

Fluticasone furoate nasal spray is more effective than fexofenadine for nighttime symptoms of seasonal allergy

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ABSTRACT

Nasal symptoms of allergic rhinitis are an important cause of sleep disturbance. Reduction of nasal symptoms, particularly nasal obstruction, has been linked to improvements in self-reported sleep quality. The enhanced-affinity intranasal corticosteroid fluticasone furoate and the oral antihistamine fexofenadine were compared with respect to nighttime symptoms of seasonal allergic rhinitis. In two randomized, double-blind, double-dummy, parallel-group studies, patients received fluticasone furoate nasal spray (FFNS), 110 µg (study 1, n = 312; study 2, n = 224); fexofenadine, 180 mg (study 1, n = 311; study 2, n = 227); or placebo (study 1, n = 313; study 2, n = 229) once daily for 2 weeks. Fluticasone furoate was more effective ($p < 0.001$) than fexofenadine and placebo in both studies with respect to the mean changes from baseline over the treatment period in the nighttime symptoms score, nighttime reflective total nasal symptom score, predose instantaneous nasal symptom score, and morning peak nasal inspiratory flow. Fluticasone furoate was more effective than placebo ($p \leq 0.001$) in study 1 and more effective than both placebo and fexofenadine ($p \leq 0.034$) in study 2 with respect to the mean changes from baseline in the nighttime reflective total ocular symptom score and predose instantaneous total ocular symptom score. In these double-dummy studies, fexofenadine did not separate from placebo in comparisons of the nighttime symptoms score or the nighttime nasal or ocular symptom measures. The incidence of adverse events was similar among groups. FFNS once daily was more effective than fexofenadine and placebo with respect to nighttime sleep disturbance caused by seasonal allergy symptoms.

(Allergy Asthma Proc 30:128–138, 2009; doi: 10.2500/aap.2009.30.3204)

Key words: Allergy, antihistamine, fexofenadine, fluticasone furoate, intranasal corticosteroid, nasal symptoms, NRQLQ, ocular symptoms, rhinitis, seasonal allergic rhinitis, sleep

Allergic rhinitis is associated with nasal symptoms (congestion, rhinorrhea, nasal itching, and sneezing) and ocular symptoms (itching/burning, tearing/watering, and redness) that can reduce patients' quality of life and impair functional ability.^{1,2} Although all of these

symptoms can be troublesome, patients rate nasal congestion as the single most bothersome symptom of allergic rhinitis.¹ Rhinitis symptoms can cause fatigue, tiredness, irritability, frustration, reduced productivity and concentration, and headache.³ When they occur at night, rhinitis symptoms may lead to sleep disturbance.^{4–7} Approximately three-quarters of rhinitis sufferers (77%) in one survey of 1181 respondents reported that their symptoms affect sleep.⁷ Nighttime symptoms of allergic rhinitis are associated with daytime impairment as illustrated by the finding in a 500,000-member managed care organization that poor sleep was a significant limitation of rhinitis patients' self-reported ability to engage in productive work.⁸

Effective management of allergic rhinitis symptoms with pharmacotherapy can improve self-reported sleep quality and mitigate self-reported daytime consequences of sleep impairment.^{9–12} Reduction in nighttime symptoms, particularly nasal congestion, has been suggested as the mechanism of these improvements.^{12,13} When nasal congestion is a major component of rhinitis, intranasal corticosteroids are the first line of pharmacotherapy.^{14,15} Intranasal corticosteroids

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Data from this study were presented in part at the annual meetings of the American College of Allergy, Asthma, and Immunology, Grapevine, Texas, November 11, 2007, and November 9, 2008, and the annual meeting of the American Academy of Allergy, Asthma, and Immunology, Philadelphia, Pennsylvania, March 15, 2008

GlaxoSmithKline funded the research (FFU109045 and FFU109047) described in this article; GlaxoSmithKline funded Dr. Sailer's work. H Kaiser, D Mohar, R Jacobs, and B Martin are all research sponsors for GlaxoSmithKline; H Kaiser and M Vandewalker are speakers for GlaxoSmithKline; L Lee, W Toler, B Prillaman, E Philpot, and A Dalal are employees of GlaxoSmithKline

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inhibit a range of inflammatory processes mediating nasal symptoms and have been consistently shown to be effective in the treatment of nasal congestion.¹⁴ Although antihistamines typically show less of an effect on congestion compared with intranasal corticosteroids,¹⁶ fexofenadine has shown significant improvement in nasal congestion over loratadine, another oral antihistamine.^{17–20} Although it is often perceived that patients prefer to administer oral tablets over nasal sprays, the intranasal route of administration does not appear to be a barrier to use in allergic rhinitis; in a 350-respondent survey, 8 of 10 adults with allergic rhinitis indicated that they would consider using a nasal spray if it were recommended by a physician.²¹

Fluticasone furoate nasal spray (FFNS)—an enhanced-affinity corticosteroid that has been approved for use by the U.S. Food and Drug Administration for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis—is delivered from a novel, side-actuated device.^{22,23} With potent anti-inflammatory activity and low (<0.5%) absolute bioavailability,²⁴ FFNS has been shown to be well tolerated and significantly more effective than placebo at relieving symptoms of allergic rhinitis in children, adolescents, and adults in double-blind, controlled clinical studies.^{23,25–31}

The two randomized, double-blind, placebo-controlled studies reported here were conducted to compare FFNS and the commonly prescribed oral antihistamine fexofenadine with respect to nighttime sleep disturbance caused by seasonal allergy symptoms. Although each agent has shown efficacy versus placebo in terms of both nasal symptoms and ocular symptoms,^{23,25–27,32–36} FFNS and fexofenadine have not been compared directly in a clinical trial to date. These trials are also the first studies comparing FFNS with a rhinitis pharmacotherapy from another therapeutic category.

METHODS

Patients

Male or female patients who were ≥ 12 years old were eligible to participate if they had a diagnosis of seasonal allergic rhinitis as defined by a clinical history of nasal allergy symptoms during each of the last two respective allergy seasons and a positive skin test (*i.e.*, wheal ≥ 3 mm larger than the diluent control for prick testing) to mountain cedar allergen (study 1) or ragweed allergen (study 2) within 12 months of screening. Patients were expected to have adequate exposure to the respective pollen during the study (*i.e.*, resided in a geographical region where exposure to mountain cedar [study 1] or ragweed [study 2] was expected to be significant and had no plans to travel outside that region for >48 hours of the study). Eligible female patients could not be pregnant at study entry, could

not be planning to become pregnant during the study, and agreed to use acceptable contraceptive methods throughout the study. Exclusion criteria included severe physical obstruction of the nose (*e.g.*, deviated septum or nasal polyp); recent nasal septal surgery or perforation; asthma, unless it was mild intermittent asthma; rhinitis medicamentosa; ocular or upper respiratory bacterial or viral infection; chronic use of medications that could affect allergic rhinitis or assessments of efficacy of study medication; and current tobacco use. Patients who had used the following medications within the prescribed periods before screening were also excluded: subcutaneous omalizumab within 5 months; corticosteroids (intranasal form within 4 weeks and inhaled, intramuscular, *i.v.*, and/or dermatologic forms, except $\leq 1\%$ hydrocortisone cream/ointment, within 8 weeks); short-acting prescription or over-the-counter antihistamines, oral or intranasal decongestants, anticholinergics, long-acting β -agonists, or oral antileukotrienes within 3 days; long-acting antihistamines within 10 days; and intranasal antihistamines or intranasal or ocular cromolyn within 14 days. All adult patients and parents/guardians of patients aged <18 years gave written informed consent. Written assent was obtained from patients who were 12 to <18 years old.

Procedures

An institutional review board approved the identical protocols for these two randomized, double-blind, double-dummy, placebo-controlled, parallel-group studies (GlaxoSmithKline protocols FFU109045 [study 1, 10 sites] and FFU109047 [study 2, 42 sites]). The first study was conducted in south central Texas during the 2006/2007 mountain cedar allergy season. The substantial pollen exposure during this 2-month season causes moderate-to-severe symptoms in susceptible patients, and patients remain highly susceptible to low amounts of pollen throughout the season.³⁷ Study 2 was conducted during the 2007 U.S. ragweed season. Pollen counts were performed in the study sites' vicinity and enrollment did not begin until the respective pollen counts reached target concentrations. Both studies consisted of a 5- to 21-day screening period followed by a 14-day treatment period. Clinic visits were scheduled on the 1st day of the screening period, the day of randomization (day 1), and at the end of the 1st and 2nd weeks of treatment (days 8 and 15, respectively).

During the screening period, patients used an electronic diary to rate symptoms. Each morning, patients completed a validated nighttime symptoms questionnaire comprised of three items: "How difficult was it to get to sleep last night because of your nose symptoms?" (rated on a scale from 0 [not at all difficult] to

3 [very difficult]), "How many times did your nose symptoms wake you up last night?" (rated on a scale from 0 [not at all] to 3 [I feel like I was awake all night]), and "How severe was your stuffy nose when you woke up?" (rated on a scale from 0 [none] to 3 [severe]). The sum of scores for the three items comprises the nighttime symptoms score, which has been shown to be a clinically meaningful measure of nighttime sleep disturbance in allergic rhinitis patients.³⁸ Patients also rated the severity of individual nasal symptoms of congestion, rhinorrhea, itching, and sneezing and individual ocular symptoms of itching/burning, tearing/watering, and redness on a scale ranging from 0 (symptom not present) to 3 (symptom difficult to tolerate; interferes with activities of daily living and/or sleeping). Patients rated these symptoms on a *reflective* basis each morning and evening and an *instantaneous* basis each morning before administering their dose. The reflective rating provides information on symptom severity over the preceding 12 hours whereas the instantaneous rating provides information on symptom severity at the moment of the assessment and reflects symptoms at the end of the 24-hour dosing interval. The four nasal symptom scores (congestion, rhinorrhea, itching, and sneezing) and the three ocular symptom scores (itching/burning, tearing/watering, and redness) were summed to arrive at total nasal and total ocular symptom scores, respectively.

To be eligible for randomization, patients must have been in the screening period for a minimum of 5 days and must have had an average nighttime symptoms score of ≥ 4.5 with an average congestion-on-awakening score of ≥ 2 , an average daytime reflective total nasal symptom score (rTNSS) of ≥ 6 with an average daytime reflective nasal congestion score of ≥ 2 , and an average daytime reflective total ocular symptom score of ≥ 4 , all based on the four highest of the last seven assessments preceding day 1. For calculation of the average nighttime symptoms and congestion-on-awakening scores, the assessment on the morning of day 1 must have been included; for the remaining three scores, the assessment on the evening before day 1 was required to be included. Patients meeting these criteria were randomized 1:1:1 on day 1 to one of three groups using the approved doses: FFNS (FFNS, 110 μg , and oral placebo capsule once daily), fexofenadine (overencapsulated fexofenadine, 180-mg oral tablet, and vehicle placebo nasal spray once daily), or placebo (oral placebo capsule and vehicle placebo nasal spray once daily). An *in vitro* dissolution study determined similar dissolution between a branded fexofenadine tablet and the overencapsulated branded fexofenadine tablet at 60 minutes. Study medication was taken each morning for 2 weeks. Except for study medication, antiallergy and antirhinitis medications were prohibited throughout the treatment period. Medications (prescription or

nonprescription) and herbal sleep remedies that induce sleep were prohibited throughout both the screening and the treatment periods.

Measures

Each morning before administering their treatment, patients completed the nighttime symptoms questionnaire and performed a reflective and an instantaneous assessment of their nasal and ocular symptom severity. An In-Check Nasal portable handheld inspiratory flowmeter and face mask (Clement-Clarke International, Harlow, U.K.) was also used at this time to measure peak nasal inspiratory flow. Three inspiratory measurements were taken and the highest measurement was recorded on the electronic diary. Patients also recorded symptom severity in a reflective manner 12 hours after dosing (evening assessment) along with a second peak nasal inspiratory flow assessment.

Health-related quality of life was assessed with the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ), a 16-item, self-administered, disease-specific instrument³⁹ that patients completed at the beginning and the end of the treatment period. The NRQLQ assesses nocturnal quality of life over a 1-week interval. Each question is scored from 0 to 6 with higher scores indicating greater impairment in quality of life. Items are grouped into four domains: sleep problems, sleep time problems, symptoms on waking in the morning, and practical problems. An overall quality-of-life score was calculated from the mean score of all items. Mean scores for each domain were also calculated.

Tolerability was assessed by recording adverse events, defined as any untoward medical occurrences regardless of their suspected cause. Compliance was assessed by patients' indication on the electronic diary whether they had administered their capsule treatment and their nasal spray on each treatment day. Compliance was calculated for each patient as the number of days on which study medication was taken divided by the number of days of exposure to double-blind study treatment.

Statistics

The primary efficacy measure was the mean change from baseline over the 2-week treatment period in the nighttime symptoms score. Baseline was defined as the average of the morning assessment on the day of randomization and the three highest scores recorded on the 6 days before randomization. The mean change from baseline in the nighttime symptoms score was also summarized for each day during the treatment period. Key secondary efficacy measures included mean changes from baseline over the treatment period in nighttime and daytime rTNSSs, nighttime and daytime reflective total

ocular symptom scores, predose instantaneous total nasal and ocular symptom scores, the NRQLQ, and morning and evening peak nasal inspiratory flow.

In the first study, sample-size calculations estimated that 317 patients in each treatment arm would provide 90% power to detect a difference of 0.85 between FFNS and fexofenadine in mean change from baseline over the 2-week treatment period in rTNSSs from the entire day (an average of the nighttime rTNSS and the daytime rTNSS). This calculation assumed a standard deviation of 3.3 and was based on a two-sided *t*-test with a 0.05 significance level. Analysis of the results from the first study and a previous fluticasone furoate ragweed study indicated that a smaller sample population could be used for the second study. With an α -level of 0.05 and an estimated standard deviation of the change from baseline in the rTNSS for the entire day over 2 weeks of 2.77 and 2.58 in the FFNS and fexofenadine treatment groups, respectively, a two-sided *t*-test yielded the need for a sample size of 209 subjects per treatment arm to show 90% power and see a difference between treatments of 0.85. Anticipating a possible early withdrawal rate of 8%, this sample size was increased to 226 subjects per treatment arm.

Efficacy analyses included all randomized patients (*i.e.*, the intent-to-treat population). Differences between treatments were tested in a pairwise fashion using analysis of covariance (ANCOVA) models with baseline value as a covariate and treatment and investigational site as main effects. Secondary efficacy measures, with the exception of peak nasal inspiratory flow and the NRQLQ, were grouped into families, each of which was subjected to a Hochberg multiplicity adjustment. The NRQLQ results and morning and evening peak nasal inspiratory flow were each assessed as a stand-alone measure analyzed without multiplicity adjustment. All multiplicity adjustments pertained to individual treatment comparisons; no multiple testing adjustments were made across pairwise comparisons.

The NRQLQ was scored according to the guidelines established by the authors of the instrument.³⁹ The mean changes from baseline at endpoint in the global score and the domain scores were compared among groups in pairwise fashion with an ANCOVA model similar to that described previously.

Adverse event data were summarized with descriptive statistics for the intent-to-treat population but no hypothesis testing was undertaken for these data. The percentages of patients with any adverse event and with specific adverse events were summarized.

RESULTS

Patients

The intent-to-treat population in study 1 included 936 patients randomized to treatment. The incidence of

premature withdrawal was 4% in the fluticasone furoate group, 8% in the fexofenadine group, and 7% in the placebo group (Table 1). The most common reason for premature withdrawal was protocol violation (Table 1). In study 2, 680 patients were randomized to treatment. The incidence of premature withdrawal was 7% in the fluticasone furoate group, 6% in the fexofenadine group, and 4% in the placebo group (Table 1).

Demographics were similar among treatment groups in both studies (Table 1). Approximately two-thirds of patients were female, and the majority of patients were white. Approximately two-thirds of patients in each group had suffered from allergic rhinitis for at least 10 years in the first study and nearly three-fourths of patients in the second study (Table 1).

Mean compliance with the treatment regimen was similar across groups. Compliance rates for capsule treatment ranged from 98.1 to 99.7% across groups in both studies. The corresponding compliance rates for nasal spray treatment ranged from 92.2 to 93.8%.

Nighttime Symptoms

Nighttime Symptoms Score. Mean (SE) nighttime symptoms scores were similar at baseline among the three treatment groups in both studies (Table 1). FFNS was significantly ($p < 0.001$) more effective than fexofenadine and placebo with respect to the mean change from baseline in the nighttime symptoms score over the 2-week treatment period in both studies (Fig. 1). Fexofenadine did not significantly differ from placebo on this measure (study 1, $p = 0.816$; study 2, $p = 0.374$). FFNS separated from placebo and fexofenadine by approximately the 2nd treatment day and differences between the fluticasone furoate group and the other two treatment groups were maintained throughout the 14-day treatment period (Fig. 2). Daily summary data were not subject to statistical hypothesis testing.

In both studies, FFNS showed greater improvement over placebo and fexofenadine with regard to all three individual components of the nighttime symptoms score—nasal congestion on awakening, nighttime awakenings due to nasal symptoms, and difficulty going to sleep because of nasal symptoms. Fexofenadine showed improvement over placebo in the scoring for difficulty going to sleep because of nasal symptoms in study 1 but not in study 2 or for any of the other two components of the nighttime symptoms score in either study.

Nighttime rTNSSs. Mean nighttime TNSSs were similar among treatment groups within the two studies at baseline (Table 1). FFNS was significantly ($p < 0.001$) more effective than fexofenadine and placebo in both studies with respect to the mean change from baseline in the nighttime reflective TNSS over the 2-week treat-

Table 1 Patient disposition, demographics, and baseline data

	Study 1			Study 2		
	FFNS (<i>n</i> = 312)	FEX (<i>n</i> = 311)	Placebo (<i>n</i> = 313)	FFNS (<i>n</i> = 224)	FEX (<i>n</i> = 227)	Placebo (<i>n</i> = 229)
Patient disposition						
Completed, <i>n</i> (%)	298 (96)	287 (92)	290 (93)	209 (93)	214 (94)	219 (96)
Withdrew, <i>n</i> (%)	14 (4)	24 (8)	23 (7)	15 (7)	13 (6)	10 (4)
Adverse event	2 (<1)	6 (2)	1 (<1)	2 (<1)	1 (<1)	1 (<1)
Lost to follow-up	1 (<1)	2 (<1)	1 (<1)	0	0	0
Protocol violation	9 (3)	10 (3)	6 (2)	5 (2)	2 (<1)	1 (<1)
Patient decision	0	2 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Sponsor terminated study	0	0	0	0	1 (<1)	1 (<1)
Lack of efficacy	1 (<1)	0	2 (<1)	0	0	0
Other	1 (<1)	4 (1)	12 (4)	7 (3)	7 (3)	6 (3)
Demographics						
Mean age, yr (SD)	37.8 (13.95)	39.6 (14.63)	37.8 (14.39)	34.0 (13.55)	34.3 (13.66)	34.8 (12.71)
Female, <i>n</i> (%)	209 (67)	199 (64)	194 (62)	152 (68)	135 (59)	139 (61)
Race, <i>n</i> (%)						
White	268 (86)	286 (92)	270 (86)	189 (84)	181 (80)	181 (79)
Black	26 (8)	9 (3)	22 (7)	29 (13)	42 (19)	40 (17)
Other	18 (6)	16 (5)	21 (7)	6 (3)	4 (2)	8 (3)
Duration of seasonal allergic rhinitis, <i>n</i> (%)						
≥2 to <5 yr	45 (14)	34 (11)	35 (11)	18 (8)	23 (10)	19 (8)
≥5 to <10 yr	57 (18)	69 (22)	78 (25)	48 (21)	43 (19)	37 (16)
≥10 yr	210 (67)	208 (67)	200 (64)	158 (71)	161 (71)	173 (76)
Baseline symptoms, peak nasal inspiratory flow, and overall NRQLQ score (SE)						
Nighttime						
Nighttime symptom score (NSS)	6.9 (0.07)	7.1 (0.07)	7.0 (0.07)	6.8 (0.09)	6.9 (0.08)	6.9 (0.08)
Reflective TNSS	9.8 (0.09)	9.8 (0.09)	9.9 (0.08)	9.7 (0.10)	9.9 (0.11)	9.8 (0.10)
Reflective TOSS	6.9 (0.08)	7.0 (0.08)	7.0 (0.09)	6.8 (0.10)	7.0 (0.10)	6.9 (0.10)
Morning PNIF, L/min	95.0 (2.38)	92.1 (2.18)	93.4 (2.15)	99.4 (2.61)	100.0 (2.76)	100.0 (2.91)
Symptom score at end of dosing						
Instantaneous TNSS	9.5 (0.09)	9.6 (0.10)	9.6 (0.09)	9.5 (0.11)	9.7 (0.12)	9.4 (0.12)
Instantaneous TOSS	6.9 (0.09)	7.0 (0.08)	7.0 (0.09)	6.8 (0.11)	7.0 (0.10)	6.9 (0.11)
Daytime						
rTNSS	9.8 (0.09)	10.0 (0.08)	10.0 (0.08)	10.0 (0.10)	10.0 (0.11)	9.9 (0.10)
Reflective TOSS	7.0 (0.08)	7.0 (0.08)	7.1 (0.08)	6.9 (0.10)	7.1 (0.10)	7.0 (0.09)
Evening PNIF, L/min	101.4 (2.55)	98.1 (2.26)	100.6 (2.30)	109.0 (2.77)	109.5 (2.88)	110.4 (3.10)
Health outcomes						
Overall NRQLQ	4.2 (0.05)	4.3 (0.06)	4.2 (0.06)	4.1 (0.07)	4.2 (0.07)	4.1 (0.06)

FFNS = fluticasone furoate nasal spray 110 µg; FEX = fexofenadine, 180 mg oral tablet; TNSS = total nasal symptom score; TOSS = total ocular symptom score; PNIF = peak nasal inspiratory flow; NRQLQ = Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire.

ment period. Fexofenadine did not significantly differ from placebo with respect to this measure (study 1, $p = 0.136$; study 2, $p = 0.632$; Table 2).

Nighttime Reflective Total Ocular Symptom Scores. Mean nighttime reflective total ocular symptom scores were similar among treatment groups within the two

studies at baseline (Table 1). In the first study, FFNS was significantly ($p = 0.001$) more effective than placebo with respect to the mean change from baseline in the nighttime reflective total ocular symptom score over the 2-week treatment period. Treatment differences with respect to this measure between FFNS and fexofenadine ($p = 0.106$) and between fexofenadine

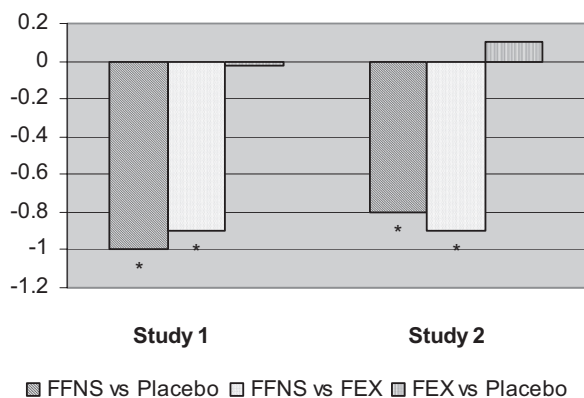


Figure 1. Least squares mean differences for comparisons between treatment groups for changes from baseline in nighttime symptoms score over the 2-week treatment period. *, Statistically significant result.

and placebo ($p = 0.286$) were, however, smaller than that between FFNS and placebo and neither difference reached statistical significance (Table 2). In the second study, FFNS was significantly more effective than both placebo ($p = 0.034$) and fexofenadine ($p = 0.002$) with respect to this end point while fexofenadine failed to reach statistical significance over placebo ($p = 0.400$).

Morning Peak Nasal Inspiratory Flow. Mean values for morning peak nasal inspiratory flow were similar among treatment groups in the two studies at baseline (Table 1). In both studies, FFNS was significantly ($p < 0.001$) more effective than fexofenadine and placebo with respect to the mean changes from baseline in morning peak nasal inspiratory flow over the 2-week treatment period. Fexofenadine did not significantly differ from placebo in terms of this measure (study 1, $p = 0.779$; study 2, $p = 0.176$; Table 2).

Predose Instantaneous TNSSs. The predose instantaneous measures indicate the duration of action of the treatment effect. Mean predose instantaneous TNSSs were similar among treatment groups within the two studies at baseline (Table 1). FFNS was significantly ($p < 0.001$) more effective than fexofenadine and placebo in both studies with respect to the mean change from baseline in predose instantaneous TNSS over the 2-week treatment period. Fexofenadine did not significantly differ from placebo with respect to this measure (study 1, $p = 0.193$; study 2, $p = 0.484$; Table 2).

Predose Instantaneous Total Ocular Symptom Scores. Mean predose instantaneous total ocular symptom scores were similar among treatment groups at baseline (Table 1). In study 1, fluticasone was significantly ($p < 0.001$) more effective than placebo with respect to the mean change from baseline in predose instantaneous total ocular symptom score over the 2-week

treatment period (Table 2). FFNS did not significantly differ from fexofenadine and fexofenadine did not differ significantly from placebo on this measure as with the nighttime reflective total ocular symptom measure (Table 2). In study 2, FFNS was significantly more effective than both fexofenadine ($p = 0.002$) and placebo ($p = 0.014$). The treatment difference between fexofenadine and placebo was not statistically significant ($p = 0.484$).

Daytime Symptoms

Daytime symptoms were also evaluated in the study during the early evening to determine any differences between the morning and evening treatment effects. All baseline daytime assessments were similar among treatment groups within each study (Table 1). As with nighttime symptoms, FFNS was significantly ($p < 0.001$) more effective in both studies than fexofenadine and placebo with respect to the mean changes from baseline in the daytime rTNSSs and evening peak nasal inspiratory flow measurements. In study 1, FFNS was significantly more effective than placebo with respect to the mean change from baseline in the daytime reflective total ocular symptom score ($p = 0.007$) but did not reach statistical significance in comparison with fexofenadine on this measure ($p = 0.106$). In study 2, FFNS was significantly more effective than both fexofenadine and placebo for this measure ($p \leq 0.034$). Fexofenadine did not significantly differ from placebo with respect to any daytime measure assessed (Table 2).

Quality of Life

Mean overall NRQLQ scores were similar among treatment groups at baseline in both studies (Table 1). FFNS was significantly ($p < 0.001$) more effective than placebo and fexofenadine in both studies with respect to the mean change from baseline in the overall NRQLQ total score over the 2-week treatment period (Table 2). Each of the individual NRQLQ domain scores (sleep problems, sleep time problems, symptoms on waking in the morning, and practical problems) showed numerical improvements corresponding to the changes in overall NRQLQ score for both FFNS and fexofenadine in both studies. Fexofenadine did not significantly differ from placebo with respect to overall NRQLQ scores in either study (Table 2).

Adverse Events

The percentage of patients with at least one adverse event was similar among groups in study 1 (16% in the fluticasone furoate group, 18% in the fexofenadine group, and 15% in the placebo group). The only adverse events reported in $>1\%$ of patients in a treatment group and reported more often with

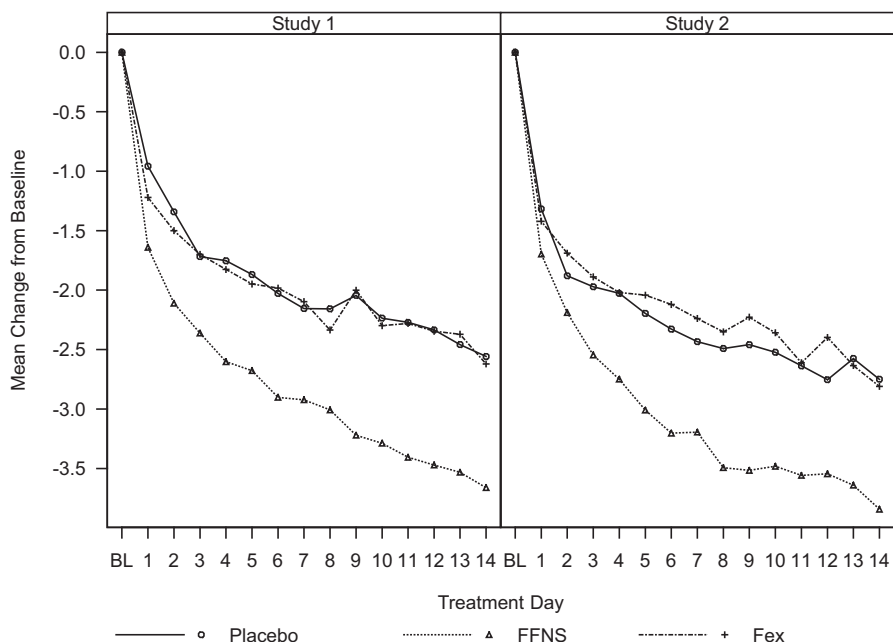


Figure 2. Mean change from baseline in nighttime symptoms score by treatment day. FFNS, Fluticasone furoate nasal spray.

active treatment than placebo was pharyngolaryngeal pain (2% FFNS, <1% fexofenadine, and 1% placebo). The number of patients who prematurely withdrew from the study because of adverse events was two in the fluticasone furoate group (one each with sinusitis and influenza), five in the fexofenadine group (one each with cholecystitis, hypersensitivity, cough, upper respiratory infection, and sinusitis), and one in the placebo group (with both sinusitis and bronchitis). Three adverse events in the fexofenadine group (cholecystitis, upper respiratory infection, and sinusitis), but none of the other adverse events leading to premature withdrawal, were designated by the investigator as having possibly been caused by study treatment.

The percentage of patients in study 2 with at least one adverse event was also similar among groups (14% in the fluticasone furoate group, 16% in the fexofenadine group, and 12% in the placebo group). The only adverse event reported in >1% of patients in a treatment group and reported more often with active treatment than placebo was epistaxis (no reports with FFNS, 2% fexofenadine, and <1% placebo). The number of patients who prematurely withdrew from the study because of adverse events was two in the fluticasone furoate group (upper respiratory infection and urticaria), one in the fexofenadine group (lymph gland infection), and one in the placebo group (viral upper respiratory infection). The adverse event of urticaria in the fluticasone furoate group was the only event considered by the investigator as possibly caused by study treatment.

DISCUSSION

Nasal symptoms have been strongly linked to sleeping difficulties and consequent impairment in next-day function and well-being in patients with allergic rhinitis.^{4-7,12,13} Nasal congestion, in particular, appears to be an important cause of sleep disturbance. The ability of pharmacotherapy to reduce nasal symptoms has been linked to improvements in sleep and next-day functioning.^{10,40} In the studies presented here, FFNS administered once daily reduced nighttime sleep disturbance from seasonal allergy symptoms better than oral fexofenadine and placebo as determined by the nighttime symptoms score, a validated measure of effects of allergic rhinitis symptoms during the night.³⁸ FFNS improved all three components of the nighttime nasal symptoms score—nasal congestion on awakening, nighttime awakenings due to nasal symptoms, and difficulty sleeping due to nasal symptoms.

The improvements in nasal symptoms during fluticasone furoate treatment were associated with statistically significant improvements in nocturnal rhinitis-specific quality of life measured with the NRQLQ. The overall NRQLQ score showed significantly greater improvement with fluticasone furoate spray than with either fexofenadine or placebo. Each of the NRQLQ domain scores (sleep problems, sleep time problems, symptoms on waking in the morning, and practical problems), although not subject to statistical hypothesis testing, reflected similar trends to the overall NRQLQ scores. The minimal clinically important difference in the NRQLQ score that constitutes a clinically relevant improvement in quality of life has been estab-

Table 2 Summary of efficacy data for secondary efficacy end points

Efficacy End Point	Study 1			Study 2		
	FFNS versus Placebo	FFNS versus FEX	FEX versus Placebo	FFNS versus Placebo	FFNS versus FEX	FEX versus Placebo
Nighttime						
Nighttime symptom score						
LS mean difference (SE)	−1.0 (0.14)	−0.9 (0.14)	−0.0 (0.14)	−0.8 (0.16)	−0.9 (0.16)	0.1 (0.16)
95% CI	−1.2, −0.7	−1.2, −0.7	−0.3, 0.2	−1.1, −0.4	−1.2, −0.6	−0.2, 0.5
p Value	<0.001	<0.001	0.816	<0.001	<0.001	0.374
Reflective TNSS						
LS mean difference (SE)	−1.3 (0.18)	−1.0 (0.18)	−0.3 (0.18)	−1.2 (0.22)	−1.3 (0.22)	0.1 (0.22)
95% CI	−1.6, −0.9	−1.4, −0.7	−0.6, 0.1	−1.6, −0.8	−1.7, −0.9	−0.3, 0.5
p Value	<0.001	<0.001	0.136	<0.001	<0.001	0.632
Reflective TOSS						
LS mean difference (SE)	−0.5 (0.15)	−0.3 (0.15)	−0.2 (0.15)	−0.4 (0.18)	−0.6 (0.18)	0.1 (0.18)
95% CI	−0.8, −0.2	−0.6, 0.0	−0.5, 0.1	−0.8, −0.1	−0.9, −0.2	−0.2, 0.5
p Value	0.001	0.106	0.286	0.034	0.002	0.400
Morning PNIF L/min						
LS mean difference (SE)	8.4 (1.59)	8.8 (1.59)	−0.4 (1.59)	8.0 (1.94)	10.6 (1.93)	−2.6 (1.93)
95% CI	5.3, 11.5	5.7, 11.9	−3.6, 2.7	4.2, 11.8	6.8, 14.4	−6.4, 1.2
p Value	<0.001	<0.001	0.779	<0.001	<0.001	0.176
Symptom score at end of dosing period						
Instantaneous TNSS						
LS mean difference (SE)	−1.3 (0.18)	−1.1 (0.18)	−0.2 (0.18)	−1.3 (0.22)	−1.5 (0.22)	0.2 (0.22)
95% CI	−1.7, −1.0	−1.4, −0.7	−0.6, 0.1	−1.7, −0.8	−1.9, −1.1	−0.2, 0.6
p Value	<0.001	<0.001	0.193	<0.001	<0.001	0.484
Instantaneous TOSS						
LS mean difference (SE)	−0.5 (0.15)	−0.3 (0.15)	−0.3 (0.15)	−0.4 (0.18)	−0.6 (0.18)	0.1 (0.18)
95% CI	−0.8, −0.2	−0.6, 0.0	−0.5, 0.0	−0.8, −0.1	−0.9, −0.2	−0.2, 0.5
p Value	<0.001	0.058	0.160	0.014	0.002	0.484
Daytime						
Reflective TNSS						
LS mean difference (SE)	−1.1 (0.19)	−0.8 (0.19)	−0.3 (0.19)	−1.2 (0.22)	−1.4 (0.22)	0.2 (0.22)
95% CI	−1.5, −0.7	−1.2, −0.4	−0.7, 0.1	−1.6, −0.7	−1.8, −0.9	−0.2, 0.6
p Value	<0.001	<0.001	0.136	<0.001	<0.001	0.632
Reflective TOSS						
LS mean difference (SE)	−0.4 (0.15)	−0.2 (0.15)	−0.2 (0.15)	−0.4 (0.18)	−0.6 (0.18)	0.2 (0.17)
95% CI	−0.7, −0.1	−0.5, 0.1	−0.5, 0.1	−0.7, −0.0	−0.9, −0.2	−0.1, 0.6
p Value	0.007	0.106	0.286	0.034	0.002	0.400
Evening PNIF L/min						
LS mean difference (SE)	7.0 (1.65)	6.3 (1.65)	0.7 (1.65)	7.3 (2.10)	9.3 (2.09)	−2.0 (2.09)
95% CI	3.8, 10.3	3.1, 9.6	−2.5, 4.0	3.2, 11.5	5.2, 13.4	−6.1, 2.1
p Value	<0.001	<0.001	0.662	<0.001	<0.001	0.350
Health outcomes						
Total NRQLQ score						
LS mean difference (SE)	−0.6 (0.11)	−0.5 (0.11)	−0.1 (0.11)	−0.6 (0.13)	−0.7 (0.12)	0.0 (0.12)
95% CI	−0.8, −0.4	−0.7, −0.3	−0.4, 0.1	−0.9, −0.4	−0.9, −0.4	−0.2, 0.3
p Value	<0.001	<0.001	0.203	<0.001	<0.001	0.791

FFNS = fluticasone furoate nasal spray, 110 µg; FEX = fexofenadine, 180 mg oral tablet; TNSS = total nasal symptom score; TOSS = total ocular symptom score; PNIF = peak nasal inspiratory flow; NRQLQ = Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire; LS mean difference = least squares mean difference; SE = standard error of the mean; CI = confidence interval.

lished as -0.42 .⁴¹ The magnitude of the differences between FFNS and fexofenadine and between FFNS and placebo in changes from baseline in the total NRQLQ score was both statistically significant and clinically meaningful because the minimal clinically important difference was met. The NRQLQ results are consistent with the reduction in TNSSs, which support the effectiveness of FFNS in controlling the nighttime symptoms that affect sleep.

In these randomized, double-blind clinical trials, FFNS significantly improved nighttime reflective nasal symptoms when compared with either placebo or fexofenadine. Furthermore, FFNS had sustained efficacy throughout the 24-hour dosing period as shown by significantly greater efficacy compared with placebo and fexofenadine in morning predose instantaneous TNSS. Improvements in these patient-reported symptom scores with FFNS were mirrored by the objective measure of morning peak nasal inspiratory flow. The nasal inspiratory flow data objectively corroborate patients' subjective assessments of the advantage of intranasal corticosteroids over antihistamines with respect to effects on nasal congestion and support previous findings indicating that FFNS administered once daily provides coverage throughout the nighttime hours against nasal manifestations of allergic rhinitis.²⁵⁻²⁷

FFNS was also effective when compared with placebo in the treatment of ocular symptoms in the first study and was significantly more effective than both fexofenadine and placebo in study 2. The greater efficacy of FFNS than placebo in the treatment of ocular symptoms corroborates previous findings in four studies of the drug in seasonal allergic rhinitis.^{23,25-27} Furthermore, FFNS is the only intranasal corticosteroid that has replicated efficacy in the treatment of both nasal and ocular symptoms in prospectively designed clinical trials. The mechanism of fluticasone furoate's efficacy for ocular symptoms has not been established although it has been suggested that the effect may occur through reduction of nasal inflammation and by modulating allergen-induced changes in reflex neuronal activity from the nose to the eye.^{16,25-27,42-45} Systemic exposure to fluticasone furoate is very low and likely insufficient to account for its ocular efficacy.

Although fexofenadine achieved numerically greater improvement over placebo on some endpoints in the two studies and has previously been shown to be more effective than oral placebo in improving nasal and ocular symptoms of allergic rhinitis,³⁵ it did not differ statistically from placebo in its effects on nighttime sleep disturbance or nighttime nasal and ocular symptoms in either study. An unusually weak response to fexofenadine does not appear to account for its lack of separation from placebo: changes from baseline in na-

sal and ocular symptoms during fexofenadine treatment in the current study were generally of similar magnitude to fexofenadine-associated changes reported in previous studies.³⁵ Instead, the lack of separation between the fexofenadine groups and the placebo groups may be attributed to the large placebo effect of the vehicle nasal spray administered to both the fexofenadine and the placebo groups. The moisturizing effect of the vehicle nasal spray likely overshadowed the therapeutic benefit of fexofenadine, placing the group near parity with the placebo group. A similar lack of treatment separation between an oral antihistamine and placebo was observed in previous double-dummy research in which both the oral antihistamine group and the placebo group were treated with placebo nasal sprays.⁴⁶

FFNS and fexofenadine were both well tolerated in this study. Both drugs were similar to placebo with respect to the overall incidence of adverse events and the incidences of specific adverse events. These results for fluticasone furoate corroborate previous findings²⁵⁻²⁸ and are consistent with its low absolute bioavailability ($<0.5\%$).²⁴

In conclusion, results of these randomized, double-blind, double-dummy, placebo-controlled studies indicate that FFNS administered once daily was well tolerated and significantly reduced nighttime sleep disturbance from symptoms of seasonal allergic rhinitis while improving nocturnal rhinitis-specific quality of life more than both fexofenadine, 180 mg, once daily and placebo. FFNS was significantly more effective than fexofenadine, 180 mg, once daily at improving nighttime nasal allergy symptoms and at least comparable in improving nighttime ocular symptoms. The greater improvements in morning predose instantaneous TNSSs and the objective measurement of morning peak nasal inspiratory flow compared with fexofenadine and placebo support the established 24-hour duration of action for FFNS and provide a rationale for its ability to reduce nighttime symptoms of seasonal allergic rhinitis.

ACKNOWLEDGMENTS

The authors acknowledge Jane Saiers, Ph.D., for assistance with writing this article, and Kristofer Klein, M.S., a GlaxoSmithKline employee, for editing assistance and article management.

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