

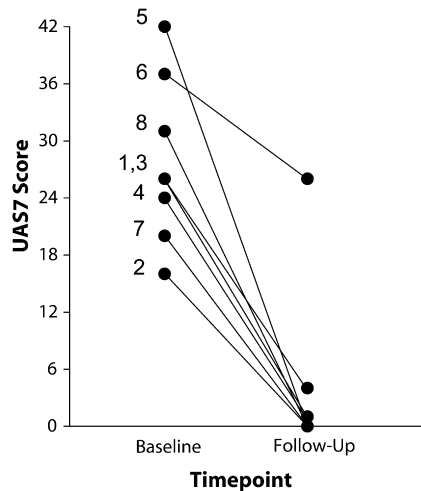


FIG 1. Response of patients (numbers from 1-8) to omalizumab therapy.

double-blind, cross-over, comparative effectiveness trials¹¹ are still needed to determine whether omalizumab works better than third-line and other fourth-line treatment options. Such research could possibly provide a sound scientific basis for promoting omalizumab to the level of a third-line recommendation in future evidence-based treatment guidelines.

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Uncontrolled allergic rhinitis during treatment and its impact on quality of life: A cluster randomized trial

To the Editor:

The treatment of allergic rhinitis is now well established. Although the majority of patients present with controlled symptoms during treatment, many are still uncontrolled, leading to the concept of severe chronic upper airway disease (SCUAD).¹ Patients with SCUAD are likely to have an impaired quality of life affecting social functioning, sleep, school results, and/or work performance. However, this concept requires validation.

As a pilot study to investigate SCUAD, the prevalence of uncontrolled rhinitis after 2 weeks of treatment and its impact on quality of life and work productivity were assessed on the basis of a *post hoc* analysis carried out from a published pragmatic, cluster-randomized trial.²

Methods have been described² and are summarized in this article's Online Repository at www.jacionline.org. For the treatment of patients with allergic rhinitis during the grass pollen season, allergy or ears, nose and throat specialists were randomized to follow a strategy based on Allergic Rhinitis and its Impact on Asthma (ARIA)³ or free-choice treatment, according to their practice. The study was performed in France.

Outcomes included a Rhinitis Total Symptom Score (RTSS4: nasal obstruction, pruritus, sneezing, and rhinorrhea) monitored daily for 14 days using a diary. The self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; 28 questions),⁴ the Allergy-Specific Work Productivity and Impairment questionnaire (WPAI-AS),⁵ and a visual analog scale (VAS) for the global evaluation of rhinitis⁶ were measured at baseline and after 14 days of treatment. Ocular symptoms were assessed both by questionnaire and the RQLQ eye symptom domain (E-RQLQ).

An *a priori* definition of SCUAD was used: a VAS level for the global evaluation of rhinitis ≥ 5 cm (0-10 cm scale) and/or severe ocular symptoms defined by the occurrence of ocular symptoms in the diary and RQLQ (E-RQLQ ≥ 2.5 , cutoff level at the 75th percentile of E-RQLQ).

The only patients considered for the analysis were those who completed the evaluation of all of the outcomes at baseline and after treatment. Because data were not normally distributed after treatment, medians 25th to 75th percentiles and nonparametric tests were used.

Patients were recruited between March 8 and July 15, 2002. A total of 399 physicians enrolled 796 patients. Two hundred ten patients (26.4%) were excluded from the analysis (see this article's Fig E1 in the Online Repository at www.jacionline.org).

At baseline, characteristics of the patients were similar and not clinically different between treatment groups (see this article's Table E1 in the Online Repository at www.jacionline.org). Most of the patients at baseline presented with moderate/severe allergic rhinitis as defined by ARIA (see this article's Fig E2 in the Online Repository at www.jacionline.org). Individual outcomes were normally distributed at baseline and skewed after treatment.

After treatment, symptom scores were reduced, and quality of life and productivity were improved. The differences between free-choice treatment and ARIA appear to be small, even if significantly different (see this article's Table E2 in the Online Repository at www.jacionline.org).

Eighty-two patients presented a VAS ≥ 5 cm, 52 (18.1%) in the free-choice treatment and 30 (10.3%) in the ARIA-based strategy. Patients with bothersome eye symptoms (ocular symptoms and E-RQLQ ≥ 2.5) corresponded respectively to 9.1% (26) and 9.0% (27). Overall, 111 (18.9%) patients presented an uncontrolled rhinitis after treatment (VAS ≥ 5 cm and/or bothersome eye symptoms): 58 with a VAS ≥ 5 cm, 29 with an E-RQLQ ≥ 2.5 , and 24 with both VAS ≥ 5 cm and E-RQLQ ≥ 2.5 . At baseline, patients in the SCUAD group were slightly younger ($P = .04$), but there were no differences in sex, tobacco-smoking habits, or asthma. They did not have more severe disease at baseline than controlled patients.

In the current study, it was found that SCUAD, a newly described phenotype of allergic rhinitis,¹ is present in around 10% to 20% of patients with allergic rhinitis. Patients with SCUAD present uncontrolled nasal and/or ocular symptoms and an impaired quality of life and work performance.

We used a cluster-randomized trial aiming to mimic real life. There was no exclusion of patients at randomization, as is often the case in clinical trials, because we wanted to study the whole range of patients regularly seen by physicians. Although the treatment was administered by specialists, it was found that the ARIA-based strategy was more effective than the free-choice treatment.²

Some limitations may exist in this article. Many methods assess the efficacy of a treatment for allergic rhinitis, but in outpatient clinics, there is no validated objective test.⁷ Symptom scores and quality of life measurements have been used. These 2 methods assess the different characteristics of the patients. The VAS is a technique used to measure subjective phenomena, and changes in VAS within patients are more appropriate for study purposes than single measurements. This is why, in the current study, we used a cutoff level (≥ 5 cm) probably greater than needed to characterize uncontrolled rhinitis. In a recent article in the same population, we found that a cutoff level of 3 cm was sufficient when the VAS was measured at 2 intervals. There was no validated ocular symptom outcome, so we selected E-RQLQ in patients with ocular symptoms reported in a diary. The cutoff level was set at the 75th percentile.

In asthma, control is a key outcome, independent of asthma medications. A similar independent relationship was proposed in allergic rhinitis.¹ However, this concept had never been defined in a study. In this study, it has been shown that the SCUAD phenotype is a common problem, as suspected in clinical practice. SCUAD should apply only to patients who, despite adequate treatment, are still uncontrolled. It was found that SCUAD was present in around 10% to 20% of these patients when VAS and ocular symptoms were considered.

Impact on quality of life and work productivity is highly relevant in SCUAD. Although improved by comparison to pretreatment, patients with SCUAD had a significantly impaired quality of life (median RQLQ before treatment and during treatment, 2.77 and 2.04, respectively) whereas the median RQLQ of controlled patients was 0.58. Moreover, all RQLQ domains were significantly altered in SCUAD when compared with controlled patients. Similar results were observed for work productivity.

Patients with SCUAD require a more effective treatment since their quality of life and work productivity remain impaired. They may be ideal candidates for specific immunotherapy or novel treatments yet to be developed. Because the current study is a *post hoc* analysis, further studies are needed to confirm the concept.

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How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint

To the Editor:

Adherence to prescriptions is crucial for all long-term treatments,¹ and this is true also for sublingual immunotherapy (SLIT), which is self-managed at home by the patients themselves. In fact, in the case of SLIT, medical supervision is usually limited to control visits or to prescription renewals. Available postmarketing studies indicate that the compliance with SLIT ranges from 50% to 95%, depending on age and on duration of treatment.² Nonetheless, the postmarketing surveys on compliance have an inherent limitation in that the observation itself can distort the results to some extent. In other words, when patients are aware that their compliance with treatment is recorded, they tend to be more adherent. Moreover, those studies assessed the adherence over limited periods, whereas SLIT should be continued for at least 3 years, according to recommendations. In everyday clinical practice, the general perception is that a large proportion of patients discontinues the prescribed SLIT, and this usually happens within the first year.

To address this latter aspect better, and to quantify the rate of discontinuations in real life, we collected the Italian sales figures from 2 large manufacturers (Stallergenes Italy, Milan, and ALK-Abelló Italy, Lainate, Milan), who kindly provided their data subdivided as per the 20 Italian administrative regions. It is to be noted that these manufactures account for more than 60% of the Italian immunotherapy market. To assess the discontinuation rates over at least 3 years, we counted, in cooperation with manufacturers' personnel, the number of SLIT treatments sold in 2006 as first prescriptions, and how many of the same SLIT prescriptions were still prescribed as renewals in the subsequent years, until 2009. This could be done easily because in Italy SLIT is a named patient product, and each treatment sold can be tracked. The figures were provided as percentages, with the initial sales in 2006 the 100% baseline. The data of the 2 manufacturers were analyzed pooled together, and subdivided per administrative region, per allergen (pollen/mite), and per modality of reimbursement.

The sales decreased from 100% to 43.7% $\pm$ 8% in the first year, to 27.7% $\pm$ 10.1% in the second year, and to 13.2% $\pm$ 7.5% in the third year. This means that, out of all the prescribed SLITs, less than 20% were continued after 3 years. No difference was detected between the 2 manufacturers in any of the 3 years (*t* test *P* > .1), and the results were consistent across the 20 administrative regions of Italy, where the figures ranged between 60% and 28% in the first year, 47% and 29% in the second year, and 16% and 6% in the third year. Of note, the lowest discontinuation rate was in the northern region Valle d'Aosta, with 60%, 47%, and 26% continuing treatment in the 3 years, respectively. The highest discontinuation rate was found in the southern region of Campania, with 28%, 17%, and 6% continuing treatment in the first, second, and third years, respectively.

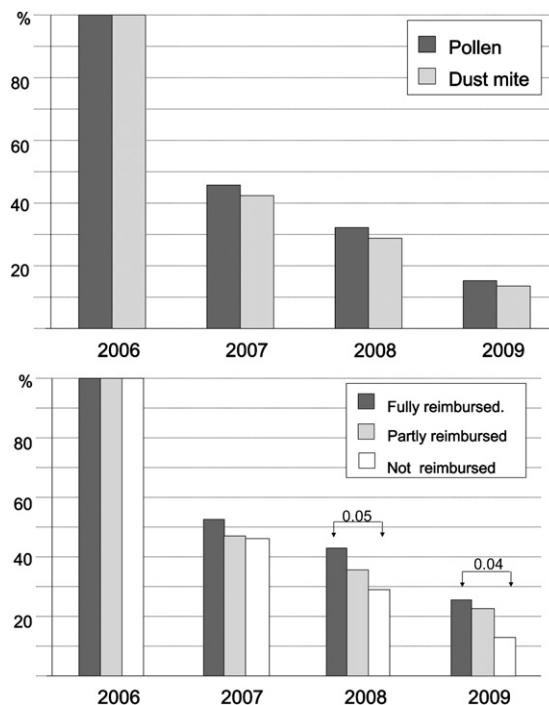


FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. *Upper panel*, Percentages for pollens and house dust mite SLITs. *Lower panel*, Percentages according to the reimbursement modality. Significant *P* values are indicated above the bars.

Some of the patients had more than 1 SLIT prescription, but none of them discontinued a single treatment only; thus, the percentages were unaffected. There was no difference between SLIT for pollens and SLIT for house dust mite, as shown in the *upper panel* of Fig 1; thus, the regimen of administration (preseasonal or continuous) does not seem to play a relevant role in the discontinuation rate. Surprisingly, the discontinuation rate was only marginally influenced by the modality of reimbursement, and a similar progressive decrease was seen in the Italian regions with full reimbursement, partial reimbursement, or no reimbursement at all (*lower panel*, Fig 1). Only in the second and third years, the difference between the regions with full reimbursement and no reimbursement became significant (*P* < .05).

Adherence to SLIT as assessed in postmarketing surveys is reported to be quite high,² reaching 95% of the prescribed doses in some cases.³ Nonetheless, these optimistic results do not fully reflect what happens in real life. In fact, the general perception of clinical allergists is that many patients discontinue their SLIT treatment and do not complete its 3-year course. The assessment of manufacturers' sales seemed to be a quite reliable approach for quantifying the phenomenon. Thus, we calculated the rate of spontaneous discontinuations by assessing the sales data of 2 large manufacturers in Italy over a 3-year period. According to these data, after 1 year from the prescription, only about 50% of the treatments were ongoing, and this percentage fell to almost 15% at 3 years. This behavior was consistent across the entire territory and identical for the 2 manufacturers. Certainly in such a survey, it was not possible to identify the reasons for discontinuation of SLIT treatments, although no discontinuation for severe adverse events was reported by the 2 producers. Among the reasons for discontinuing SLIT, the cost would be considered one

METHODS

Interventions

This investigator cluster-randomized, multicenter, multinational, open-label, parallel study compared 2 therapeutic strategies in allergic rhinitis during a 2-week treatment period. Allergy, ears, nose, and throat and chest specialists practicing in all regions of France were randomized into 2 groups and were to enroll 2 patients only. Each physician recruited the first 2 patients who, during the grass pollen season, suffered from allergic rhinitis due to pollen allergy. Physicians from the first group enrolled patients and followed a simple strategy based on the ARIA guidelines^{E1} using a VAS level to assess severity. Patients with a VAS level ≥ 5 cm (scale, 0–10 cm) were considered as having moderate to severe rhinitis.^{E2} Physicians from the second group (free-choice treatment group) enrolled patients and treated them as usual in normal practice. The investigators assigned to the free-choice treatment group were not instructed to use the results of the VAS. Only depot corticosteroids were disallowed.

Participants

Patients were included in the study after approval of the protocol by the Ethics Committee of Montpellier, France, and after written informed consent was obtained. All patients fulfilled the following inclusion criteria: (1) a history of allergic rhinitis for at least 2 years^{E3} during the grass pollen season, (2) a diagnosis of grass pollen allergy using skin prick tests and/or serum grass pollen-specific IgE (Pharmacia CAP System), and (3) no concomitant treatment. None of the patients were excluded for comorbidity.

Outcomes

Outcomes included an RTSS4 monitored daily using a diary,^{E4} the disease-specific RQLQ (28 questions),^{E5} the WPAI-AS,^{E6} and VAS for the global evaluation of rhinitis.^{E7} There was no validated ocular symptom outcome. We therefore used ocular symptoms which were assessed both by questionnaire and E-RQLQ. The only patients considered for the analysis were those who completed the evaluation of all outcomes at baseline and after treatment.

Patients were asked to fill in the RQLQ and WPAI-AS questionnaires at baseline and after 14 days of treatment, and to send them back to the central monitoring office. VAS levels were monitored by the physicians before and at the end of the treatment period. Patients were asked to read the text of the VAS and to indicate their perception of the disease, but were not informed about how to use it. However, in the free-choice treatment group, VAS was not used to determine the strategy because it is not used in practice.

Definition of uncontrolled allergic rhinitis

Uncontrolled allergic rhinitis was defined by a VAS level of global assessment of rhinitis and/or ocular symptoms at the end of a 2-week treatment. The VAS was chosen because it has been widely used for the assessment of subjective symptoms such as pain,^{E8} and it is considered to be a robust, sensitive, and reproducible method of expressing severity. Even if the VAS is of most value when looking at change within individuals rather than comparing across a group of individuals at 1 time point,^{E9} the latter comparison is still allowed. That comparison is of interest because the within-group comparisons do not provide information about the control of the disease during treatment, the residual level of impairment not being the end point investigated. In a previous study,^{E7} at a single time point, a cutoff of 5 cm (0–10 cm scale) was able to differentiate mild and moderate/severe allergic rhinitis, as defined by ARIA.^{E1} In the current study, the characterization of patient severity before treatment was made using a VAS level of ≥ 5 cm.^{E2,E10} We therefore used this cutoff level to define uncontrolled rhinitis during treatment.

Ocular symptoms are bothersome for patients,^{E11,E12} and these are the least controlled during pharmacologic treatment.^{E4,E10} In the current study, ocular symptoms were assessed both by questionnaire and E-RQLQ, because used alone, neither of these 2 measurements appeared sufficient for the characterization of uncontrolled symptoms. The questionnaire (“Do you have ocular symptoms? Yes or No”) could not quantify symptoms. Although within-group differences between pretreatment and during treatment are used to assess the significance between quality of life results in randomized trials,^{E5,E13} these do not provide information about the control of the disease during treatment. Moreover, although the minimal clinically-relevant difference for the

global RQLQ score has been tested, the E-RQLQ as a single domain has not been validated. We therefore decided to group answers to both questions and proposed a cutoff level at the 75th percentile of E-RQLQ in patients presenting with ocular symptoms (E-RQLQ ≥ 2.5).

Sample size

Because the current analysis was an exploratory *post hoc* analysis, the sample size was not calculated.

Randomization

Physicians were randomized by computer allocation from the list of French physicians. However, it was ensured that 2 or more physicians working in the same practice group were not randomized to the 2 different strategies as this might have induced a bias. In this case, only the first was enrolled.

Statistical analysis

Qualitative data were expressed in percentages and frequencies. Normality of distributions was studied by using the Kurtosis and Skewness tests. Because distributions were not normal after treatment, medians and 25th to 75th percentiles defined quantitative data. Because the current analysis was part of a larger study, comparisons for the principal patient characteristics at inclusion were carried out between included and nonincluded patients by using χ^2 and Wilcoxon-Mann-Whitney tests, respectively. Comparisons between the first and the second visit were made by using the Wilcoxon paired test. The analysis was performed with SAS version 8.1 (SAS Institute, Cary, NC), with the significance level set at 5% (.05).

Assessment of compliance

Compliance was assessed by query at the end of the posttreatment period. Of the 839 patients considered for analysis of efficacy, 164 (19.5%) missed answering the question, 82 in each treatment group. Six hundred thirty-nine patients (76.2%) declared they were compliant, 312 (74.8%) in the guidelines group and 327 (77.5%) in the free-choice treatment group. Thirty-six (4.3%) declared they were not compliant, 23 (5.5%) and 13 (3.1%) in each group, respectively.

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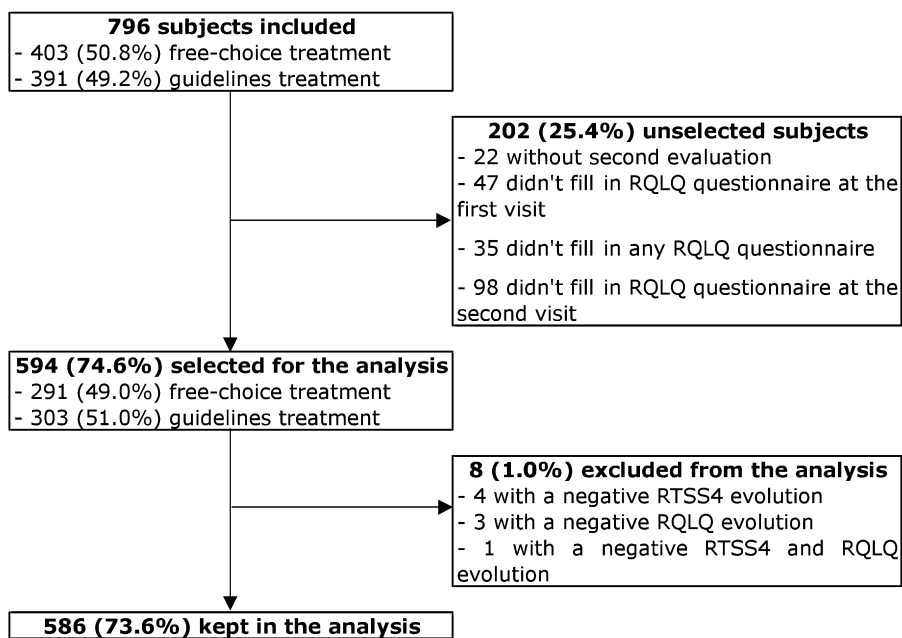


FIG E1. Participant flow.

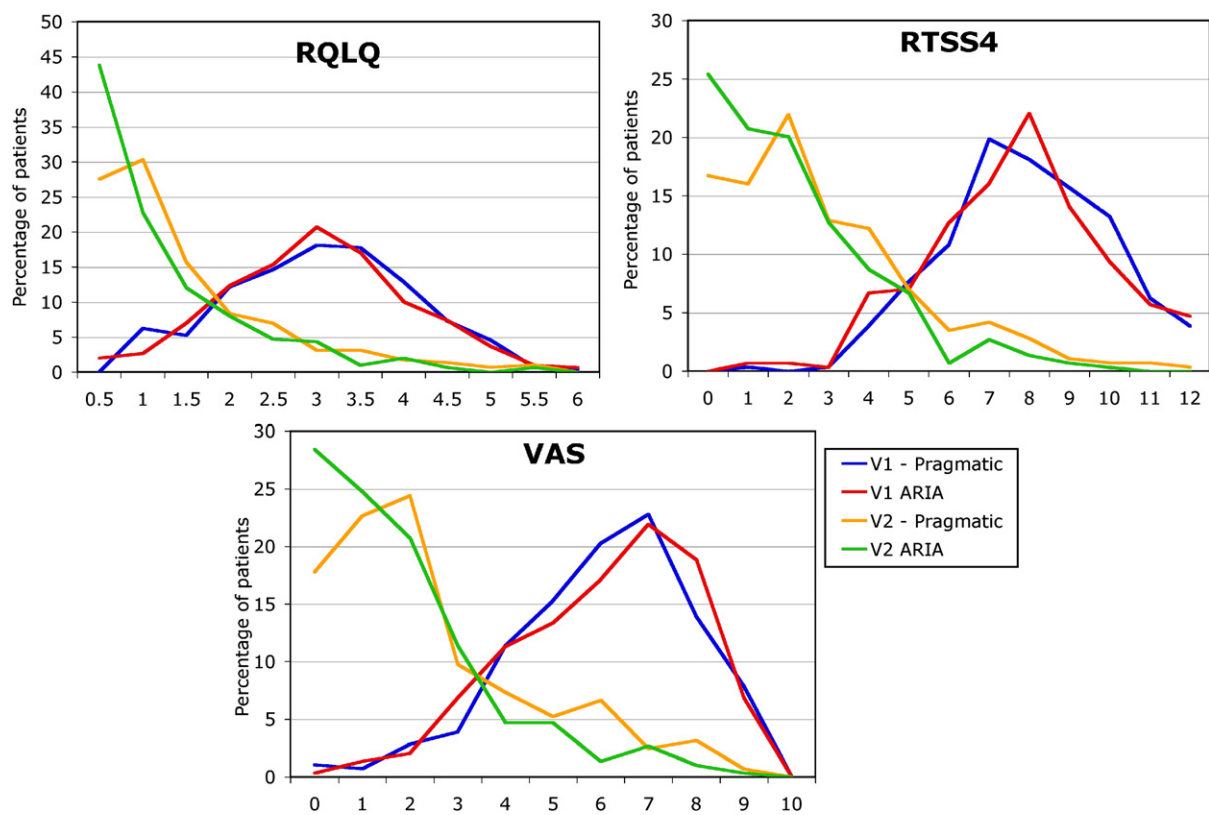


FIG E2. Repartition of patients depending on the strategy. V1, Visit at baseline; V2, visit after 2 weeks of treatment.

TABLE E1. Demographic characteristics

		Free-choice treatment		ARIA-based strategy	
No.		287		299	
Men	%	128	44.6%	129	43.1%
Age (y)		33.5 (24.6-41.9)		35.5 (27.4-43.1)	
Asthma	%	70	24.4%	60	20.1%
Tobacco	no	189	65.8%	192	64.2%

Results are frequencies and percentages or medians and interquartiles.

TABLE E2. Efficacy of the 2 treatment strategies

	Free-choice treatment	ARIA-based strategy
VAS		
V1	6.5 (5.0-7.7)	6.8 (5.0-8.0)
V2	2.0 (1.0-4.0)*	1.7 (0.7-3.0)**
RQLQ global score		
V1	2.8 (2.0-3.5)	2.7 (2.0-3.4)
V2	0.9 (0.4-1.6)*	0.6 (0.3-1.3)**
RTSS4		
V1	8.0 (7.0-9.0)	8.0 (6.0-9.0)
V2	2.0 (1.0-4.0)*	2.0 (0.0-3.0)*
WPAIS-AS—missed productivity at work		
V1	30 (20-50)	30 (20-50)
V2	10 (0-30)*	10 (0-20)**
WPAIS-AS—missed daily activities		
V1	40 (30-60)	40 (30-60)
V2	20 (10-30)*	10 (0-20)**
Eye symptoms		
V1	191 (66.6%)	187 (62.5%)
V2	107 (37.3%)	100 (33.4%)

V1, Visit at baseline; V2, visit after 2 weeks of treatment.

Results are frequencies and percentages or medians and interquartiles.

* $P < .001$ by comparison to V1 (Wilcoxon paired test).

** $P < .001$ by comparison to V1 and $P < .01$ by comparison to free-choice treatment (Wilcoxon-Mann-Whitney test).