

Efficacy of daily intranasal fluticasone propionate on ocular symptoms associated with seasonal allergic rhinitis



Paul Ratner, MD^{*}; Julius Van Bavel, MD[†]; Dale Mohar, MD[‡]; Robert L. Jacobs, MD[§]; Frank Hampel, MD^{||}; William Howland, MD[¶]; and Ritu Karwal, MSc[#]

^{*} Sylvania Research Associates, San Antonio, Texas

[†] Isis Clinical Research, Austin, Texas

[‡] Kerville Research Associates, Kerrville, Texas

[§] Biogenics Research Institute, San Antonio, Texas

^{||} Central Texas Health Research, New Braunfels, Texas

[¶] Sirius Clinical Research, Austin, Texas

[#] GlaxoSmithKline Consumer Healthcare, Parsippany, New Jersey

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ABSTRACT

Background: Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa characterized by symptoms of nasal discharge, itching, sneezing, and congestion. Ocular symptoms are commonly associated with AR and include itching or burning, tearing or watering, and redness. Intranasal corticosteroids are a mainstay of treatment, and their effect on nasal symptoms is well described.

Objective: To demonstrate that a 14-day course of 200 µg/d of nasal fluticasone propionate is superior to placebo in relieving ocular symptoms associated with AR.

Methods: This was a randomized, double-blind, parallel group, multicenter study comparing 200 µg/d of fluticasone propionate with placebo in patients with seasonal allergic rhinitis. The primary end point was mean change from baseline in patient-rated reflective total ocular symptom score (rTOSS). Key secondary end points included mean change from baseline in the morning and evening rTOSS, end-of-treatment assessment of response, and effect on activities of daily living. The primary analysis was performed using analysis of covariance with a linear fixed-effects model.

Results: Fluticasone was statistically significantly more efficacious in reducing the ocular symptoms of AR than placebo. The least squares mean difference in the change from baseline of rTOSS was −0.36 ($P = .002$). A statistically significant difference in mean change from baseline was observed in favor of fluticasone for morning and evening rTOSS. Significantly more patients taking fluticasone achieved an overall response compared with placebo. Fluticasone had a significantly greater effect on daily living activities and was well tolerated.

Conclusion: This study supports the efficacy of fluticasone in treating ocular symptoms associated with AR.

Trial Registration: clinicaltrials.gov Identifier: NCT01817790.

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Introduction

Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa induced by an IgE-mediated response to aeroallergens that is clinically characterized by symptoms of nasal discharge, itching, sneezing, and nasal blockage or congestion.¹ AR can be classified as seasonal AR (SAR), which is caused by an IgE-mediated reaction to seasonal aeroallergens with variable duration of allergen exposure,

or perennial AR, which is caused by an IgE-mediated reaction to perennial aeroallergens.² Ocular symptoms are commonly associated with AR, particularly with SAR, and include intense itching, burning, redness, watering, and eyelid swelling. Studies have found that approximately 40% of patients with AR will have ocular symptoms during their worst month of AR symptoms.^{3,4} More than half of patients surveyed in the Allergies in America study reported ocular manifestations of AR as extremely or moderately bothersome, and these ocular symptoms can have a negative effect on a patient's quality of life, with impairments in mental health and activities of daily living and limitations in social activities.^{3,5}

Intranasal corticosteroids are the most effective class of medications used for the treatment of AR and are the cornerstone of

Reprints: Paul Ratner, MD, 7711 Louis Pasteur Dr, Ste 406, San Antonio, TX 78229; E-mail: pratner@sylvaniaresearch.com.

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pharmacologic therapy.² Fluticasone propionate is a synthetic corticosteroid that is currently approved in the United States for the management of the nasal symptoms of SAR, perennial AR, and non-AR in adults and pediatric patients 4 years or older.⁶ Although the current indication for fluticasone is limited to the treatment of nasal symptoms, several large, well-controlled studies in which fluticasone propionate maintained adequate control of nasal symptoms when administered at a dose of 200 $\mu\text{g}/\text{d}$ also suggested that ocular symptoms were improved with the use of fluticasone.^{7,8} This study was designed to investigate the efficacy of fluticasone on ocular symptoms associated with AR.

Methods

This study used a randomized, double-blind, parallel-group, multicenter design that compared 200 $\mu\text{g}/\text{d}$ of fluticasone propionate vs placebo in patients with SAR to assess the effectiveness on ocular symptoms associated with AR. At visit 1 (prescreen), patients signed an informed consent or assent form and were screened for eligibility (patient assent was obtained for patients aged 12–17 years). Prescreening may have been completed in advance of allergy season. Patients returned for visit 2 (screening or placebo lead-in visit) to begin the 5-day placebo lead-in period after the mountain cedar (*Juniperus ashei*) pollen count maintained 50 grains of pollen per cubic meter of air for 3 consecutive days. On a daily basis during the screen/placebo lead-in phase, patients used the placebo spray and assessed the severity of ocular itching or burning, tearing or watering, redness, and nasal congestion through the use of a diary card. After the screen/placebo lead-in phase, eligible patients were randomly assigned to a treatment group for a total of 14 days of either 200 $\mu\text{g}/\text{d}$ of fluticasone propionate or placebo nasal spray administered in the morning. An objective measure of conjunctival redness was assessed on a 4-point scale (range, 0–3, with 0 indicating absent; 1, mild, 2, moderate; and 3, severe) by physician (or qualified designee) at baseline (visit 3) and final visit (visit 4). Patients maintained a diary in which they recorded product use, reflective nasal congestion symptom score (rNCSS), reflective ocular symptoms, and instantaneous ocular symptoms daily. Reflective total ocular symptom score (rTOSS) and instantaneous total ocular symptom score (iTOSS) were calculated programmatically during analysis. Patients also completed the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) at baseline and final visit and completed a self-rated end-of-treatment assessment for overall symptom relief after treatment.

All patients provided written informed consent (if patients were younger than 18 years, written informed consent was provided by a legal parent or guardian). The final protocol, protocol amendments, and consent forms were reviewed and approved by a single, central institutional review board (Quorum Review, Seattle, Washington) that operates in accordance with Code of Federal Regulation 21, Part 56, International Conference on Harmonisation Guidelines for Good Clinical Practice and with current local requirements in the United States.

Primary and Secondary Objectives

The primary objective of this study was to demonstrate that a 14-day course of 200 $\mu\text{g}/\text{d}$ of fluticasone propionate is superior to placebo in relieving ocular symptoms associated with AR as determined by mean change from baseline in patient-rated rTOSS. The secondary objectives of the study were to evaluate fluticasone compared with placebo in terms of mean change from baseline in both the morning and evening rTOSS; mean change from baseline in both the individual morning reflective symptom score and the evening reflective symptom score for each symptom of itching or burning, tearing or watering, and redness; mean change from baseline in

morning predose iTOSS; end-of-treatment assessment of response to therapy for ocular symptoms; effect of rhinitis on activities of daily living and overall well-being using the MiniRQLQ overall scores and individual domains; and mean change from baseline in daily rNCSS. In addition, an objective assessment of conjunctival redness was performed by a physician or qualified designee.

Inclusion Criteria

Eligible patients were 12 years or older with a history of AR for 2 years or longer, had a positive skin test result to an allergen relevant to the pollen season and geographic region (mountain cedar), were in overall good general health, and were able to provide voluntary, written informed consent. Patients were required to have allergic conjunctivitis symptoms of at least moderate severity with an iTOSS of 4 or higher and an instantaneous nasal congestion symptom score of 2 or higher on the morning of randomization and a mean iTOSS of 4 or higher and an instantaneous nasal congestion symptom score of 2 or higher for 3 of the 5 days during the placebo lead-in.

Exclusion Criteria

Patients who were pregnant or breastfeeding, had known or suspected intolerance or hypersensitivity to the study materials, or had nasal disorders that investigators believed would have interfered with participation in the study were excluded. In addition, patients with a history or current evidence of a clinically significant uncontrolled disease, such as respiratory disease, cardiac arrhythmias, congestive heart failure, malignant tumor, diabetes mellitus, or hypertension, were excluded. Additional exclusion criteria were current infection, impairments in learning, long-term or intermittent use of corticosteroids, and intended travel outside the geographic region for more than 48 hours.

Selection and Timing of Dose

The currently approved dose of fluticasone propionate is 200 μg , which has been found to maintain adequate control of nasal symptoms when administered once daily.⁶ It has also been suggested that ocular symptoms were improved with the use of 200 $\mu\text{g}/\text{d}$ of fluticasone propionate.^{7,8} Therefore, 200 $\mu\text{g}/\text{d}$ was selected as the dose for this study. All patients received placebo nose spray at visit 2, and each patient was instructed to use the study treatment each morning by self-administering 2 sprays in each nostril daily for a total of 14 treatment days.

Statistical Analysis

All efficacy parameters were summarized in terms of number, mean, SD, minimum, and maximum for both treatment groups at baseline (day 1) and day 14. Mean change from baseline in efficacy parameters (except end-of-treatment assessment) for a 14-day course was analyzed with analysis of covariance using a linear fixed-effects model. The model included fixed factors for treatment and site and baseline value as covariate. For end-of-treatment assessment, patient scores for the assessment of effectiveness of treatment were analyzed using a Cochran-Mantel-Haenszel test, controlling for investigator site.

Treatment with 200 $\mu\text{g}/\text{d}$ of fluticasone propionate was compared with placebo using the least squares means from the model. This test was 2-sided and was conducted at a significance level of $\alpha = .05$. Adjusted means, 95% confidence intervals (CIs), within-treatment *P* values for each treatment group, treatment group difference, 95% CI of the difference, and the between-treatment *P* values based on the statistical model described above were also presented for all efficacy parameters (except end-of-treatment assessment).

Results

Disposition and Demographics

A total of 855 patients were screened at 6 investigative sites, 626 patients were randomized, and 614 patients completed the study. Twelve patients withdrew from the study; 2 withdrew because of adverse events (AEs), 1 was lost to follow-up, 3 were excluded because protocol violations (as identified by the investigator), 4 withdrew consent, and 2 withdrew for other reasons. The most common reason for screen failure was not meeting study criteria. Of the 626 patients randomized, 314 were randomized to receive 200 µg/d of fluticasone propionate and 312 were randomized to receive placebo. Demographics and baseline characteristics were similar between the 2 groups (Table 1). The mean age was 40.5 years, with 12% of patients aged 12 to 17 years. Most patients were female (66%) and white (86.6%). Patients had moderate-severe disease with baseline a TOSS nearing 7 (scale, 0–9) and an NCSS of approximately 2.5 (scale, 0–3).

Primary Outcome

The primary efficacy end point was mean change from baseline over the treatment period in daily rTOSS. Each rTOSS assessment is composed of the sum of 3 ocular symptoms for eye itching or burning, tearing or watering, and redness with each symptom scored on a scale of 0 (absent symptoms) to 3 (severe symptoms). The least squares mean change from baseline in rTOSS was significantly greater for fluticasone than for placebo (−0.97 vs −0.61; $P = .002$) (Table 2 and Fig 1).

Secondary Outcomes

At baseline, mean morning rTOSS and evening rTOSS were similar for both treatment groups, and mean change from baseline during the entire treatment period was greater for fluticasone than for placebo (Fig 2). The least squares mean difference between the 2 treatment groups was statistically significant for both morning rTOSS (difference, −0.33; $P = .006$) and evening rTOSS (difference, −0.41; $P < .001$). Similar results were observed when the individual morning reflective score and evening reflective score were evaluated for each symptom: itching or burning, tearing or watering, and redness. At baseline, mean morning and evening reflective scores for eye itching or burning, tearing or watering, and redness were similar between treatment groups, and least squares mean change from baseline was greater in the fluticasone group than in the placebo group for all measurements. After 14 days, the least squares mean difference between the 2 treatments was significant for morning (difference, −0.10; $P = .01$) and evening (difference, −0.15; $P < .001$) eye itching or burning score, significant for morning (difference, −0.13; $P = .002$) and evening (difference, −0.18; $P < .001$) eye tearing or watering symptom score, and significant for morning (difference, −0.10; $P = .03$) and evening (difference, −0.10; $P = .04$) eye redness symptom score.

Morning predose iTOSS was used to assess the treatment effect at the end of the dosing interval and was the sum of the 3 individual ocular symptom score assessments performed at the moment immediately before taking their dose every morning. At baseline, the mean morning predose iTOSS was similar for both treatment groups. The least squares mean change from baseline during the entire treatment period in morning predose iTOSS was greater for fluticasone (−0.83) compared with placebo (−0.55). The least squares mean difference between the 2 treatments (−0.28) was statistically significant ($P = .01$).

At the final study visit, patients were asked to evaluate their overall response to therapy during the entire treatment period using a 7-point categorical scale. For this end point, the patient assessments were analyzed using the Cochran-Mantel-Haenszel

Table 1

Baseline demographics and disease characteristics (safety population)

Characteristic	No. (%) of patients ^a		
	Placebo (n = 312)	Fluticasone (n = 314)	Overall (N = 626)
Sex			
Male	111 (35.6)	102 (32.5)	213 (34.0)
Female	201 (64.4)	212 (67.5)	413 (66.0)
Race			
American Indian or Alaska Native	0	1 (0.3)	1 (0.2)
Asian	2 (0.6)	1 (0.3)	3 (0.5)
Black or African American	38 (12.2)	36 (11.5)	74 (11.8)
White	270 (86.5)	272 (86.6)	542 (86.6)
Native Hawaiian or Other Pacific Islander	1 (0.3)	1 (0.3)	2 (0.3)
Multiple	1 (0.3)	3 (1.0)	4 (0.6)
Ethnicity			
Hispanic	124 (39.7)	144 (45.9)	268 (42.8)
Non-Hispanic	188 (60.3)	170 (54.1)	358 (57.2)
Age, mean (SD), y	40.5 (16.36)	40.4 (14.55)	40.5 (15.47)
Age range, y	12–79	12–79	12–79
TOSS (maximum score, 9), mean (SD)			
Daily reflective	6.98 (1.365)	6.75 (1.364)	6.87 (1.368)
Morning instantaneous	6.89 (1.360)	6.81 (1.399)	6.85 (1.379)
Morning reflective	7.01 (1.391)	6.88 (1.358)	6.95 (1.375)
Evening reflective	6.95 (1.434)	6.63 (1.497)	6.79 (1.474)
NCSS (maximum score, 3), mean (SD)			
Daily reflective	2.56 (0.363)	2.54 (0.381)	2.55 (0.372)
Morning instantaneous	2.59 (0.399)	2.63 (0.382)	2.61 (0.390)
Morning reflective	2.61 (0.384)	2.59 (0.372)	2.60 (0.377)
Evening reflective	2.51 (0.404)	2.48 (0.454)	2.50 (0.430)

Abbreviations: NCSS, nasal congestion symptom score; TOSS, total ocular symptom score.

^aData are presented as number (percentage) of patients unless otherwise indicated.

test controlling for investigative site. The treatment difference between fluticasone and placebo on the overall response to therapy was statistically significant ($P = .01$). A total of 177 patients receiving fluticasone reported improvement, with 22 (7.0%), 76 (24.3%), and 79 (25.2%) patients reporting significant, moderate, and mild improvement, respectively. A total of 146 patients receiving placebo reported improvement, with 16 (5.2%), 59 (19.1%), and 71 (23.0%) patients reporting significant, moderate, and mild improvement, respectively. Similarly, 55 patients receiving fluticasone reported mild to significant worsening compared with 66 patients receiving placebo. In addition, 97 patients in the placebo group reported no change compared with 81 patients in the fluticasone group (Table 3).

In comparing the least squares mean change from baseline between the 2 groups, patients in the fluticasone group experienced statistically significant improvements in overall effect of

Table 2

Mean change from baseline in daily rTOSS during the treatment period (intent-to-treat population)

Variable	Placebo (n = 312)	Fluticasone (n = 314)
Baseline		
Mean (SD)	6.98 (1.365)	6.75 (1.364)
Range	3.70 to 9.00	3.60 to 9.00
Postbaseline (day 14)		
Mean (SD)	6.35 (1.686)	5.85 (1.767)
Range	0.50 to 9.00	0.30 to 9.00
Change from baseline		
Mean (SD)	−0.63 (1.525)	−0.91 (1.625)
Range	−7.10 to 4.40	−5.50 to 3.80
Least square mean (SE) ^a	−0.61 (0.084)	−0.97 (0.083)
Least square mean difference (95% CI) ^a		−0.36 (−0.59 to −0.31)
Between-treatment P value ^a		.002

Abbreviations: CI, confidence interval; rTOSS, reflective total ocular symptom score.

^aFrom analysis of covariance model: treatment and site as fixed factors and baseline score as covariate. The least square mean difference is fluticasone minus placebo.

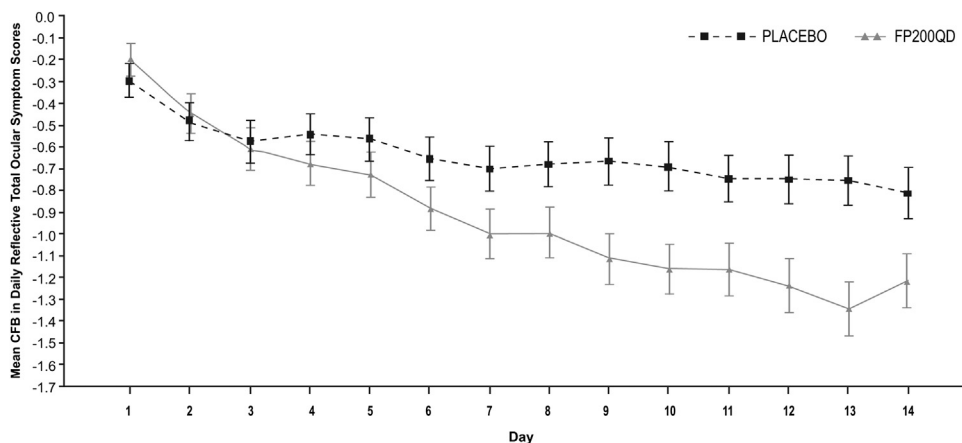


Figure 1. Mean change from baseline (CFB) in daily reflective total ocular symptom score during the treatment period (intent-to-treat population, N = 626). Each symptom was measured on a 4-point scale: 0, absent symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. Total ocular symptom score is the sum of 3 individual ocular symptoms scores (itching or burning, tearing or watery eyes, and eye redness) from the morning or evening. Error bars represent between-subject variability.

AR on daily living activities as assessed by the MiniRQLQ. The overall least squares mean difference between groups was -0.47 ($P < .001$). Differences in each of the individual 5 domains were also significantly greater for fluticasone compared with placebo (Fig 3).

The daily rNCSS was calculated as the mean of the evening symptom score and the morning symptom score of the next day before morning dosing. At baseline, mean daily rNCSS was similar for both treatment groups. The least squares mean change from baseline in rNCSS during the entire treatment period was greater for fluticasone (-0.35) compared with placebo (-0.21). The least squares mean difference between the 2 treatments (-0.14) was statistically significant ($P < .001$). Mean change from baseline was greater for patients receiving fluticasone than for those receiving placebo during the treatment period (Fig 4).

Conjunctival redness was evaluated by the investigator (or qualified designee) as an objective clinical sign of AR. At baseline, the mean conjunctival redness was similar for both treatment groups. The least squares mean change from baseline during the entire treatment period in conjunctival redness assessed by a physician was similar for both treatment groups. The least squares mean difference between the 2 treatments (-0.01) was not statistically significant ($P = .86$).

Safety

A total of 20 TEAEs were reported by 16 patients (2.6%) during the study. The most frequently reported AEs were pyrexia (3 reports in 3 patients [0.5%]), headache (2 reports in 2 patients [0.3%]), and bronchitis (2 reports in 2 patients [0.3%]). Almost all the TEAEs were reported as mild or moderate in intensity. Two AEs were reported as severe: a single report of bronchitis and a single report of influenza in one patient who was receiving placebo. Two AEs were reported to be related to study treatment by the investigator: 1 report of headache in a patient receiving 200 $\mu\text{g}/\text{d}$ of fluticasone propionate and 1 report of epistaxis in a patient receiving placebo. Both these treatment-related AEs were of mild or moderate intensity. Two patients experienced AEs that led to discontinuation from the study: 1 patient experienced an exacerbation of allergies and 1 patient developed bronchitis and influenza. Both were considered treatment related. There were no deaths or serious AEs reported.

Discussion

AR is an IgE-mediated inflammatory disorder of the upper airway that affects up to 40 million Americans annually.^{9,10} The primary symptoms of AR include nasal congestion, sneezing,

rhinorrhea, and nasal itching; however, AR is often accompanied by nonnasal allergy symptoms, including itchy eyes and tearing.² Although the current fluticasone indication is limited to the treatment of nasal symptoms, the potential benefits of intranasal corticosteroids in relieving eye symptoms of allergy are well recognized. The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines state that intranasal corticosteroid preparations such as fluticasone have comparable efficacy to oral or intranasal antihistamines for relieving ocular symptoms associated with AR.¹¹

To provide evidence of the effectiveness of fluticasone for the relief of ocular symptoms associated with AR, the sponsor previously conducted 2 studies that assessed ocular relief as a primary end point. These studies demonstrated the efficacy of intranasal 200 $\mu\text{g}/\text{d}$ of fluticasone propionate compared with placebo and 10 mg/d of oral loratadine in reducing ocular symptoms associated with SAR.^{7,8} In addition, several large, well-controlled studies in which fluticasone propionate maintained adequate control of nasal symptoms when administered at 200 $\mu\text{g}/\text{d}$ suggested that ocular symptoms were improved with use of fluticasone.⁷ The current study was designed to investigate the efficacy of fluticasone on treating ocular symptoms associated with SAR. This study was conducted based on Food and Drug Administration (FDA) feedback (October 2012 meeting) and in accordance with current FDA guidelines related to AR trials and was conducted in Southcentral Texas from December 4, 2012, through February 16, 2013, during the time the mountain cedar (*Juniperus ashei*) trees, commonly found in this area, annually release their pollen. Participating patients had confirmed allergy to mountain cedar as determined by skin testing and history and met predefined minimum symptom criteria for inclusion.

The study objectives and end points were based on 3 SAR studies of comparable design on fluticasone furoate nasal spray for the relief of ocular symptoms.^{12,13} For this study, in addition to assessing statistical significance, a criterion for evaluating success of the observed absolute treatment difference between 200 $\mu\text{g}/\text{d}$ of fluticasone propionate and placebo was arbitrarily set as 0.6 or greater (in favor of fluticasone) in mean change from baseline for daily rTOSS. The magnitude of this treatment difference was selected based on the observed results in previous FFNS studies.^{12,13} In the current study, the results indicate that the difference between fluticasone and placebo was statistically significant as determined by mean change from baseline in patient-rated rTOSS during a 14-day course. The observed treatment difference in rTOSS between fluticasone and placebo was -0.36 , which was below the criterion stated to achieve the primary objective. The predefined treatment difference was an ambitious criterion and should not be viewed as the absolute threshold for clinical success of fluticasone

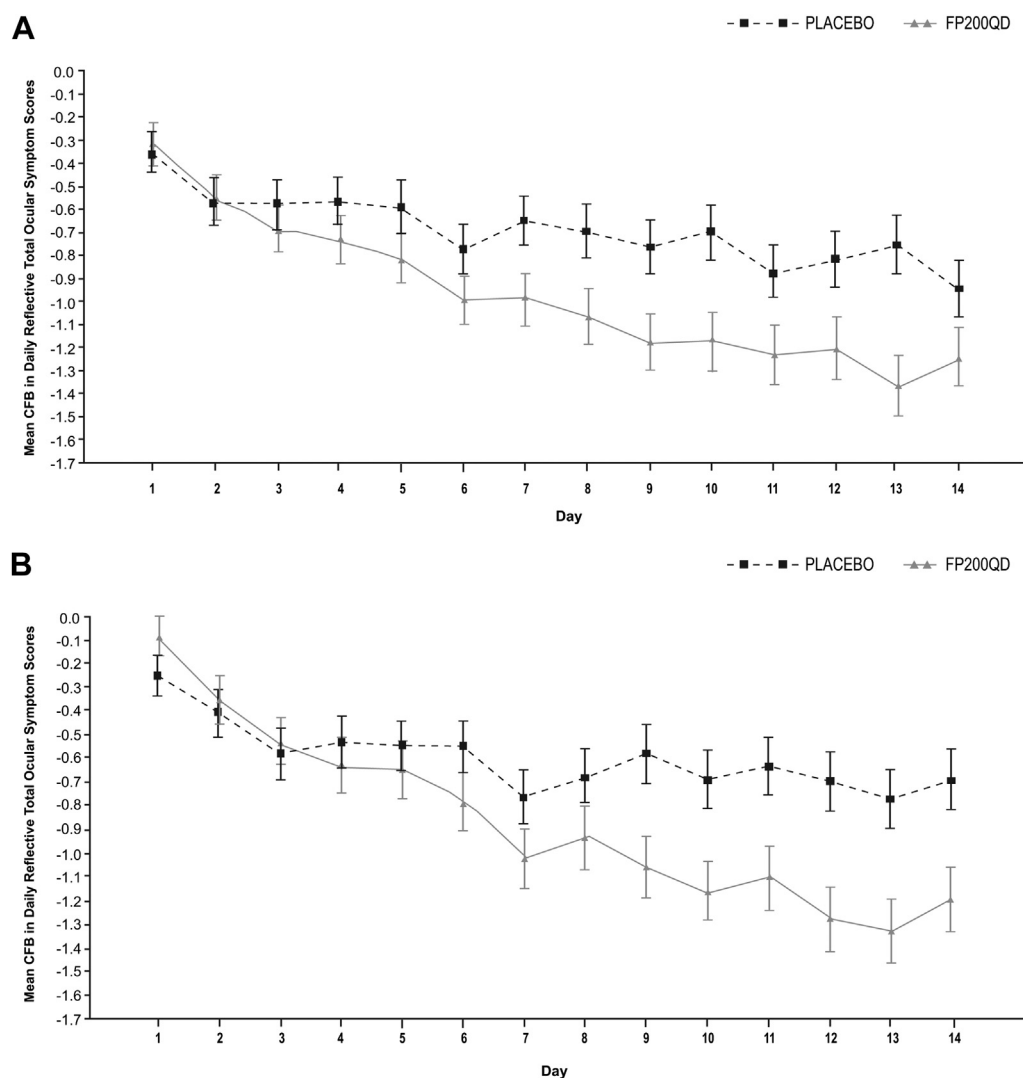


Figure 2. Mean change from baseline (CFB) in morning (A) and evening (B) reflective total ocular symptom score during the treatment periods (intent-to-treat population, N = 626). Each symptom was measured on a 4-point scale: 0, absent symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. Total ocular symptom score is the sum of 3 individual ocular symptoms scores (itching or burning, tearing or watery eyes, and eye redness) from the morning or evening. Error bars represent between-subject variability.

for ocular symptoms. Notably, as seen in this study with fluticasone, other intranasal corticosteroids have a similar positive effect on the relief of ocular symptoms, with observed treatment differences at 2 weeks of -0.34 and -0.40 for triamcinolone acetate and mometasone furoate, respectively, results that were considered by the authors to be clinically meaningful.^{14,15} Furthermore, the results of

the secondary end points from the current study indicated that treatment differences in symptom reduction were statistically significant in favor of fluticasone over placebo for morning rTOSS, evening rTOSS, individual morning and evening reflective symptom scores, iTOSS, and rNCSS.

In this study, redness was assessed through objective and subjective measures. A physician assessment for conjunctival redness provided the objective measurement of redness, and patients self-rated their own symptoms to subjectively assess the degree of eye redness. There was no minimal severity standard required for conjunctival redness at enrollment, and the baseline physician assessment score was slight to moderate in intensity for conjunctival redness for both groups. Mean change from baseline scores in physician assessment of redness at 14 days reflected a within-treatment statistically significant improvement for both fluticasone and placebo; however, a statistically significant difference in mean change from baseline scores between fluticasone and placebo was not observed. Exhibiting a statistically significant improvement is difficult given the slight to moderate nature of the baseline scores. Subjective measures are recognized as the preferred measure of effectiveness as described in the FDA guidance around AR trials. Therefore, although the objective measurement of conjunctival

Table 3
Analysis of overall evaluation of response to therapy (intent-to-treat population)

Response	No. (%) of patients	
	Placebo (n = 312)	Fluticasone (n = 314)
Total response provided	309	313
Significantly improved	16 (5.2)	22 (7.0)
Moderately improved	59 (19.1)	76 (24.3)
Mildly improved	71 (23.0)	79 (25.2)
No change	97 (31.4)	81 (25.9)
Mildly worse	20 (6.5)	21 (6.7)
Moderately worse	24 (7.8)	24 (7.7)
Significantly worse	22 (7.1)	10 (3.2)
Between-treatment P value ^a	.01	

^aUsing Cochran-Mantel-Haenszel test controlling for investigative site.

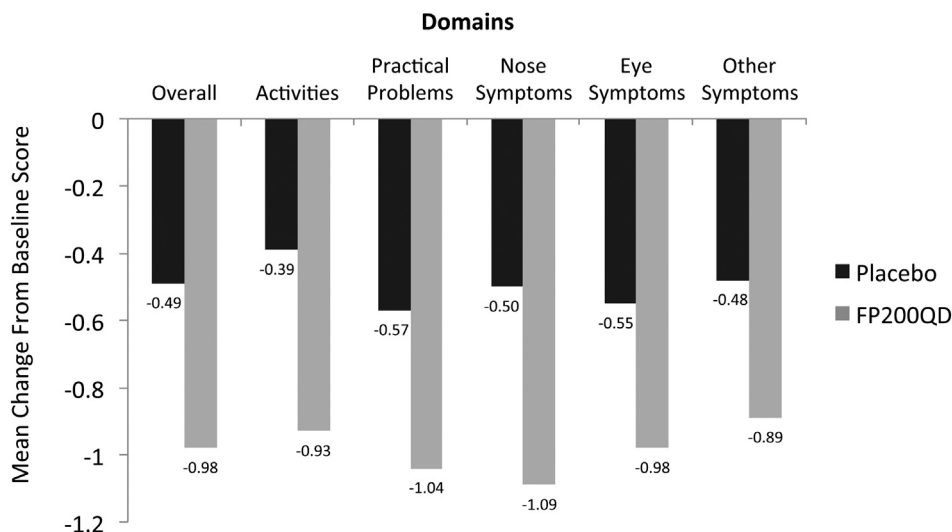


Figure 3. Overall and individual domain mean change from baseline scores for MiniRQLQ (intent-to-treat population, N = 626).

redness was not statistically significant, the subjective scores on self-rated daily redness were statistically significant.

An additional analysis of the mean change from baseline in daily reflective symptom scores revealed a statistically significant difference between fluticasone and placebo for each individual symptom (eye itching or burning, tearing or watering, and redness). Patients completed an end-of-treatment assessment at the final visit to self-evaluate their overall response to therapy. Fluticasone provided a statistically significant positive response to therapy during the entire treatment period. The MiniRQLQ was administered at baseline and final visit to determine the effect of treatment on AR in terms of activities of daily living and overall well-being. The scores for fluticasone revealed statistically significant differences compared with placebo in the overall questionnaire score and in the individual domain scores. The minimally important difference (MID) associated with a change that is meaningful to the patient is 0.70.^{16,17} The scores for fluticasone revealed a statistically

significant positive difference in the overall questionnaire score and in the individual domain scores across the 14-day study that exceeded the MID. Of note, the eye symptoms domain score exceeded the MID, and the score was similar to the nasal symptom domain score. The within-treatment changes from baseline scores for placebo were statistically significant but were not clinically meaningful, emphasizing the effect of fluticasone on AR in relation to activities and symptoms vs placebo.

Overall, 200 μ g/d of fluticasone propionate was well tolerated, and no new safety signals were identified. Two TEAEs were considered to be treatment related and were consistent with AEs known to be associated with use of intranasal corticosteroid sprays. There were no serious AEs reported and no deaths.

FDA's guidance on the conduct of AR trials recognizes that patient's self-rated symptom scores are the preferred measures of effectiveness.¹⁸ This study design included several self-rated assessments, and the results of the study revealed statistically

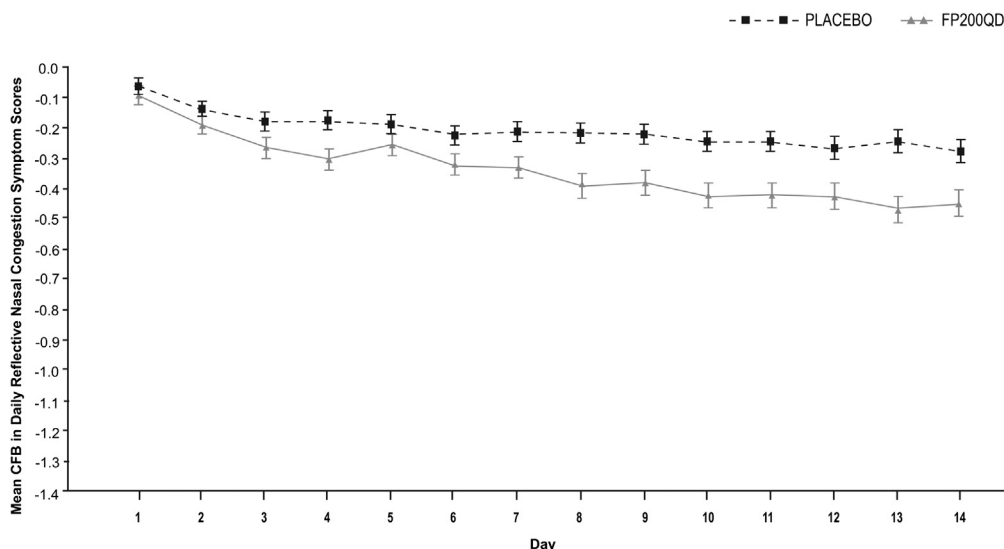


Figure 4. Mean change from baseline (CFB) in reflective nasal congestion symptom score (rNCSS) during the treatment period. The daily rNCSS was calculated as the mean of the evening symptom score and the morning symptom score of the next day before morning dosing (intent-to-treat population, N = 626).

significant differences and numerically greater responses for fluticasone over placebo for the primary and secondary end points, with the exception of physician-assessed conjunctival redness. These results were consistent across all patient-rated ocular symptoms, MiniRQLQ, and end-of-treatment assessments. The consistency in all the subjective measures of the efficacy and the level of statistical significance observed in the primary and secondary end points provide strong support for the efficacy of fluticasone in treating ocular symptoms. The 200- μ g/d dose of fluticasone propionate was well tolerated in this study, and no new safety issues were identified. This study supports the efficacy of 200 μ g/d of fluticasone propionate in treating ocular symptoms. Given that 200 μ g/d of fluticasone propionate revealed statistically significant improvements for the primary and secondary end points compared with placebo and that fluticasone has recently been approved for over-the-counter use, fluticasone is well positioned as a cost-effective and accessible treatment option to markedly improve the quality of life in a larger number of patients with nasal and ocular symptoms. These data supplement findings observed in previous fluticasone studies and are aligned with recommendations in the ARIA guidelines.

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