

Fexofenadine Improves the Quality of Life and Work Productivity in Japanese Patients with Seasonal Allergic Rhinitis during the Peak Cedar Pollinosis Season

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Key Words

Fexofenadine · Japanese cedar pollinosis · Quality of life · Seasonal allergic rhinitis · Work productivity

Abstract

Background: Although currently in its infancy, quality of life (QOL) research in Japan is rapidly expanding and is expected to become a standard outcome measure in clinical trials. In Japan, QOL has not previously been assessed in patients with allergic rhinitis (AR); we report the first clinical study applying the recently validated Japanese translations of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) Questionnaire to assess the effects of the oral antihistamine, fexofenadine, on QOL and work productivity due to cedar pollinosis. **Patients and Methods:** A randomized, double-blind, placebo-controlled, single-site study was conducted during the peak cedar pollinosis season in Japan. After a 7-day run-in period, subjects were randomized to receive fexofenadine HCl 60 mg twice daily (bid) or placebo for 2 weeks. **Results:** Overall, 206 Japanese subjects with AR were included in the intention-to-

treat population (fexofenadine, n = 104, and placebo, n = 102). Fexofenadine statistically significantly improved overall QOL compared with placebo (p = 0.005) and improvements were reported in the RQLQ domains: activities (p = 0.047), practical problems (p = 0.003), nasal symptoms (p = 0.003) and eye symptoms (p ≤ 0.001). Clinically significant improvements in practical problems, eye symptoms and activity limitations, exceeding the 0.05 level, were observed with fexofenadine. These improvements in QOL were associated with significant symptom relief (p < 0.001 vs. placebo). Improvements in impairment at work were also reported with fexofenadine. **Conclusion:** In Japan, this is the first clinical study to show that fexofenadine HCl (60 mg b.i.d.) improves overall QOL and work productivity in patients with seasonal AR using validated Japanese instruments.

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Introduction

Allergic rhinitis (AR) is a very common disorder with a reported prevalence of 10–20% in Japan [1]. Japanese cedar (*Cryptomeria japonica*) pollen is the most common and potent seasonal allergen in Japan causing allergic pollinosis. The prevalence of cedar pollinosis is estimated to be approximately 12 or 13% in the Japanese population

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[2]. Although AR is not a life-threatening illness, the clinical symptoms associated with AR can significantly disrupt patients' quality of life (QOL) and impair daily living activities such as work productivity or school performance [3, 4]. Given the burden of the symptoms of AR on patients' well-being, effective treatments should improve patients' QOL, and QOL should be included as an outcome measure in clinical trials assessing the overall effectiveness of treatment.

In Japan, QOL research is in its infancy, however, it is rapidly expanding and may soon be adopted as an outcome measure for clinical trials assessing the overall effectiveness of treatments for AR. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) Questionnaire, originally developed in English, measure the impact of AR symptoms on QOL and patient productivity [5–7]. For use in different ethnic populations, cross-cultural validation of the translated questionnaires is required; therefore the RQLQ and WPAI-AS Questionnaires were translated into Japanese and validated for use in a Japanese population [8, 9].

The mainstay of treatment for Japanese patients with AR is oral antihistamines [10]. These agents have been shown to effectively relieve the clinical symptoms of AR such as sneezing; itchy nose, palate and/or throat; rhinorrhea, and itchy, watery and/or red eyes. Fexofenadine is a potent, selective, non-sedating, H_1 -receptor antagonist with proven efficacy in the relief of clinical symptoms of AR, including nasal congestion [11–18]. In addition to its anti-allergic effects, fexofenadine has anti-inflammatory properties at clinically relevant concentrations [19–21]. Furthermore, health outcome studies have shown that fexofenadine HCl 60 mg twice daily (b.i.d.) significantly improves patient-reported QOL and decreases work impairment [22]; however, these studies have not been performed in Japan where problems from cedar pollinosis are significant.

Here we present results from the first study assessing the effect of fexofenadine HCl 60 mg b.i.d. on QOL and work/school productivity in Japanese patients with seasonal AR (SAR), using the recently validated translations of the RQLQ and WPAI-AS Questionnaires.

Patients and Methods

Study Population

The study population consisted of male and female SAR subjects, aged 20–55 years. For study participation, subjects had to demonstrate a positive Japanese cedar-pollen-specific IgE test (> class 2

severity), have cedar pollinosis symptoms for 2 or more years and reside within the urban area of Tokyo (to ensure equivalent exposure to pollen). Subjects were also required to have a total symptom score (TSS; sneezing, nasal discharge, nasal blockage and itching eyes) >4 with two or more individual symptoms rated higher than moderate on the 1st day of study treatment.

Subjects were excluded from the study if they had experienced symptoms before the beginning of the Japanese cedar pollinosis season, had complications of nasal disease (perennial allergic nasal disease, vasomotor rhinitis, acute or chronic non-allergic rhinitis, acute/chronic sinusitis, or infective rhinosinusitis, infective rhinitis), were traveling abroad during the study period or were deemed ineligible for participation by the investigator (due to cognitive impairment, for example).

Study Design

This was a randomized, double-blind, placebo-controlled study that was conducted at the Waseda Clinic in Tokyo, Japan. The study consisted of an initial screening visit, a 7-day run-in period and a 14-day treatment period (fig. 1).

Upon completion of the run-in period, subjects were randomly assigned to receive either oral fexofenadine HCl 60 mg b.i.d. or placebo b.i.d. for 14 days. Subjects were instructed to take their study treatment in the morning and evening. At the clinic, all subjects were required to complete the Japanese versions of RQLQ and WPAI-AS Questionnaires during the run-in period, on the 1st day of study drug administration and after 2 weeks of study treatment.

The study was designed and monitored in accordance with the principles of Good Clinical Practice, as set out in the Declaration of Helsinki and its amendments. Written informed consent was obtained from all study participants. Ethical approval was obtained from the institutional review board of the participating center.

Study Instruments

Quality of life was assessed using the Japanese version of the RQLQ, which measures the effects of AR symptoms on seven domains: activities, sleep, no nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional function. Each question was scored using a 7-point scale (0 = not troubled to 6 = extremely troubled). Domain scores were expressed as a mean of all items within the domain, and the overall RQLQ score was calculated by taking the mean across all items. A change in RQLQ domain scores >0.50 was interpreted as a clinically meaningful minimally important difference [23]. Performance impairment due to allergy symptoms was assessed using the Japanese translation of the WPAI-AS instrument, which has been validated to measure generic and allergy-specific performance impairment in work and classroom productivity and regular activity [9]. WPAI-AS scores were expressed as impairment percentages and scores ranging from 0 to 100%, with higher scores reflecting greater impairment and greater loss of productivity.

Outcomes

The primary outcome measure was the change from baseline in the overall QOL score over the entire 2-week treatment period. Secondary outcomes were the change from baseline in each of the seven RQLQ domains, and WPAI-AS scores including percent work/classroom impairment, percent work/classroom time missed due to AR symptoms, overall work/classroom impairment and regular daily activity impairment.

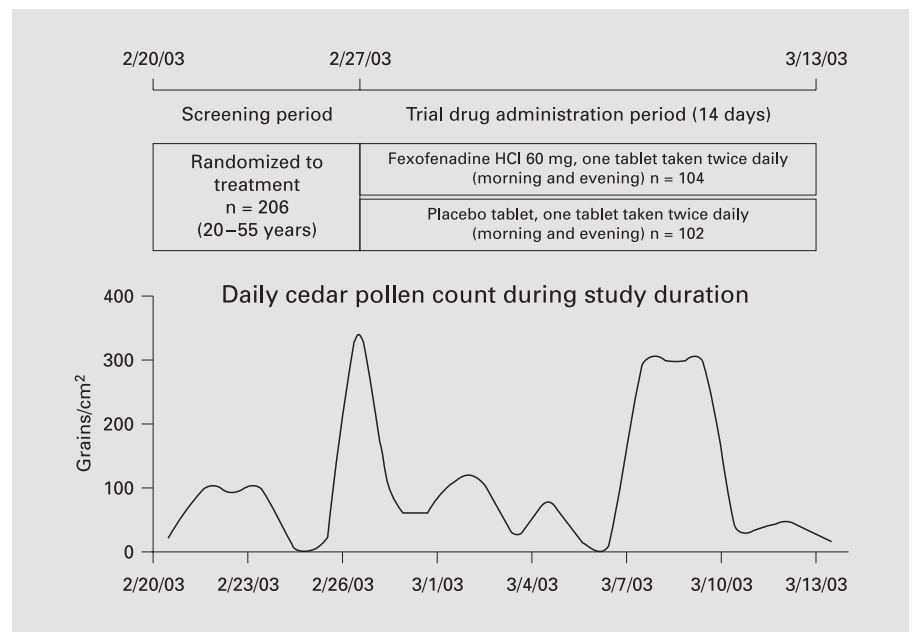


Fig. 1. Study design.

Symptom Assessments

Throughout the run-in and treatment periods, subjects completed symptom diaries to subjectively rate the severity of their individual allergy symptoms. The TSS was defined as the sum of the five individual symptom scores: (1) sneezing; (2) nasal discharge; (3) nasal blockage; (4) itchy eyes, and (5) watery eyes. Patients assessed each symptom using a five-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe, and 4 = very severe. The baseline TSS was calculated as the mean of the daily TSS scores during the run-in period, and the treatment TSS was calculated as the mean of the daily TSS scores during the treatment period.

Statistical Analysis

The study was powered (90%) to detect a 0.5-point difference in the overall QOL score of the RQLQ compared to baseline, at a 5% significance level, assuming a standard deviation of 1.23. A sample size of 258 subjects was required for the study. Analyses were performed on the intention-to-treat (ITT) population, which comprised those subjects who received at least one dose of study treatment and completed a baseline assessment and at least one other valid QOL assessment.

The statistical analysis focused on assessing significant differences between fexofenadine HCl 60 mg b.i.d. and placebo b.i.d. in the RQLQ and the WPAI-AS scores using general linear models, adjusting for covariates, at a significance level of 0.05. Secondary statistical analyses evaluated improvements in the individual scale scores of the RQLQ and WPAI-AS during treatment using general linear models. Changes in TSS were analyzed using a t test with significance declared at the 0.05 level.

Results

Baseline Characteristics

A total of 250 subjects were screened and 210 were randomized to receive treatment during the peak cedar pollinosis season (February and March 2003). The mean cedar pollen count during the entire study duration was 101.2 grains/cm² (maximum = 295.1 grains/cm², minimum = 4.3 grains/cm²; fig. 1).

Of the 210 subjects randomized, 3 subjects did not complete any health-related QOL questionnaire, and 1 subject received rescue medication, and they were, therefore, not included in the analysis presented here. Overall, 206 subjects were included in the ITT population; 104 subjects in the fexofenadine HCl 60 mg b.i.d. group, and 102 subjects in the placebo group. All 206 randomized subjects completed the 2-week study period.

There were no differences between the two treatment groups for demographic characteristics (table 1). The mean age of the patients in the fexofenadine group was 32.7 years versus 34.3 years in the placebo group. The majority of patients were male (60% fexofenadine; 57% placebo), most were working (76% fexofenadine; 87% placebo) and few were taking classes (18% fexofenadine; 15% placebo).

Baseline RQLQ scores were comparable between the two treatment groups (table 2). The mean overall QOL score was 1.8, showing that patients were troubled by AR

symptoms. Individual RQLQ domain scores at baseline indicated that patients were less troubled by their symptoms during sleep and more troubled in practical problems, activities and nasal symptom domains.

Using the WPAI-AS Questionnaire, all subjects reported high levels of activity impairment (42.4% fexofenadine; 39.0% placebo) at baseline (table 2). Similarly, overall work impairment (39.5% fexofenadine; 36.7% placebo), impairment while working (39.1% fexofenadine; 36.6% placebo) and overall classroom impairment (33.0% fexofenadine; 31.4% placebo) levels were high (table 2).

Table 1. Baseline characteristics by treatment group (ITT population)

Characteristics		Fexofenadine HCl 60 mg b.i.d. n = 104	Placebo n = 102
Age, years (mean $\pm$ SD)		32.7 $\pm$ 9.8	34.3 $\pm$ 9.9
<i>Patients</i>			
Gender	Male	62 (60%)	58 (57%)
	Female	42 (40%)	44 (43%)
Working	Yes	79 (76%)	89 (87%)
	No	25 (24%)	13 (13%)
Taking classes	Yes	19 (18%)	15 (15%)
	No	85 (82%)	87 (85%)

Table 2. RQLQ and WPAI-AS scores at baseline (%; ITT population)

	Fexofenadine HCl 60 mg b.i.d.		Placebo	
	mean $\pm$ SD	n	mean $\pm$ SD	n
Overall QOL	1.8 $\pm$ 1.0	104	1.8 $\pm$ 1.0	102
Activities	2.3 $\pm$ 1.2	103	2.2 $\pm$ 1.1	102
Sleep	1.0 $\pm$ 1.0	104	1.0 $\pm$ 1.1	102
No nose/eye symptoms	1.4 $\pm$ 1.2	104	1.4 $\pm$ 1.1	102
Practical problems	2.7 $\pm$ 1.3	104	2.7 $\pm$ 1.3	102
Nasal symptoms	2.3 $\pm$ 1.1	104	2.2 $\pm$ 1.3	102
Eye symptoms	1.8 $\pm$ 1.3	104	1.8 $\pm$ 1.1	102
Emotional function	1.6 $\pm$ 1.3	104	1.7 $\pm$ 1.1	102
Activity impairment	42.4 $\pm$ 26.9	104	39.0 $\pm$ 23.4	102
Work time missed	1.1 $\pm$ 4.5	79	0.3 $\pm$ 1.7	89
Impairment at work	39.1 $\pm$ 27.6	79	36.6 $\pm$ 25.8	89
Overall work impairment	39.4 $\pm$ 27.9	79	36.7 $\pm$ 25.9	89
Class time missed	3.1 $\pm$ 8.1	18	0.0 $\pm$ 0.0	15
Classroom impairment	29.4 $\pm$ 26.8	19	31.4 $\pm$ 32.8	14
Overall classroom impairment	33.0 $\pm$ 26.9	18	31.4 $\pm$ 32.8	14

Outcomes

Quality of Life. Fexofenadine HCl 60 mg b.i.d. was statistically superior to placebo in improving overall QOL in Japanese subjects with SAR ($p = 0.005$). Figure 2 shows mean changes from baseline in overall QOL scores in the fexofenadine HCl group compared with placebo at the end of the 2-week study treatment period. Additionally, the fexofenadine group reported significantly greater improvements than the placebo group for four of the seven RQLQ domains: activities ($p = 0.047$), practical problems ($p = 0.003$), nasal symptoms ($p = 0.003$) and eye symptoms ($p \leq 0.001$). Furthermore, significant improvements in practical problems, eye symptoms and activity limitations, exceeding the levels considered to reflect clinically important changes (>0.5) [23], were also observed in the fexofenadine group (table 3).

Impairment (WPAI-AS). Fexofenadine HCl also resulted in statistically significant improvements in 'impairment at work' due to allergy symptoms over the entire 2-week treatment period. Overall work impairment decreased by 5.5% in the fexofenadine group, which was significantly different to the 3.4% increase in the placebo group ($p = 0.016$; fig. 3). In addition, 'impairment while working' due to allergy symptoms significantly decreased by 5.6% in the fexofenadine group and increased by 3.2% in the placebo group ($p = 0.019$). There were no significant differences between the two treatment groups for the percentage of work time missed. The activity impairment scores in the fexofenadine group demonstrated significant

Fig. 2. Changes in overall RQLQ and individual RQLQ domains (baseline vs. study end). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.0001$, vs. placebo.

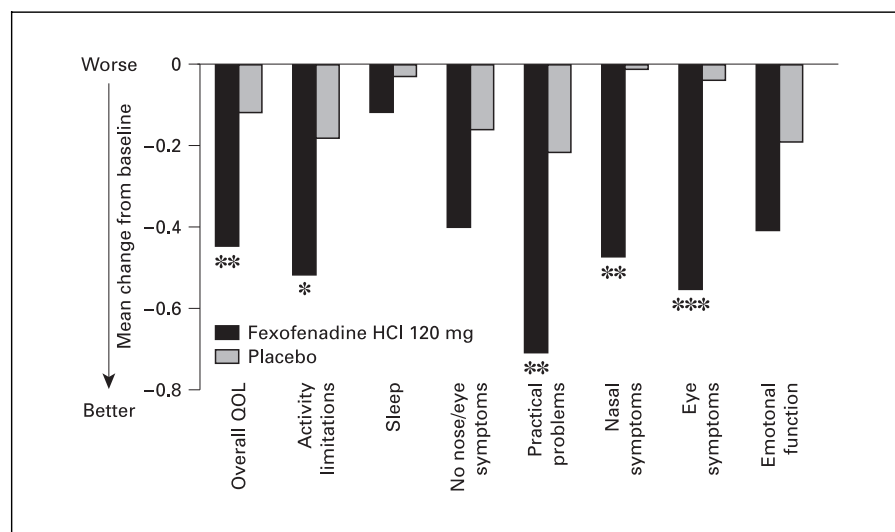
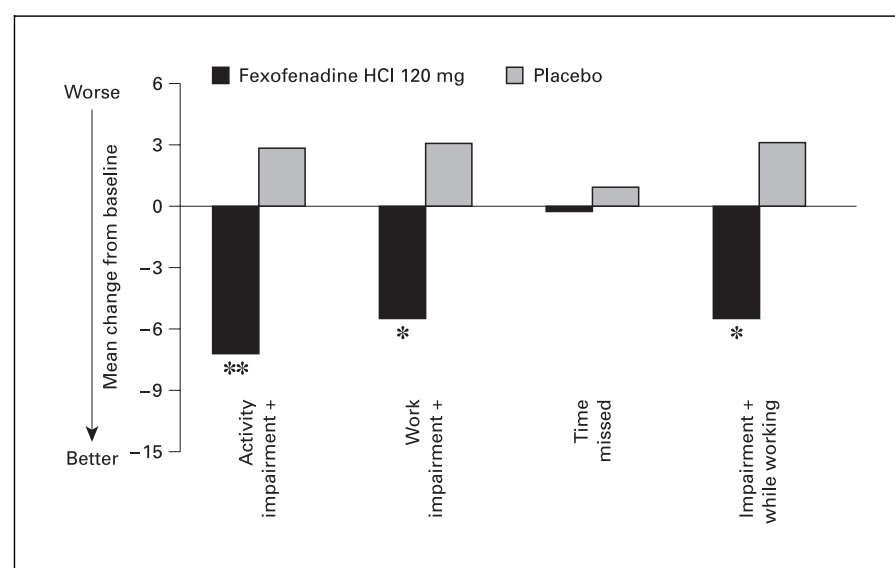


Fig. 3. Changes in work and activity impairment (baseline vs. study end). * $p \leq 0.05$, ** $p \leq 0.01$, vs. placebo.



reductions compared with the placebo group ($p = 0.0027$), since in the placebo group increases in impairment were observed. Concerning overall classroom impairment, there were no significant differences between fexofenadine and placebo.

Symptom Severity. The baseline TSS was comparable between the two treatment groups: 6.6 and 6.9 for the fexofenadine and placebo groups, respectively. At the end of the treatment period, subjects in the fexofenadine group reported significantly greater reductions in their TSS than those receiving placebo (end of treatment TSS: 6.1 vs. 7.7 for fexofenadine and placebo, respectively; $p < 0.001$).

Table 3. Mean change in scores from baseline for RQLQ domains (ITT population)

RQLQ domains	Fexofenadine HCl 60 mg b.i.d., n = 104	Placebo n = 102	p
Activities	-0.52	-0.18	0.0467
Sleep	-0.12	-0.03	–
No nose/eye symptoms	-0.40	-0.16	–
Practical problems	-0.72	-0.22	0.0034
Nasal symptoms	-0.48	-0.01	0.0032
Eye symptoms	-0.56	-0.04	0.0006
Emotional function	-0.41	-0.19	–
Overall QOL	-0.45	-0.12	0.0052

Discussion

In Japan, Japanese cedar (*C. japonica*) pollen is the most common and potent seasonal allergen causing allergic pollinosis with a prevalence of approximately 12 or 13% in the Japanese population [2]. In addition to controlling the bothersome clinical symptoms of AR such as itching, sneezing, runny nose and watery red eyes, effective antihistamine therapy should also result in improvements in patients' QOL and allow them to perform normal daily activities. We report here the first clinical study to use the validated Japanese translations of the RQLQ and WPAI-AS in Japan to demonstrate improvements in QOL and work productivity in patients with cedar pollinosis with a newer-generation antihistamine.

The findings presented here demonstrate that fexofenadine HCl 60 mg b.i.d. statistically significantly improved the overall QOL in Japanese subjects with SAR compared with placebo during the 2-week treatment period. Although statistically significant changes were observed in all RQLQ domains, clinically relevant changes were reported in several domains. Fexofenadine-treated subjects experienced improvements in the baseline symptoms (bothersome), practical problems, eye symptoms and activity limitations, exceeding the levels considered to reflect clinically important changes (>0.5) [23]. Furthermore, the improvement in QOL was associated with significant symptom relief in the fexofenadine treatment group.

Allergic rhinitis is a condition that induces work absenteeism and a reduction in work productivity. Importantly, it has been reported that the use of sedating antihistamines causes a further decrease in work productivity [24]. Although this was a small study, the results presented here demonstrate that fexofenadine is associated with improved patient function as shown by statistically significant reductions in impairment scores due to allergy in daily activities and at work. In the placebo group, the overall scores increased from baseline for work-related impairment items, suggesting that work productivity continued to decline over the 2-week placebo treatment period. These findings suggest that fexofenadine may reduce indirect health care costs by increasing work productivity; therefore, it may be a cost-effective therapy. In Japan in 2004, given an average working day of 8 h on an hourly wage of 2,000 yen [25] and that the difference reported here in overall work impairment between the two treatment groups was 8.9%, these findings could be translated into a saving of approximately 1,420 yen/day. In a month, this would be equivalent to 28,400 yen or almost

USD 260, based on the assumption that there are 20 working days per month. However, cost-effectiveness studies are warranted to further assess these benefits.

The results discussed here are consistent with those previously published, in which fexofenadine statistically significantly improved QOL in patients with SAR and chronic idiopathic urticaria [13, 22, 26, 27]. For example, Tanner et al. [22] assessed the impact of fexofenadine HCl 60 mg b.i.d. on patients' QOL in a pooled analysis of two placebo-controlled trials in patients with SAR. Statistically significant ($p \leq 0.05$) improvements in overall RQLQ scores were reported for patients receiving fexofenadine HCl 60 mg b.i.d. compared with placebo [22]. In a more recent study, van Cauwenberge et al. [13] assessed the impact on patients' QOL following once-daily administration of fexofenadine HCl 120 mg, loratadine 10 mg or placebo in the treatment of SAR. A total of 509 patients aged 12–75 years completed the QOL assessment (RQLQ). For all treatment groups (fexofenadine, loratadine and placebo), there was a statistically significant improvement in overall QOL compared to baseline ($p < 0.0001$); however, the improvement in the fexofenadine group was significantly greater than that obtained in both loratadine ($p \leq 0.03$) and placebo groups ($p \leq 0.005$). In addition, fexofenadine was statistically significantly better than both loratadine and placebo in reducing overall mean 24-hour reflective symptom scores for itchy, watery or red eyes and nasal congestion from baseline ($p \leq 0.05$), whereas loratadine was not different from placebo on these two symptom scores [13]. Furthermore, in patients with chronic idiopathic urticaria, fexofenadine HCl 60 mg b.i.d. statistically significantly improved overall QOL compared with placebo, as assessed using the Dermatology Life Quality Index Questionnaire [26]. These results corroborate the findings presented here with fexofenadine improving overall QOL in Japanese subjects with SAR.

Although changes in classroom impairment measures were not statistically significant compared with those at work, the relatively small population of students included in this study may explain these findings. Further studies are, therefore, needed in larger adolescent/student populations to assess improvements in classroom activities. However, it has previously been shown that fexofenadine treatment is associated with statistically significant improvements in the percentage of classroom time missed and classroom impairment ($p < 0.05$) [22].

In Japan, QOL has not previously been assessed in patients with AR and this is the first clinical study to demonstrate the usefulness of the recently translated and validated RQLQ and WPAI-AS instruments in assessing

QOL in a Japanese patient population with SAR during the peak cedar pollinosis season. The RQLQ and WPAI-AS instruments are well-established tools for assessing QOL as an outcome measure in clinical trials in the United States of America and Europe [5–7]. Both Questionnaires were recently translated and validated for use in a Japanese population, as QOL measurements will soon be adopted as an outcome measure for clinical trials [9]. The results presented here support the use of the Japa-

nese versions of RQLQ and WPAI-AS Questionnaires for assessing the impact of SAR symptoms on QOL and work productivity in Japan.

In conclusion, this is the first clinical study to show that fexofenadine HCl 60 mg b.i.d. improves overall QOL and work productivity in Japanese patients with SAR during the peak cedar pollinosis season, using the recently validated RQLQ and WPAI-AS Japanese instruments.

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