n = 233) | Desloratadine 5 mg (n = 242) | P-value (Kruskal–Wallis test) |
|------------------------|-------------------|---------------------------|------------------------------|-------------------------------|
| Activities             | –1.5 (1.6)        | –2.0 (1.6)                | –1.9 (1.6)                   | 0.008                         |
| Sleep                  | –1.0 (1.6)        | –1.1 (1.5)                | –1.3 (1.6)                   | 0.020                         |
| Non-hay fever symptoms | –1.0 (1.4)        | –1.3 (1.3)                | –1.3 (1.3)                   | 0.020                         |
| Practical problems     | –1.7 (1.9)        | –2.2 (1.8)                | –2.1 (1.8)                   | 0.023                         |
| Nasal symptoms         | –1.6 (1.7)        | –1.9 (1.6)                | –1.9 (1.6)                   | 0.095                         |
| Eye symptoms           | –1.2 (1.6)        | –1.6 (1.6)                | –1.6 (1.4)                   | 0.011                         |
| Emotional              | –1.1 (1.4)        | –1.4 (1.5)                | –1.2 (1.3)                   | 0.075                         |
| Total RQLQ             | –1.3 (1.3)        | –1.6 (1.2)                | –1.6 (1.2)                   | 0.005                         |

Results are expressed as mean (SD) change from baseline at treatment day 14.

Table 4. Adverse events (AEs) reported over 2 weeks of treatment

|                                             | Placebo<br>(n = 245) | Bilastine<br>20 mg (n = 233) | Desloratadine<br>5 mg (n = 242) |
|---------------------------------------------|----------------------|------------------------------|---------------------------------|
| Patients reporting $\geq 1$ AE              | 62 (25.3%)           | 66 (28.3%)                   | 79 (32.6%)                      |
| Incidence $\geq 2\%$ in any treatment group |                      |                              |                                 |
| Headache                                    | 25 (10.2%)           | 26 (12.0%)                   | 27 (11.2%)                      |
| Somnolence                                  | 8 (2.4%)             | 9 (3.9%)                     | 9 (3.7%)                        |
| Fatigue                                     | 6 (2.4%)             | 6 (2.6%)                     | 3 (1.2%)                        |
| Drug-related AEs                            | 48 (19%)             | 48 (21%)                     | 48 (20%)                        |
| Withdrawals due to AEs                      | 5 (2%)               | 1 (<1%)                      | 2 (<1%)                         |
| Serious AEs                                 | 0                    | 0                            | 0                               |

to those of the active groups. Although the underlying cause of this relatively large 'placebo-effect' is presently not clear, such high treatment effects for placebo have also been demonstrated by other authors investigating the effects of other antihistamines in SAR patients (25). Furthermore, bilastine 20 mg significantly decreased the discomfort associated with rhinitis from day 7 onwards, and improved the patients' quality of life and the investigators' CGI scores by the end of the 2 week treatment period, compared with placebo. Comparison with desloratadine 5 mg indicated that bilastine 20 mg was not different to desloratadine 5 mg in this cohort of patients. Indeed, both active drugs were well tolerated and demonstrated a safety profile similar to placebo. Collectively the results confirm that a therapeutic dose of bilastine 20 mg is efficacious and safe for the treatment of clinic symptoms of allergic rhinitis.

This is first study to document the efficacy of bilastine in allergic rhinitis patients. Despite the preference of the ARIA classification for rhinitis (1) for the identification and investigation of allergic rhinitis patients involved in modern-day clinical trials, patients defined according to the traditional classification of SAR were investigated in the present study, because the study was conceived and conducted at a time when the ARIA classification had not been fully validated. The findings of this study are nevertheless in accordance with the pharmacokinetic and pharmacodynamic studies of bilastine, which have demonstrated bilastine to have high selectivity and affinity for the  $H_1$  human receptor (17), and the ability to antagonize histamine-induced skin reactions with comparable or greater potency than cetirizine and fexofenadine, respectively (18). Phase I studies with single and multiple doses of bilastine have further demonstrated a consistent pharmacokinetic profile with a fast absorption ( $t_{\max}$  = 1–1.5 h), linearity (5–220 mg), and no evidence of drug accumulation (5–100 mg) (26), and no evidence of modified psychomotor performance (22) nor cardiotoxicity at doses of bilastine 20, 40, and 80 mg (27). Indeed, the low cardiotoxic potential for bilastine was further indicated by preclinical data which demonstrated bilastine-mediated blockage of HERG current ( $I_{K_r}$ ) to occur at concentrations 6 times greater than those observed for

desloratadine and cetirizine (6.5 vs 1.4  $\mu\text{M}$  and 1.1  $\mu\text{M}$   $\text{IC}_{50}$ , respectively) (21).

The effect of desloratadine observed in the present study is also in accordance with the findings of other studies in SAR patients (28, 29). The close similarity in the efficacy of bilastine and desloratadine seen in our study, however, is surprising because differences have been noted in the pharmacokinetic and pharmacodynamic profiles of the two drugs. In particular, bilastine is absorbed much faster ( $t_{\max}$  of 1–1.5 h) and has a faster onset of action (mean 0.5 h) (19) than desloratadine, for which  $t_{\max}$  > 3 h and onset of action 0.5–3 h has been documented (30–32). Moreover, the consistent elimination half-life ( $t_{1/2\text{elim}}$ ) of 10–12 h documented for bilastine, compared with a slightly less consistent  $t_{1/2\text{elim}}$  of 13–30 h documented for desloratadine (30, 33) suggests that bilastine may have an overall more favorable pharmacological profile than desloratadine, although this needs to be confirmed in studies directly comparing the pharmacological properties of these two agents. More recently, using a similar study design to the present study, Kuna et al. (34) have compared the efficacy of bilastine with cetirizine. The authors demonstrated that bilastine 20 mg and cetirizine 10 mg once daily were equally and statistically superior to placebo in improving reflective and instantaneous AUC TSS, and all composite and individual nasal/non nasal scores from baseline. However, patients treated with bilastine demonstrated a significantly lower incidence of treatment-related AEs, particularly somnolence and fatigue, than patients treated with cetirizine. This suggests that bilastine may have a more favourable safety profile compared with cetirizine, although this would also need to be confirmed in studies specifically designed and powered to directly compare the safety profiles of these two agents.

Bilastine has also been shown to possess anti-inflammatory activity similar to cetirizine and fexofenadine (18), suggesting that the efficacy of bilastine in improving both nasal and nonnasal symptoms may be mediated via mechanisms other than and in addition to  $H_1$  histamine receptor antagonism. This also needs to be confirmed in studies specifically designed and powered to test this hypothesis.

In summary, bilastine 20 mg once daily for 2 weeks effectively relieved the symptoms of SAR, including nasal and nonnasal symptoms, and improved the quality of life of patients. While the overall efficacy results demonstrate bilastine 20 mg to be superior to placebo, the safety results demonstrate that bilastine 20 mg is also safe and with a safety profile that is not different to placebo in patients with allergic rhinitis. From a clinical view point, available evidence from studies directly comparing the efficacy and safety of bilastine, desloratadine and cetirizine suggest that although all three agents appear to be equally efficacious in the treatment of symptoms of allergic rhinitis, bilastine may have a slightly more favourable safety profile.

## Acknowledgments

The authors thank the investigators at all study centres as shown: **Belgium:** E.P. Hamans (Antwerpen-Edegem); P. van Cauwenberge, T. de Belder, L. Sys (Gent); A.A. Schmelzer, J. van Vliet, P. Van-nieuwenhuysse (Antwerpen); G. D'Hont (Brugge); M.B.M. Jorissen, G. Gevers (Leuven). **Bulgaria:** M.A. Mandazhieva-Pepelanova, S.P. Slavov, N. Georgieva (Sofia); K.P. Kissiova, C.H. Odzhakova, M.T. Peneva (Varna); T. Karchev, O. Mojanov, T. Ivanov (Sofia); R.Y. Benchev, M.N. Alexieva, Z.Z. Zhelyazkova (Sofia). **France:** L. Fouquert (Grasse); F. Wessel, Y. Dubreil (Nantes); S. Huet (Bernay); D. Ortolan (Villejuif). **Germany:** K.F. Lukat, B. Lange (Düsseldorf); N.C. Stuhmann, E. Decot (Dreieich); N. Pasch, G. Mereurs (Aachen); K. Hörmann, A. Baisch (Mannheim); L. Klimek, I. Hansen, S. Gene, K. Malzahn, M. Spielhaupter (Wiesbaden). **Poland:** J. Kaczmarek, M.B. Marciniak (Lodz); Z. Nowacki, A. Otto-Markiewicz, J. Markiewicz (Krakow); V. Caban (Wadowice); W. Skucha, J. Janicka, M. Szadkowska-Bach, L. Cichon-Szyperko, E. Wawarczyk (Proszowice); B. Lukasiewicz-Swierczynska, M. Swierczynska (Bielsko-Biala); P. Nalepa, C. Straczek, K. Kommata (Krakow); A. Pajor, A. Kucia, W. Sibila (Gliwice); G. Pinis, A. Dyczek (Krakow); T. Adamek-Guzik, G. Mysik-Czerniawska, K. Prochowska, T. Guzik (Krakow); I. Markiewicz-Bendkowska (Bystra Slaska); J. Iwko, E.A. Juszczak (Gliwice); M. Nowakowski, E. Wieckowska, A. Madaj (Gliwice).

**Portugal:** N.B. Tavares, G.M.S.D. Loureiro (Coimbra); M.A.S. Morais, A.P.M. Gaspar, M.G. Pires, J. Fernandes, P. Leiria (Lisboa); M.G.H. Vaz, A. Coimbra, A. Moreira, F. Oliveira (Porto). **Romania:** I. Bradu, O. Popa-Velea (Bucaresti); R.S. Bumbacea, S. Samuila (Bucaresti); A. Iacomini (Bucaresti); C. Radu, R. Grigore (Bucaresti); V. Zainea, M. Negrila (Bucaresti). **Spain:** E. Pinto (L'Hospitalet de LL., Barcelona); A. Roger, T. Dordal, M. Viñas (Badalona, Barcelona); C. Vidal, V. Rodríguez, M. Armasen (Santiago de Compostela, Coruña); G. Gastaminza, M.T. Audicana, E. Fernández, D. Muñoz, N. Bernedo, M.A. Echenagusia (Vitoria); R. Aragón, M. Prados (Mérida, Badajoz); A. Basomba, R. Almero, A. Campos, A. Giner (Valencia); J. Sastre, M. Lluch, AP. Novalbos (Madrid); R. Pérez, P. Carretero, F. García, S. Juste (Burgos); M. Fernández-Rivas, M.D. Alonso, E. González, A. Rosado, C. Vila, M. Tejedor (Alcorcón, Madrid); E. Martí, L. Pau (Barcelona); I. Dávila, E. Laffond, E. Moreno (Salamanca); A. Cadahía, V. Cardona, M. Guillard (Barcelona); M.A. Gonzalo, R. Pérez (Badajoz); C. González, M.M. García, S. Varela (Ourense); J. Conde, A. Conde, M. Hernández (Sevilla); F. Guerra, J.L. Justicia, M.J. Barahona (Córdoba); C. Martínez-Cóccera, M.P. Agustín, I. Reig, L. Vázquez (Madrid). The authors also thank FAES FARMA, S.A., Spain, for financial support; MDS Pharma Services Inc. for technical assistance for development of study, data management and statistical analysis; and Cristina Vidal, MD for editorial assistance with preparation of the manuscript.

## References

- Bousquet J, Van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108**(Suppl. 5):S147–S334.
- Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004; **24**: 758–764.
- Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. *Allergy* 2006; **61**:693–698.
- Task Force on Allergic Disorders. The Allergy Report. American Academy of Allergy Asthma and Immunology; <http://www.aaaai.org/professionals.stm> (accessed January 2007).
- van Hoecke, Vastesaeger N, Dewulf L, Sys L, Van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy* 2006; **61**:705–711.
- Schoenwetter WF, Dupclay L, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality of life burden of allergic rhinitis. *Curr Med Res Opin* 2004; **20**:305–317.
- Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis. *Pharmacoeconomics* 2004; **22**:345–361.
- Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001; **108**(Suppl. 1):S2–S8.
- Weir E. The burden of rhinitis: nothing to sniff at. *CMAJ* 2003; **169**:694.
- Demoly P, Bencherioua AM, Crampette L, Dhivert-Donnadieu H, Godard P, Michel FB. From allergic rhinitis to sinus diseases (sinusitis/nasal polyps): epidemiologic and experimental links. *Rev Mal Respir* 2000; **17**:925–930.
- Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol* 2000; **105**:S605–S609.
- Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. *Ann Allergy Asthma Immunol* 1999; **82**:296–305.
- Bachert C. The role of histamine in allergic disease: re-appraisal of its inflammatory potential. *Allergy* 2002; **57**:287–296.
- Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005; **353**:1934–1944.
- Gelfand EW, Plaut M, Washington T. Current trends in allergic reactions: a multidisciplinary approach to patient management. *Interdisciplinary Med* 2003; **5**:1–12.
- van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR et al. Consensus statement on the treatment of allergic rhinitis. *Allergy* 2000; **55**:116–134.
- Corcóstegui R, Labeaga L, Innerarity A, Berisa A, Orjales A. Preclinical pharmacology of bilastine, a new selective histamine H<sub>1</sub> receptor antagonist: receptor selectivity and in vitro antihistaminic activity. *Drugs R D* 2005; **6**:371–384.
- Corcóstegui R, Labeaga L, Innerarity A, Berisa A, Orjales A. In vivo pharmacological characterisation of bilastine, a potent and selective histamine H<sub>1</sub> receptor antagonist. *Drugs R D* 2006; **7**:219–231.
- Sologuren A, Valiente R, Crean C, McLaverty A. Relationship of dose to inhibition of wheal and flare for 5 doses of bilastine and 10 mg cetirizine. *J Clin Pharmacol* 2007; **47**(9):1198 (abstract 69).
- Lucero ML, Orjales A, Morag N. In vitro hepatic metabolism of [14C] bilastine. *Drug Metabol Rev* 2007; **39**(Suppl. 1):114 (abstract 160).
- FAES FARMA S.A. Bilastine, Investigational Drug Brochure version 8.0, July 2007. FAES FARMA S.A. [www.faes.es](http://www.faes.es).
- García-Gea C, Clos S, Antinjoan RM, Gich I, Valiente R, Barbanj MJ. Crossover, randomised, double-blind, double-dummy, placebo and positive standard-controlled trial to assess the possible interaction on CNS effects between bilastine 20 mg and 80 mg) and alcohol (0.8 g/kg) after single simultaneous administration in healthy subjects. *Pharmacol Toxicol* 2006; **99** (Suppl. 1):30. (abstract).

23. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**: 77–83.
24. Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997;**9**:S742–S749.
25. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 2000;**30**:891–899.
26. Crean C, Roupe K, Sologuren A, Valiente R. The pharmacokinetics of bilastine after single and 14 days once daily administration. *Basin Clin Pharmacol Toxicol* 2007;**101**(Suppl. 1): 148.
27. Sologuren A, Valiente R, Allison M, Tyl B. Lack of significant effect of bilastine on ventricular repolarization. A thorough QT/QTc study. *Allergy* 2008;**63**(Suppl. 88):85 (abstract 189).
28. Meltzer EO, Prenner BM, Nayak A. Efficacy and tolerability of once-daily 5mg desloratadine, an H1 antagonist, in patients with seasonal allergic rhinitis: assessment during the spring and fall allergy seasons. *Clin Drug Invest* 2001;**104**(Suppl. 1):383–384.
29. Bachert C, Virchow JC, Plencker A. Desloratadine in the treatment of seasonal allergic rhinitis: results of a large observational study. *Clin Drug Invest* 2002;**22**(Suppl. 2):43–52.
30. Lehman JM, Blaiss MS. Selecting the optimal oral antihistamine for patients with allergic rhinitis. *Drugs* 2006;**66**:2309–2319.
31. Golightly LK, Greos LS. Second-generation antihistamines. Actions and efficacy in the management of allergic disorders. *Drugs* 2006;**65**:341–384.
32. Molimard M, Diquet B, Benedetti MS. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. *Fundamental Clin Pharmacol* 2004;**18**:399–411.
33. Henz BM. The pharmacological profile of desloratadine: a review. *Allergy* 2001;**56**:7–13.
34. Kuna P, Nowacki Z, van Cauwenberghe P, Lukat K, Spicakova M, Agache I et al. A phase 3 study comparing the efficacy and safety of once daily bilastine with cetirizine and placebo for the treatment of seasonal allergic rhinitis. *Allergy* 2007;**62**(Suppl. 83):132 (abstract).