
Efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis: a randomized, placebo-controlled study

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Background: Levocetirizine, a second-generation antihistamine for symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria, has not been previously studied in US patients.

Objective: To assess the efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis (SAR).

Methods: This multicenter, double-blind trial randomized adults with SAR, sensitized to at least 1 grass allergen, to receive levocetirizine, 5 mg, or placebo once daily in the evening for 2 weeks. The primary end point was the 24-hour reflective Total 5-Symptom Score (T5SS; sum of rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus) during the entire treatment period. Secondary assessments included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Work Productivity and Activity Impairment–Allergy Specific (WPAI-AS) questionnaire, and Epworth Sleepiness Scale (ESS), each assessed at week 1, week 2, and the end of treatment.

Results: The intent-to-treat population comprised 287 patients taking levocetirizine and 290 taking placebo, with no significant between-group differences at baseline. Levocetirizine resulted in significantly greater improvement from baseline vs placebo in the T5SS ($P < .001$), overall RQLQ score ($P < .001$), general and work-related WPAI-AS subscores ($P < .05$), and ESS score ($P < .001$). Overall incidence of treatment-emergent adverse events was 14.4% for levocetirizine and 18.4% for placebo. The incidence of somnolence and fatigue was 0.7% and 1.8% with levocetirizine and 1.0% and 0% with placebo, respectively.

Conclusions: Levocetirizine was well tolerated and was significantly more effective than placebo in improving the naso-ocular symptoms and health-related quality of life in US patients with SAR.

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Allergic rhinitis (AR) has been reported to affect up to 58 million Americans annually^{1–3} and poses a significant cost burden.^{4–7} Uncontrolled AR symptoms result in the loss of workplace and classroom productivity estimated at 3.6 million workdays and 2 million school days annually.^{8–10} In addition, AR negatively affects daily functioning, well-being,

and overall health-related quality of life (HRQOL)^{11–14} by contributing to nocturnal sleep loss or disturbance, daytime sleepiness, fatigue, and decreased overall cognitive functioning.^{14,15}

Levocetirizine, the active enantiomer of cetirizine, is a potent and highly selective histamine₁ antihistamine.^{16,17} Levocetirizine is approved by the Food and Drug Administration (FDA) for treatment of symptoms associated with seasonal AR (SAR) and perennial AR in patients 6 months and older based on clinical efficacy demonstrated in well-controlled trials.^{18,19} In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted previously outside the United States,^{18,19} levocetirizine, 5 mg, once daily in the evening was studied for a total treatment duration of 6 months in patients with persistent AR as defined by the Allergic Rhinitis and its Impact on Asthma guidelines. Primary end points included the Total 5-Symptom Score (T5SS), which is the sum of rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus scores, and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score. Levocetirizine was shown to improve quality of life and symptoms and to decrease the overall costs of the disease during the 6-month treatment period. Specifically, levoceti-

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rizine significantly improved both the RQLQ overall score and the T5SS score from week 1 to 6 months (all P values $<.001$). To date, no published study has assessed both end points as prospectively defined and adequately powered measures in patients with SAR. In addition, before its approval by the FDA, no clinical studies have been conducted with levocetirizine in the United States. This study evaluated the effect of levocetirizine, 5 mg, once daily on T5SS, including nasal congestion and ocular symptoms, HRQOL, work productivity, and daytime sleepiness in US adults with SAR.

METHODS

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 39 sites in the United States during the spring of 2008. Men and women aged 18 to 65 years were eligible for enrollment if, within the previous year, they had a documented positive skin prick test result to at least 1 spring grass allergen indigenous to the patient's environment and present in the air during the study period. Before enrollment, the local grass pollen count had to be greater than 10 grains/m³ for 3 consecutive days, as documented by a reliable local or regional pollen-reading station. In addition, eligible patients had to have moderate to severe SAR symptoms (defined as a minimum mean 24-hour reflective T5SS of ≥ 7 of 15) between the screening and randomization visits (baseline period). Pregnant women, breastfeeding mothers, and women of childbearing age not using a medically acceptable method of contraception were excluded, as were patients with ear, nose, throat, or eye infections during the 2 weeks preceding the initial visit and patients with asthma requiring daily treatment with other than an inhaled β_2 -agonist as needed. Patients were also excluded if they had, among other diseases, atopic dermatitis or urticaria that required antihistamine or corticosteroid treatment; an associated ear, nose, or throat disease, such as vasomotor rhinitis or nasal polyps; other clinically significant diseases, such as glaucoma or cardiovascular or hepatic diseases; or any condition likely to disturb the absorption, distribution, metabolism, or excretion of the investigational drug. The protocol for this study was approved by the institutional review boards of the respective study centers, and patients provided written informed consent before trial participation.

After a single-blind, 3- to 9-day placebo run-in period, eligible patients were randomly assigned (1:1) to receive either levocetirizine, 5 mg (Xyzal; sanofi-aventis US LLC, Bridgewater, New Jersey, and UCB Pharma, Smyrna, Georgia) or placebo to be taken once daily in the evening for 14 days. Treatment for breakthrough symptoms was not provided.

The T5SS was used to assess changes in allergic rhinoconjunctival symptoms. The T5SS measures not only the typical symptoms normally responding to antihistamines (rhinorrhea, sneezing, and nasal and ocular pruritus) but also nasal congestion, which is, in the clinical setting, 1 of the most bothersome symptoms for patients with AR. In addition to the T5SS, efficacy assessments also included the T4SS (the T5SS minus nasal congestion), the Total Nasal Symptom Score

(TNSS; the sum of sneezing, rhinorrhea, nasal itching, nasal congestion, and postnasal drip), and the Total Ocular Symptom Score (TOSS; the sum of ocular itching or burning, ocular tearing or watering, and ocular redness). Individual rhinoconjunctival symptoms were evaluated each day of the study by means of a daily electronic diary that was filled out in the evening before taking the study drug; the diary rated 24-hour reflective symptoms with a 4-point scale to rate each symptom from 0 (absent) to 3 (severe). The use of electronic diaries promotes and monitors the daily recording of symptom scores and prompts for missing data. Efficacy was also evaluated using the global physician's and patient's rating of efficacy at the last study visit.

Impact on patient HRQOL was assessed via the RQLQ.^{20,21} The RQLQ is a disease-specific, validated, reproducible instrument for evaluating HRQOL on the basis of how symptoms and treatments affect each patient's physical, social, and emotional well-being. Performance impairment due to allergy symptoms was assessed using the Work Productivity and Activity Impairment–Allergy Specific (WPAI-AS) instrument, which has been validated to measure generic and allergy-specific performance impairment of work and classroom productivity and of regular daily activity.^{22,23}

Daytime somnolence was assessed using the Epworth Sleepiness Scale (ESS), the standard for measuring daytime sleepiness in adults.^{24,25} Patients are asked to rate, on a scale of 0 to 3, the chances of dozing off or falling asleep during 8 situations encountered in daily life, with total scores ranging from 0 to 24. Higher scores on the ESS indicate greater somnolence, with a score of 10 or more indicating sleepiness. Reductions from baseline therefore indicate improvement in this parameter. The RQLQ, WPAI-AS, and ESS instruments were administered at baseline, week 1, week 2, and end of treatment (defined as the last available postbaseline observation). Adverse events were recorded at each visit during treatment.

The primary efficacy end point was the change from baseline in the T5SS during 2 weeks of treatment. The primary efficacy analyses were based on the intent-to-treat (ITT) population by using the analysis of covariance (ANCOVA) method, with treatment and center as the factor and baseline mean score as the covariate. Analysis of the results revealed a significant interaction between the treatment and the baseline mean T5SS ($P = .04$), suggesting that the treatment effect was lower (or even null) for low baseline mean values (no room for improvement) and was greater for high baseline mean values compared with the overall mean treatment effect. Nevertheless, the results of the sensitivity analysis performed on the per protocol population, for which the interaction between the treatment and the baseline mean T5SS is not significant, confirmed those obtained with the ITT population.

A sample size of 278 assessable (ITT) patients (treatment arm) was expected to have 90% power to detect a difference of 0.8 between active treatment and placebo in the mean 24-hour reflective T5SS during the total treatment period, with an SD of 2.9 and a 2-sided α error of .05. Accounting for a 30% screening failure rate between visit 1 and visit 2,

Table 1. Baseline Demographic Characteristics of the Intent-to-Treat Population

Characteristic	Levocetirizine group (n=287)	Placebo group (n=293)
Age, mean (SD), y	38.7 (11.5)	37.5 (11.7)
Sex, No. (%)		
Male	118 (41.1)	111 (37.9)
Female	169 (58.9)	182 (62.1)
Race, No. (%)		
White	216 (75.3)	215 (73.4)
Black	58 (20.2)	61 (20.8)
Asian	8 (2.8)	8 (2.7)
Mixed race	5 (1.7)	9 (3.1)
Weight, mean (SD), kg	80.6 (20.4)	83.6 (20.7)
Height, mean (SD), cm	169.4 (10.4)	169.2 (10.2)
BMI, mean (SD)	28.1 (6.6)	29.2 (6.4)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

approximately 730 patients had to be screened in this study to randomize 556 patients. This sample size also provided a 90% power to detect a mean change of at least a 0.36 unit from baseline in RQLQ overall score between the levocetirizine and placebo groups, at the .05 confidence level, assuming a pooled SD of 1.3.

Secondary efficacy end points were analyzed with an ANCOVA model as for the primary end point, except for the global physician's rating of efficacy, which was analyzed using the Wilcoxon rank-sum test. SAS statistical software, version 9.1, for Windows XP (SAS Institute Inc, Cary, North Carolina) was used to create all derived variables and statistical calculations. Treatment effects were tested on an α level of .05.

RESULTS

Study Population

Of 824 patients screened at 39 study sites, 580 were randomized to treatment with either levocetirizine (n=287) or placebo (n=293) and comprised the ITT population. Overall, the mean age of the participants was 38 years, 61% were female, and 74% were white (Table 1). All but 14 patients (2.4%; 7 in each group) completed the study (Figure 1). Baseline values for the primary and secondary variables were similar between the 2 groups (Table 2).

Reasons for discontinuation included adverse events in 3 patients (1 taking levocetirizine, 2 taking placebo), lack of efficacy in 3 patients (2 taking levocetirizine, 1 taking placebo), loss of efficacy in 1 patient (placebo), 1 patient lost to follow-up (placebo), and other reasons in 6 patients (4 taking levocetirizine, 2 taking placebo).

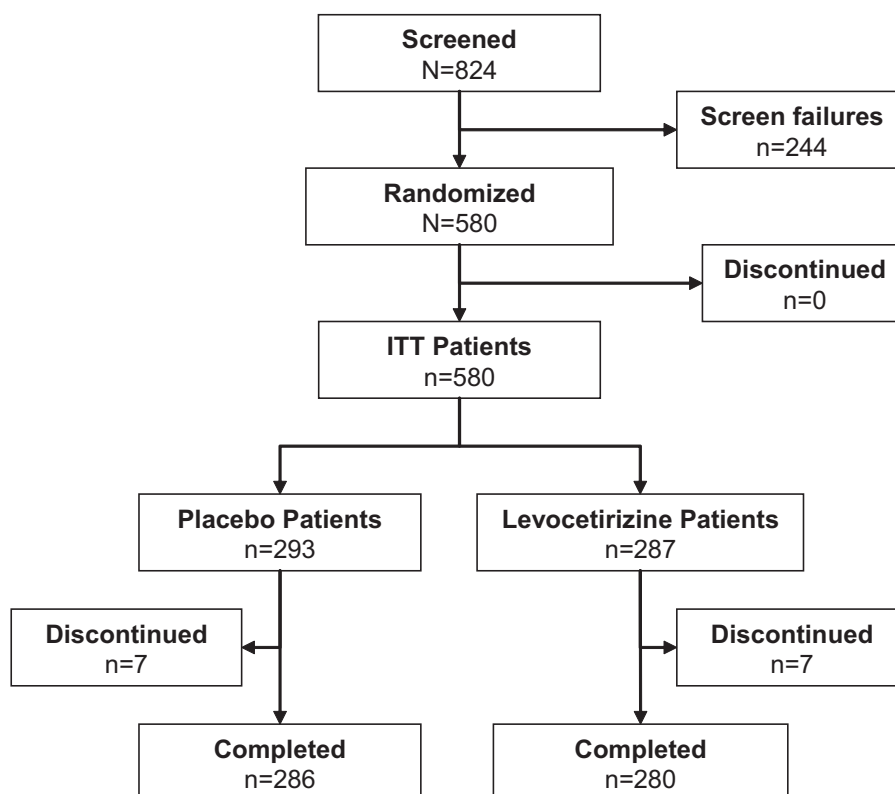


Figure 1. Disposition of patients. Diagram indicates study flow and patients who discontinued participation in the study.

Table 2. Baseline Values for Secondary Efficacy Variables

	Levocetirizine group		Placebo group	
	No. of patients	Mean (SD) baseline value	No. of patients	Mean (SD) baseline value
RQLQ scores				
Total	285	3.43 (1.15)	293	3.35 (1.08)
Activities	233	4.18 (1.31)	241	4.14 (1.23)
Sleep	285	3.08 (1.43)	293	3.04 (1.44)
Nonnose/eye symptoms	284	3.09 (1.30)	293	2.97 (1.27)
Practical problems	284	3.86 (1.40)	292	3.84 (1.36)
Nasal symptoms	284	3.91 (1.23)	292	3.87 (1.23)
Eye symptoms	285	3.39 (1.49)	293	3.23 (1.52)
Emotional	285	3.00 (1.48)	293	2.83 (1.47)
ESS score	284	10.7 (4.8)	293	10.4 (4.8)
WPAI-AS				
Work time missed due to allergy, %	214	3.80 (11.15)	225	3.32 (9.42)
Impairment while working due to allergy, %	216	51.57 (24.14)	227	49.30 (24.01)
Overall work impairment due to allergy, %	214	52.46 (24.63)	223	50.07 (24.26)
Class time missed due to allergy, %	22	5.83 (13.25)	30	5.98 (11.22)
Impairment in the classroom due to allergy, %	22	50.45 (22.99)	30	56.00 (28.60)
Overall classroom impairment due to allergy, %	22	52.71 (24.13)	30	57.39 (29.12)
Activity impairment due to allergy, %	273	57.95 (23.83)	280	56.46 (22.56)

Abbreviations: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; WPAI-AS, Work Productivity and Activity Impairment–Allergy Specific.

Efficacy

There was significantly greater reduction (improvement) from baseline in the T5SS with levocetirizine vs placebo during the total treatment period (-0.89) and during the first and second treatment weeks individually (-0.89 at week 1 and -0.88 at week 2; $P < .001$ for both weeks and overall; Table 3 and Figure 2). Improvement with levocetirizine compared with placebo was also significantly greater during each treatment week and during the total treatment period ($P < .001$ for both weeks and overall) in the T5SS component scores for sneezing, rhinorrhea, nasal pruritus, and ocular pruritus but not nasal congestion (Table 3). Similarly, significant improvement from baseline with levocetirizine vs placebo during the total treatment period was noted in the mean T4SS (-0.81 ; $P < .001$), mean TNSS (-0.74 ; $P < .001$), and mean TOSS (-0.54 ; $P < .001$).

Baseline scores for the RQLQ, WPAI-AS, and ESS are given in Table 2. The mean (SD) RQLQ overall scores decreased (HRQOL improved) from baseline to the final visit (2.41 [1.37] for placebo and 2.13 [1.21] for levocetirizine) in both treatment groups. Improvement in the mean overall RQLQ score at the final visit was significantly greater in the levocetirizine group than in the placebo group ($P < .001$), with a treatment difference of -0.34 (36.6% improvement over placebo) at the final visit. This improvement in overall RQLQ score was seen as early as 1 week, with a treatment difference of -0.31 (50.8% improvement over placebo, $P < .001$). All component scores of the RQLQ also improved significantly ($P < .05$; Figure 3). At the end of treatment, both levocetirizine and placebo improved component scores

on the WPAI-AS questionnaire compared with baseline (Figure 4). The mean percentage of overall work impairment improved more from baseline in the levocetirizine group compared with the placebo group (adjusted mean difference between groups of -4.44% , $P < .05$). Levocetirizine demonstrated significantly better effectiveness vs placebo in the general score and in all work-related subscores (4 of the 7 WPAI-AS component scores; $P < .05$).

Significant improvement was seen from baseline to the end of treatment in mean (SD) ESS scores with both placebo (9.4 [5.0]; $P < .001$) and levocetirizine (8.9 [4.8]; $P < .001$), with reduction (improvement) in mean ESS scores from baseline 80% greater with levocetirizine (-1.8 [16.8%]) vs placebo (-1.0 [9.6%]). Improvement at the end of treatment with levocetirizine was significantly greater compared with placebo (treatment difference of -0.68 ; $P = .03$) (Figure 5).

According to the global patients' rating of efficacy, a significantly greater proportion of patients showed a slight, moderate, or marked improvement with levocetirizine vs placebo (66.2% vs 52.9%; $P < .001$). In addition, according to the global physician's rating of efficacy, a significantly greater proportion of physicians noted slight, moderate, or marked improvement with levocetirizine vs placebo (67.9% vs 51.2%; $P < .001$).

Safety and Tolerability

The number of patients reporting treatment-emergent adverse events with levocetirizine (41; 14.4%) and placebo (54; 18.4%) was similar. The most common ($\geq 1.0\%$) treatment-emergent adverse events are listed in Table 4. The incidence

Table 3. Change From Baseline in T5SS and Its Individual Components

	Levocetirizine group			Placebo group			Levocetirizine difference vs placebo, adjusted mean	P value
	No. of patients	Baseline score, mean	Treatment score, adjusted mean	No. of patients	Baseline score, mean	Treatment score, adjusted mean		
T5SS								
Week 1	283	10.54	8.16	291	10.44	9.05	−0.89	<.001
Week 2	278	10.55	7.42	285	10.43	8.30	−0.88	<.001
Total treatment period	284	10.55	7.83	291	10.44	8.72	−0.89	<.001
Sneezing score								
Week 1	284	2.08	1.56	291	2.08	1.79	−0.23	<.001
Week 2	279	2.09	1.42	285	2.07	1.63	−0.22	<.001
Total treatment period	284	2.08	1.50	291	2.08	1.72	−0.23	<.001
Rhinorrhea score								
Week 1	284	2.07	1.59	292	2.09	1.80	−0.21	<.001
Week 2	279	2.07	1.46	285	2.09	1.63	−0.17	.008
Total treatment period	284	2.07	1.53	292	2.09	1.73	−0.19	<.001
Nasal congestion score								
Week 1	284	2.24	1.92	292	2.27	1.97	−0.05	.38
Week 2	279	2.24	1.70	285	2.27	1.82	−0.12	.06
Total treatment period	284	2.24	1.82	292	2.27	1.90	−0.08	.12
Nasal pruritus score								
Week 1	284	2.06	1.61	292	2.10	1.78	−0.17	.002
Week 2	279	2.06	1.47	285	2.11	1.63	−0.15	.02
Total treatment period	284	2.06	1.55	292	2.10	1.71	−0.16	.003
Ocular pruritus score								
Week 1	283	2.09	1.49	292	1.90	1.70	−0.21	<.001
Week 2	278	2.09	1.38	285	1.89	1.59	−0.20	.002
Total treatment period	284	2.09	1.44	292	1.90	1.66	−0.21	<.001

Abbreviation: T5SS, Total 5-Symptom Score.

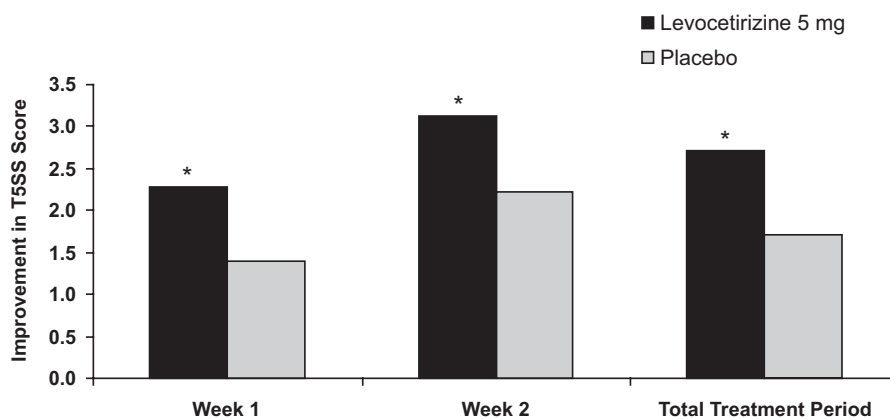


Figure 2. Reduction (improvement) in mean Total 5-Symptom Score (T5SS) during weeks 1 and 2 and during the total treatment period. Levocetirizine treatment resulted in a mean improvement of T5SS for all time points assessed. * $P < .001$.

of somnolence reported with levocetirizine was low (0.7%) and was comparable to that of placebo (1.0%). The incidence of fatigue was higher with levocetirizine (1.8%) compared with placebo (0%). The incidence of dry throat was also higher with levocetirizine (1.4%) compared with placebo (0%). One patient (0.4%) in the levocetirizine group and 2 patients (0.7%) in the placebo group discontinued participa-

tion in the study because of an adverse event. One serious treatment-emergent adverse events (cellulitis) (0.4%) was reported in the levocetirizine group.

DISCUSSION

Results of this multicenter trial in an adult US patient population with SAR demonstrated that 2-week treatment with

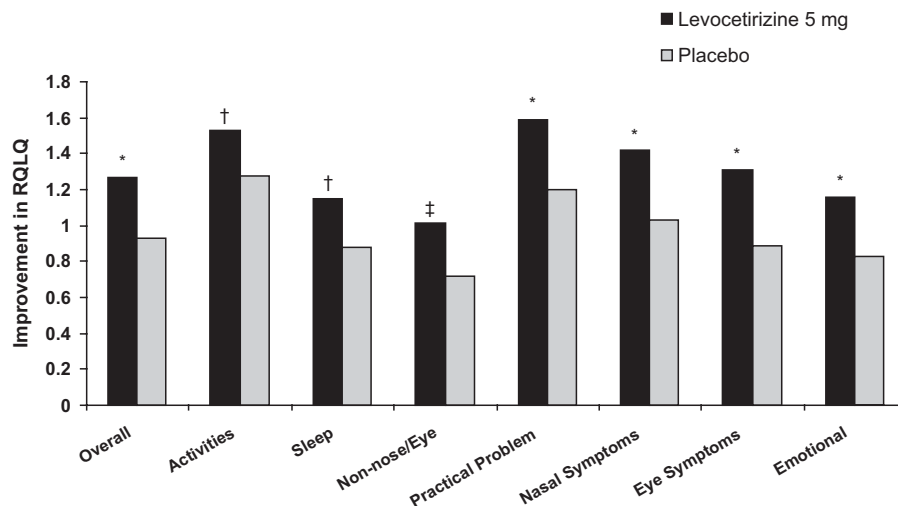


Figure 3. Reduction (improvement) from baseline to end of treatment in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores. Improvement in the mean overall RQLQ score and improvement in all component scores at final visit was significantly greater in the levocetirizine group than in the placebo group. * $P < .001$. † $P < .05$. ‡ $P < .01$.

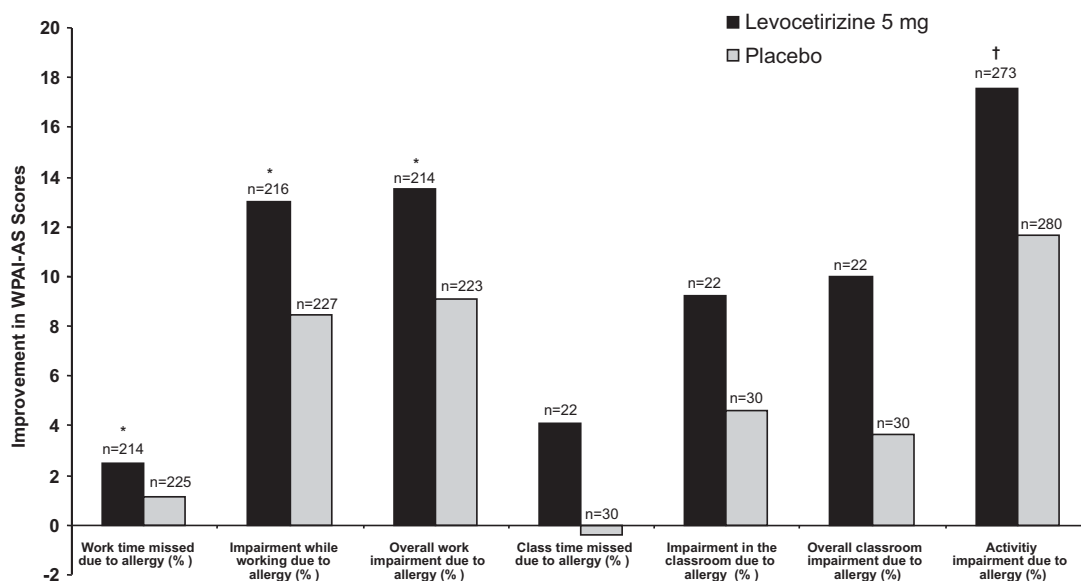


Figure 4. Improvement from baseline to end of treatment in work productivity scores. At end of treatment, both levocetirizine and placebo improved component scores on the Work Productivity and Activity Impairment–Allergy Specific (WPAI-AS) questionnaire compared with baseline, but levocetirizine demonstrated significantly better effectiveness vs placebo in the general and all work-related WPAI-AS component scores. * $P < .05$. † $P < .001$.

levocetirizine, 5 mg, once daily in the evening was significantly more effective than placebo in relieving multiple aggregates of allergic rhinoconjunctivitis symptoms, including T5SS, T4SS, TNSS, and TOSS. Levocetirizine also demonstrated a favorable impact on patients' HRQOL, as indicated by significant improvement compared with placebo in change from baseline in overall and all individual component RQLQ scores at the end of treatment.

These results are consistent with those from the Xyzal in Persistent Rhinitis Trial (XPRT), a 6-month trial performed

outside the United States in 551 patients with persistent AR wherein once-daily levocetirizine, 5 mg, showed significant improvement in T5SS and overall RQLQ score compared with placebo at 4 weeks and 6 months.¹⁹ In XPRT, the overall RQLQ score improved 47.5% over placebo with levocetirizine at the end of 4 weeks of treatment and remained statistically significant in favor of levocetirizine after 6 months. In this study, RQLQ scores improved over placebo by 50.8% at 1 week and 36.6% at the end of 2 weeks. These improvements are substantial and corroborate the positive

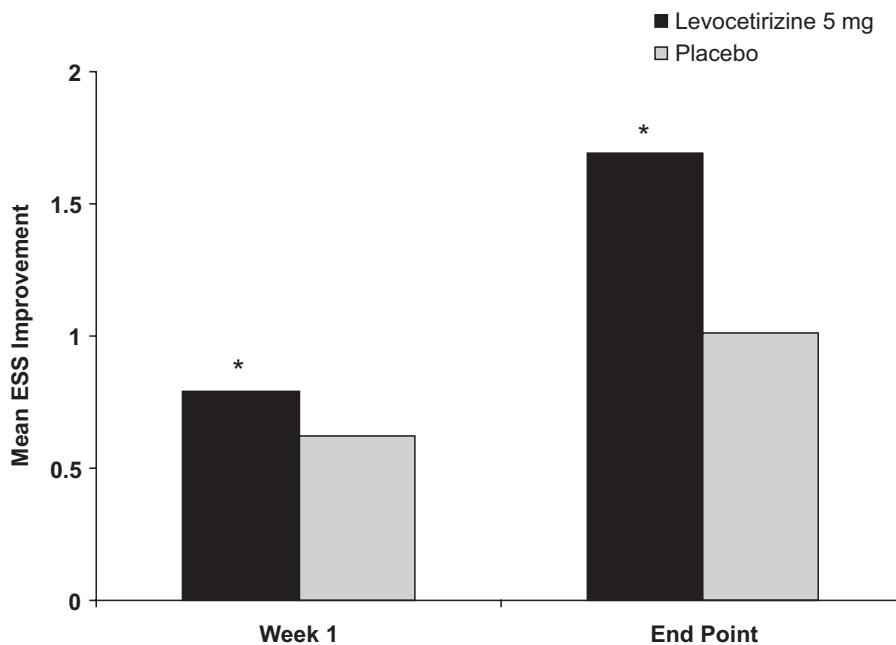


Figure 5. Improvement from baseline to end of treatment in Epworth Sleepiness Scale (ESS) scores. There was significant improvement over baseline (mean [SD], 10.4 [4.8] for placebo and 10.7 [4.8] for levocetirizine) in mean ESS scores with both placebo and levocetirizine, although improvement at the end of treatment with levocetirizine was significantly greater compared with placebo. * $P < .05$.

Table 4. Number of Patients With an Incidence of Treatment-Emergent Adverse Events of 1% or Higher

Adverse event	Levocetirizine, 5 mg, group, No. (%) (n=285)	Placebo group, No. (%) (n=293)
Headache	13 (4.6)	12 (4.1)
Fatigue	5 (1.8)	0
Dry throat	4 (1.4)	0
Pharyngolaryngeal pain	3 (1.1)	2 (0.7)
Pain	3 (1.1)	1 (0.3)
Cough	2 (0.7)	3 (1.0)
Somnolence	2 (0.7)	3 (1.0)
Nasal septal disorder	1 (0.4)	3 (1.0)

impact of significant reduction in symptom severity on HRQOL. However, unlike XPERT, this study did not show a significant improvement in nasal congestion in the levocetirizine group.¹⁹ The study duration of 2 weeks may not have been sufficient to show an effect on this symptom, which is typically resistant to antihistamine therapy.²⁶

Similar to previous studies of levocetirizine,^{19,27} the present study also provided additional evidence of the favorable effect of levocetirizine on productivity in allergy patients. In addition to its negative impact on quality of life, AR has been shown to reduce productivity in the workplace, which is affected by symptom severity and allergen exposure.^{10,28} Reilly et al²³ have previously reported that impairment while at work or in the classroom in patients with moderate to severe allergy symptoms ranges from 35% to 40% of normal

productivity. In this study, both levocetirizine and placebo improved all measures of impairment in work, school, and daily activities compared with baseline; however, levocetirizine resulted in a significant improvement vs placebo in the general score and in the 3 work-related components (work time missed, impairment while working, and overall work impairment) of the WPAI-AS instrument and in activity impairment due to allergy. There was a consistent trend in the other 3 components (all school related) of the WPAI-AS, although the results did not reach statistical significance. This lack of significance may be attributable to the small sample size (small number of patients in a classroom environment). As mentioned herein, these findings are consistent with findings of the previously mentioned 6-month study in patients with persistent AR in which long-term treatment with levocetirizine resulted in improved work productivity and overall reduced pharmacoeconomic disease burden in terms of indirect costs related to work productivity.¹⁹

In this particular study, the incidence of treatment-emergent somnolence was similar to placebo, but the rate of fatigue was higher with levocetirizine. The US product labeling for levocetirizine carries a warning concerning sedation based on higher rates of somnolence adverse reactions vs placebo (6% vs 2%) in clinical trials conducted outside the United States at the once-daily, 5-mg evening dose in patients 12 years or older.¹⁸ Diversity in ethnic backgrounds, languages, and cultures, a highly subjective appreciation of a sense of fatigue and sleepiness, the potential for cross-interpretation of these terms, the version of the medical term

coding dictionary used, and even slight variations in the method of collecting adverse reaction data in clinical trials are just a few examples of variables that ultimately affect the final reported rate of somnolence and fatigue adverse reactions during the regulatory drug product approval. In addition, the effect of body mass index, physical conditioning, the amount and timing of caffeine consumption, and sleeping habits could have played a role in the observed difference in somnolence and fatigue between the US-based vs ex-US-based reports. Because these variables were not quantified, it is difficult to pinpoint a single reason for the difference in the rate of somnolence with levocetirizine between this US study and studies conducted abroad. In addition, published psychometric studies with levocetirizine have shown a lack of impairment in cognitive and psychomotor functions²⁹ and in driving ability.³⁰

Fatigue, daytime sleepiness, and cognitive or psychometric impairment have been reported in patients with AR.^{13,31,32} Sedating antihistamines are known to cause or aggravate somnolence.³³ Although the ESS has not been validated specifically in patients with AR, the mean ESS score at baseline was greater than 10, indicating excessive daytime somnolence in this US sample of the population. Interestingly, the statistically significant improvements from baseline in the mean ESS score and in the T5SS observed in this study in both the levocetirizine and placebo groups can be entirely independent signals or could suggest a possible link between the improvement in allergic rhinoconjunctivitis symptoms and decreased daytime sleepiness^{13,32} via a common pathway. Taking this observation a step further, the significant difference from baseline seen with levocetirizine over placebo in both the mean T5SS and ESS score suggests that if such a common pathway exists, it may be favorably affected by a course of treatment with levocetirizine. However, many questions remain:

- What is the minimum important difference in the mean ESS score in patients with AR?
- Is the relationship between AR symptom severity and the extent of daytime sleepiness linear or nonlinear?
- How do various interventions affect this relationship?
- What are the determinants of a treatment response?
- What is the time lag between onset of significant symptom improvement and a meaningful decrease in daytime somnolence?
- What is the contribution of confounding comorbidities, such as obesity and obstructive sleep apnea?

Further exploration using carefully selected populations and improved tools are undoubtedly needed to unravel the complete answers to these questions.

In conclusion, this study showed that levocetirizine, 5 mg, taken once daily in the evening for 14 days significantly improved the sum of 5 common naso-ocular symptoms in this US population of patients with SAR. In addition, levocetirizine compared with placebo had a favorable impact on patients' HRQOL, work productivity, and daily functioning and even appeared to reduce daytime sleepiness as measured by

the ESS. The results of this study indicate that levocetirizine, 5 mg/d, is well tolerated and constitutes an effective choice for once-daily treatment of SAR symptoms in US adults.

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