

## Asthma, rhinitis, other respiratory diseases

# Comparison of once-daily ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, and placebo in the treatment of seasonal allergic rhinitis

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**Background:** Ebastine and loratadine are 2 nonsedating second-generation H<sub>1</sub> antihistamines with once-daily dosing.

**Objective:** We compared the efficacy and safety of ebastine 20 mg and 10 mg, loratadine 10 mg, and placebo administered once daily for 4 weeks in controlling the symptoms of seasonal allergic rhinitis (SAR).

**Methods:** In a double-blind, placebo-controlled, randomized, parallel-group study, 565 patients with ragweed SAR, ages 12 to 70 years, received either ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, or placebo once daily for 4 weeks. Patients recorded morning and evening reflective scores (past 12 hours) as well as snapshot scores (at time of recording) for nasal discharge, congestion, sneezing, itching, and total eye symptoms. Total symptom score (TSS) is the sum of these 5 scores.

**Results:** Ebastine 20 mg produced significantly greater ( $P < .05$ ) reductions from baseline compared with loratadine 10 mg over the entire treatment period in the mean daily reflective (42.5% vs 36.3%) and mean morning snapshot (40.3% vs 31.3%) TSS. The overall improvement in daily reflective and morning snapshot TSS was comparable between ebastine 10 mg and loratadine 10 mg and significantly better than placebo ( $P < .05$ ). The total percent of patients with adverse events was similar among all 4 treatment groups ( $P = .78$ ).

**Conclusion:** Ebastine 20 mg given once daily was significantly superior to loratadine 10 mg given once daily at improving the rhinitis total symptom score throughout the day and at awakening over a 4-week period. Ebastine 20 mg and 10 mg doses were both efficacious and well tolerated in the treatment of SAR. (*J Allergy Clin Immunol* 2000;105:1101-7.)

**Key words:** Antihistamine, ebastine, loratadine, seasonal allergic rhinitis

### Abbreviations used

QTc: Q-T interval corrected for heart rate

SAR: Seasonal allergic rhinitis

Allergic rhinitis is estimated to affect approximately 20% of the US population.<sup>1,2</sup> The disorder is commonly classified as either seasonal allergic rhinitis (SAR, primary cause is pollen) or perennial allergic rhinitis (PAR, causes include dust mites, animal danders, and mold spores). Although the disease is generally viewed as a minor nuisance, the direct and indirect costs of this condition carry considerable economic implications.<sup>3</sup>

H<sub>1</sub>-receptor antagonists have been the traditional first-line therapy in the treatment of allergic rhinitis.<sup>4</sup> Ebastine (4-diphenylmethoxy-1-[3-(4-terbutylbenzoyl)-propyl] piperidine) is a potent once-daily nonsedating second-generation H<sub>1</sub> antihistamine, first marketed in 1990 and now available in more than 30 countries. It is currently under review by the US Food and Drug Administration.

The safety and efficacy of ebastine have been documented in placebo-controlled and comparative trials in the treatment of perennial allergic rhinitis<sup>5,6</sup> and SAR.<sup>7-10</sup> At the time of initiation of this study, only one randomized, placebo-controlled, double-blind study of 306 patients has compared the efficacy and safety of ebastine 20 mg and loratadine 10 mg during a 14-day treatment of SAR.<sup>10</sup> Ebastine 20 mg was found to be significantly superior to placebo ( $P < .05$ ) in the overall assessment of efficacy and in reducing the intensity of sneezing, runny nose, watery eyes, and itchy eyes. Loratadine 10 mg was significantly different from placebo only in reducing the intensity of watery eyes on day 7. Treatment tolerability was comparable between the ebastine 20 mg and placebo groups, whereas a significantly greater number of patients in the loratadine 10 mg group had adverse events ( $P = .011$ ).<sup>10</sup>

The objective of the current study was to compare the efficacy and safety of ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, and placebo administered once daily in controlling the symptoms of SAR over a 4-week period.

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TABLE I. Patient demographics

Variable	Treatment group				Total
	Ebastine 20 mg	Ebastine 10 mg	Loratadine 10 mg	Placebo	
Patients enrolled	143	140	141	141	565
Discontinued (%)	25 (17)	21 (15.0)	21 (15)	25 (18)	92 (16)
Completed study (%)	118 (83)	119 (85)	120 (85)	116 (82)	473 (84)
Sex					
Male (%)	67 (47)	72 (51)	61 (43)	77 (55)	277 (49)
Female (%)	76 (53)	68 (49)	80 (57)	64 (45)	288 (51)
Age (y)					
Mean ( $\pm$ SD)	37.5 $\pm$ 12.4	38.6 $\pm$ 11.8	38.1 $\pm$ 12.6	38.7 $\pm$ 12.8	38.2 $\pm$ 12.4
Range (minimum, maximum)	12, 69	12, 68	12, 70	12, 70	12, 70
12-17 y (%)	10 (7)	8 (6)	7 (5.0)	11 (8)	36 (6)
>17 y (%)	133 (93)	132 (94)	134 (95)	130 (92)	529 (94)
Weight (pounds)					
Mean ( $\pm$ SD)	170 $\pm$ 41	173 $\pm$ 45	171 $\pm$ 40	173 $\pm$ 42	172 $\pm$ 42
Median	166.5	165.0	165.0	170.5	167.0
Range (minimum, maximum)	79, 292	90, 325	76, 285	92, 292	76, 325
Years with allergy					
Mean ( $\pm$ SD)	21.6 $\pm$ 13.7	21.1 $\pm$ 12.5	19.5 $\pm$ 12.5	21.5 $\pm$ 12.2	20.9 $\pm$ 12.7
Median	17.7	20.0	16.6	20.5	18.6
Range (minimum, maximum)	2, 68	3, 56	2, 52	2, 53	2, 68

## METHODS

### Patients

Patients of either sex, aged 12 to 70 years, were screened for trial entry. The admission criteria required a clinical diagnosis of ragweed SAR for at least 2 years, a documented positive skin prick test to ragweed allergen within 1 year before enrollment defined as a wheal and flare greater than or equal to that produced by histamine 1 mg/mL control or at least 5 mm greater in diameter than that produced by saline solution control, and a minimum baseline reflective total symptom score of at least 42 of 105 points during at least 3 of the last 4 days of screening, including the morning of randomization.

Patients were excluded from the study if they were pregnant or lactating; had a history of hypersensitivity to antihistamines; had any clinical disorder or concomitant illness that might affect evaluation of the study medications; had initiated immunotherapy within 1 month of the study or were unable to maintain it at a stable dose; or had received decongestants within 2 days,  $H_1$  antagonists (except astemizole) within 7 days, short-acting systemic or topical corticosteroids and intranasal cromolyn within 21 days, depot corticosteroids within 2 months, or astemizole within 12 weeks. This study was conducted in compliance with the Declaration of Helsinki and in accordance with the local Ethical Committees. All patients or legal guardians gave their written informed consent before admittance to the trial.

### Study design

This study was a double-blind, placebo-controlled, randomized, parallel-group comparative study conducted in 14 centers in the southern United States from September 12 through November 6, 1997. The study consisted of a screening period of up to 28 days with the last 5 days as a baseline period, followed by a 28-day randomized double-blind treatment period.

Patients were provided with a daily diary card and were instructed to score their nasal discharge (anterior and/or posterior), nasal congestion, nasal itching, sneezing, and total eye symptoms (itchy/watery eyes) on a scale of 0 = absent, 1 = mild, 2 = moderate, or 3 = severe, every morning and evening over the previous 12 hours (reflective score) and at the time of recording (snapshot

score). Patients also recorded any adverse events or concomitant medications throughout the study period. Patient enrollment was completed within a 1-week period after verification of sufficient ragweed pollen in the study site environment.

Eligible patients were randomized to treatment with ebastine 20 mg, ebastine 10 mg (Rhône-Poulenc Rorer Pharmaceuticals), loratadine 10 mg (Schering), or placebo. Treatment was blinded by inserting 1 or 2 ebastine 10 mg tablets, 1 loratadine 10 mg tablet, or no tablets (placebo) into an opaque capsule containing inactive excipients. Patients were instructed to take one capsule immediately after breakfast with 8 ounces (240 mL) of water.

At the first and final visits, patients underwent a full medical history, physical examination, standard laboratory panel, and an electrocardiogram. At the final visit physicians and patients gave global evaluations of efficacy compared with baseline on a scale of 0 = greatly improved, 1 = somewhat improved, 2 = no change, 3 = somewhat worsened, and 4 = greatly worsened.

### Statistical methods

The study population size (150 patients/group) was determined to achieve an 80% power to detect a difference of 1 unit in the mean change from baseline in the daily reflective total symptom score between 2 treatments, assuming an SD of 2.9 units and a 10% discontinuation rate.

The efficacy and safety analyses were performed on the intent-to-treat population, which comprised all randomized patients who took at least one capsule of study medication. The following 4 composite scores were calculated: total symptom score (sum of all 5 individual scores), total symptom score without congestion, nasal index (sum of the 4 nasal symptom scores), and nasal index without congestion. The primary efficacy variable was the change from baseline in mean daily (average of morning + evening) reflective total symptom score over the entire treatment duration (overall).

Analysis of covariance, with the studied variable as dependent, treatment and investigator as factors and important baseline variables as covariates, was used to analyze changes from baseline during treatment. Treatment effect was evaluated with use of a 2-sided test. A *P* value <.05 was considered significant. The primary comparison was between ebastine 20 mg and loratadine 10 mg. Com-

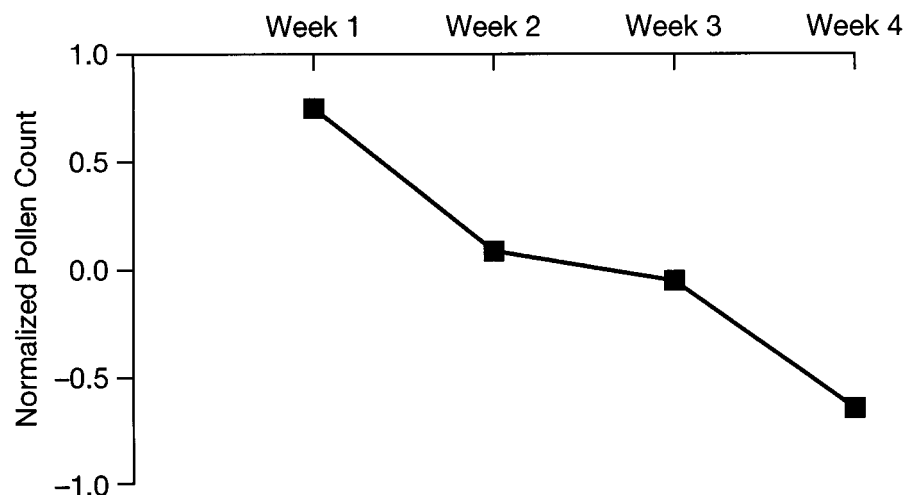


FIG 1. Normalized pollen count over 4 weeks.

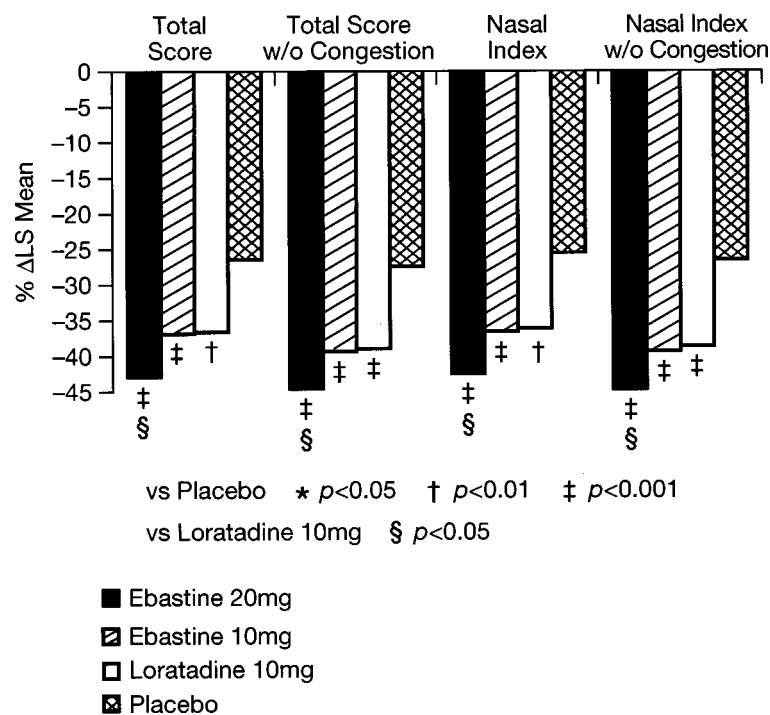


FIG 2. Overall percent change from baseline, mean daily reflective composite scores.

parisons of ebastine 10 mg to loratadine 10 mg were only performed when the difference between ebastine 20 mg and loratadine 10 mg was statistically significant. Secondary comparisons were between each of the 3 active treatments versus placebo. The Cochran-Mantel-Haenzel test was used to compare the overall proportion of patients with adverse events among treatment groups and the patient dropout rates because of treatment failure.

## RESULTS

### Study population

Of the 565 patients enrolled in this study, 473 (83.7%) evenly distributed patients completed the trial. Table I provides a summary of the demographic data. No statis-

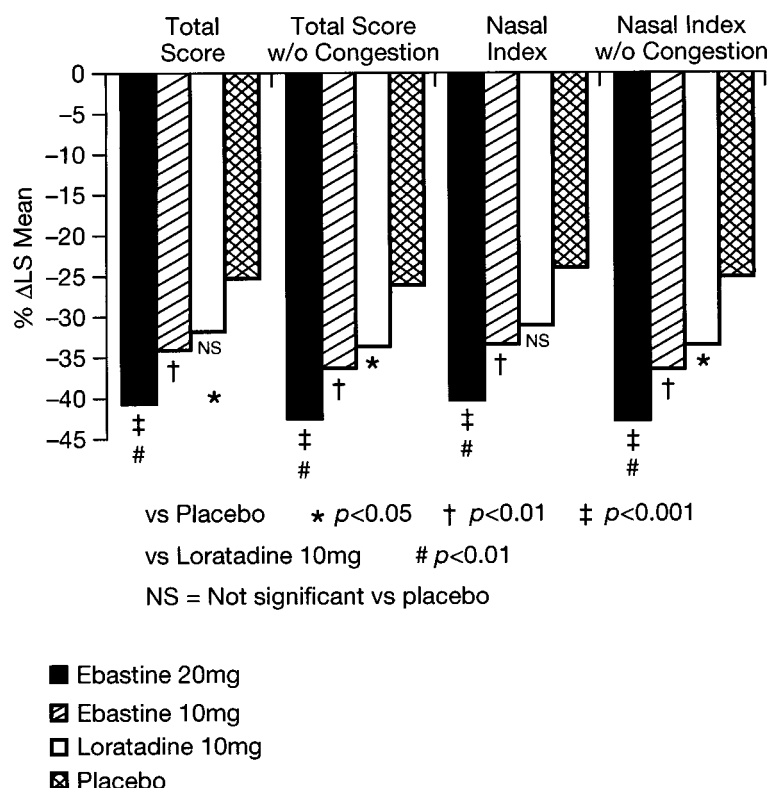


FIG 3. Overall percent change from baseline, mean morning snapshot composite scores.

tically significant differences were observed at baseline for mean daily reflective total symptom score among the treatment groups (mean range = 9.71 to 9.90, SD  $\pm$  0.21,  $P \geq .63$ , scale 0-15).

### Pollen count

The normalized plot of pollen count during the study period is illustrated in Fig 1.

### Overall efficacy

**Ebastine versus loratadine.** The ebastine 20 mg group had statistically significant ( $P < .05$ ) greater mean reductions from baseline compared with the loratadine 10 mg group in all 4 daily reflective and morning snapshot composite scores (Figs 2 and 3), as well as in the individual scores of nasal discharge ( $P = .0225$  for daily reflective,  $P = .0014$  for morning snapshot), nasal congestion ( $P = .0324$  for morning snapshot), and sneezing ( $P = .0214$  for daily reflective and  $P = .0072$  for morning snapshot).

Comparisons between ebastine 10 mg and loratadine 10 mg revealed no statistically significant differences in either the daily reflective or the morning snapshot scores overall.

**Active treatments versus placebo.** Compared with placebo, there were significantly greater overall reductions from baseline with ebastine 20 mg (18/18 scores,  $P < .001$ ), ebastine 10 mg (17/18 scores,  $P < .05$ ), and loratadine 10 mg (13/18 scores,  $P < .05$ ). The 18 scores equal 9 overall mean daily reflective scores plus 9 overall mean morning

snapshot scores (9 = 4 composite + 5 individual scores).

### Weekly efficacy

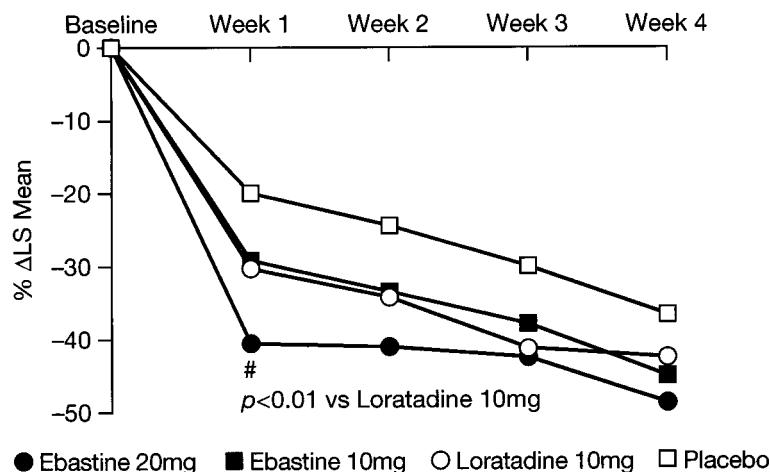
**Ebastine versus loratadine.** The ebastine 20 mg group showed a statistically significant ( $P < .05$ ) greater mean reduction from baseline versus the loratadine 10 mg group in 12 of 36 daily reflective scores and in 23 of 36 morning snapshot scores (36 = 9 scores  $\times$  4 weeks).

At week 4, ebastine 20 mg consistently provided greater improvement from baseline versus loratadine 10 mg. This difference reached statistical significance ( $P < .05$ ) in one daily reflective score (nasal discharge) and in 7 of 9 morning snapshot scores. For those 7 morning snapshot scores, the difference between ebastine 10 mg and loratadine 10 mg was not statistically significant.

The weekly percent change from baseline for the mean daily reflective total symptom score is shown in Fig 4.

**Active treatments versus placebo, daily reflective scores.** Compared with placebo, the ebastine 20 mg, ebastine 10 mg, and loratadine 10 mg groups exhibited a statistically significant ( $P < .05$ ) greater mean reduction from baseline in 36 of 36, 30 of 36, and 23 of 36 weekly scores, respectively.

At week 4, the ebastine 20 mg, ebastine 10 mg, and loratadine 10 mg groups demonstrated statistically significant difference versus placebo in 9 of 9, 8 of 9, and 1 of 9 scores, respectively.



The difference between Ebastine 10mg and Ebastine 20mg vs. placebo was statistically significant at week 1, 2, 3 and 4.

The difference between Loratadine 10mg vs. placebo was statistically significant at week 1, 2, 3.

The difference between Ebastine 20mg vs. Loratadine 10mg was statistically significant at week 1.

FIG 4. Weekly percent change from baseline, mean daily reflective total symptom score.

*Active treatments versus placebo, morning snapshot scores.* In comparison with placebo, the ebastine 20 mg, ebastine 10 mg, and loratadine 10 mg groups exhibited statistically significant ( $P < .05$ ) greater mean reduction from baseline in 35 of 36, 23 of 36, and 7 of 36 total weekly scores, respectively.

At week 4, the ebastine 20 mg, ebastine 10 mg, and loratadine 10 mg groups demonstrated statistically significant difference versus placebo in 9 of 9, 6 of 9, and 0 of 9 scores, respectively.

### Dropout because of treatment failure

Dropout because of treatment failure was the most common reason of discontinuation from this study. A statistically significant ( $P = .030$ ) lower rate of dropout from treatment failure was seen with the ebastine 20 mg group (4.2%) compared with placebo (10.6%) but not with the ebastine 10 mg or loratadine 10 mg groups (5.7% each).

### Patient and physician global evaluations at the final visit

Both patient and physician global evaluations at the final visit were significantly better for each active treatment group compared with placebo, with no significant difference among the 3 active treatments. The patient and physician global evaluations yielded similar ratings: 56.6% and 54.9% improved, 33.2% and 34.2% no change, and 8.8% and 9.9% worsened according to patient and physician evaluations, respectively.

### Safety

Overall, the ebastine 20 mg and 10 mg doses were found to be safe and well tolerated. No statistically significant ( $P = .7805$ ) difference was observed among the 4 study groups in the number of patients who reported one or more adverse events. The majority of adverse events were of mild or moderate intensity, and most were considered by the investigators to be unrelated or remotely related to study medication. No deaths occurred during the study. Fifteen of the 565 patients (2.7%) discontinued the study because of adverse events. Most discontinuations because of adverse events were considered unrelated to the study drug. Headache was reported by the highest percent of patients in this study in all 4 groups (ebastine 20 mg, 6.3%; ebastine 10 mg, 4.3%; loratadine 10 mg, 8.5%; placebo, 4.3%). Other adverse events reported by  $>2.1\%$  of patients in the active treatment groups and  $>$ placebo were back pain (ebastine 10 mg, 2.9%; placebo, 1.4%), pain (loratadine 10 mg, 2.8%; placebo, 0%), prolonged Q-T interval corrected for heart rate  $>444$  milliseconds (QTc) (ebastine 20 mg, 3.5%; ebastine 10 mg, 4.3%; loratadine 10 mg, 3.5%; placebo, 0.7%), somnolence (ebastine 10 mg, 3.6%; loratadine 10 mg, 3.5%; placebo, 1.4%), epistaxis (loratadine 10 mg, 2.8%; placebo, 0.7%), and rhinitis (ebastine 20 mg, 4.9%; ebastine 10 mg, 2.9%; loratadine 10 mg, 5.0%; placebo, 2.8%).

The QTc value for those patients who had QTc prolongation in this study ranged from 446 to 473 millise-

onds (ebastine 20 mg), 446 to 482 milliseconds (ebastine 10 mg), 445 to 599 milliseconds (loratadine 10 mg), and 446 milliseconds (placebo).

## DISCUSSION

This study compared ebastine 20 mg and 10 mg given once daily with loratadine 10 mg given once daily and placebo in the treatment of SAR. Loratadine, an effective and safe second-generation H<sub>1</sub> antihistamine, was chosen as an appropriate positive standard against which the efficacy and safety of ebastine could be assessed.

The ebastine 20 mg group had a statistically significant greater overall mean reduction from baseline compared with the loratadine 10 mg group in 6 of 9 mean daily reflective scores including the primary efficacy variable "total symptom score." These results demonstrate that a 4-week treatment with once-daily ebastine 20 mg is significantly more efficacious than once-daily loratadine 10 mg in the treatment of SAR. Patients in the ebastine 10 mg and loratadine 10 mg groups had nearly identical reductions in mean daily reflective scores, suggesting that ebastine 10 mg is comparable in efficacy compared with loratadine 10 mg in the treatment of SAR.

The 4-week double-blind treatment duration was incorporated into our study design to provide a sufficient duration of treatment for rhinitis symptoms throughout the ragweed season as well as to assess treatment tolerability. At the end of the 4th week, while patients in the ebastine groups continued to experience significantly greater differences over placebo in their mean daily reflective scores (9/9 ebastine 20 mg, 8/9 ebastine 10 mg), patients in the loratadine 10 mg group exhibited a significant difference versus placebo in only 1 of 9 scores. These findings support that the efficacy of once-daily ebastine 20 mg and 10 mg at improving the symptoms of SAR is significant and sustained throughout a 4-week period during the ragweed pollen season.

The failure of loratadine 10 mg to provide a significant difference versus placebo at week 4 in this study was unexpected because loratadine is not associated with a buildup of tolerance over time.<sup>11</sup> A possible explanation for this observed lack of sustained efficacy over time with loratadine 10 mg could be the natural drop in ambient pollen count over the course of this trial (Fig 1), which could have attenuated the severity of SAR symptoms in patients, thus narrowing their window of therapeutic perception. Alternatively, if this explanation is true, it suggests that the efficacy of ebastine 20 mg and 10 mg can be significantly perceived over a wider range of ambient pollen counts and for a greater number of days during the SAR season.

Unfortunately, a comparison of our findings to data from published placebo-controlled studies with loratadine 10 mg given once daily in SAR was not possible because of the shorter (<4 weeks) treatment duration in these studies. This difference in sustained efficacy after 4 weeks of treatment between ebastine (20 mg and 10 mg) and loratadine (10 mg) merits confirmation in additional clinical trials.

Several previous studies have reported on the circadian rhythms of allergic rhinitis, with the majority (60%-70%) of patients having maximum intensity of allergic rhinitis symptoms in the morning.<sup>12,13</sup> Consequently, it seems logical that the optimal therapy for allergic rhinitis should target the early morning hours when symptoms are at their worst. In this study, all study medications were to be taken once daily immediately after breakfast. The morning snapshot scores particularly assessed the efficacy of the active medications at awakening, before the next dosing, when the plasma drug level and symptomatic relief are at their lowest. Therefore, with ebastine 20 mg achieving a significantly greater overall improvement from baseline over loratadine 10 mg in 7 of the 9 morning snapshot scores, we concluded ebastine 20 mg given once daily to be significantly more efficacious than loratadine 10 mg given once daily in controlling the symptoms of SAR at awakening in the morning.

It is well established now that not all second-generation H<sub>1</sub> antihistamines are nonsedating.<sup>14,15</sup> In this study somnolence was reported by no more than 3.6% of patients in each of the active treatment groups versus 1.4% of patients in the placebo group. This rate is consistent with previous data on ebastine supporting the nonsedating property of this agent and the absence of a dose-related increase in somnolence.<sup>16,17</sup>

In this study the percent of patients who had a prolonged QTc interval (>444 milliseconds) was similar among the ebastine and loratadine groups. With the exception of one patient (45-year-old woman, loratadine 10 mg group) who had a 164-millisecond increase from baseline in QTc (final QTc = 599 milliseconds), all increases in QTc interval leading to a final value >444 milliseconds fell well within the average spontaneous intraindividual diurnal variation of this parameter for healthy subjects, as reported in the literature by Morganroth et al<sup>18</sup> (76 ± 19 milliseconds) and Molnar et al<sup>19</sup> (117 ± 21 milliseconds). The data on QTc interval for the 2 ebastine groups are comparable to those obtained in an analysis of pooled cardiac data from 842 patients treated with ebastine 1 to 30 mg per day and 360 placebo recipients in 5 multicenter studies, where no patient recorded a QTc interval >500 milliseconds.<sup>16</sup>

## CONCLUSIONS

- Ebastine 20 mg given once daily for 4 weeks in the treatment of SAR was significantly superior to loratadine 10 mg given once daily at improving the rhinitis total symptom score throughout the day and at awakening.
- Ebastine 20 mg and 10 mg given once daily but not loratadine 10 mg given once daily demonstrated a significantly sustained efficacy over placebo at the end of the 4-week treatment period.
- Ebastine 10 mg given once daily and loratadine 10 mg given once daily provided a similar symptomatic relief overall.
- Ebastine 20 mg and 10 mg given once daily for 4

weeks are safe in patients 12 to 70 years old with SAR, with the number of patients experiencing adverse events comparable to that of placebo.

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