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ORIGINAL ARTICLE

Effectiveness of fluticasone furoate 110 µg once daily in the treatment of nasal and ocular symptoms of seasonal allergic rhinitis in adults and adolescents sensitized to mountain cedar pollen*

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Key words: Fluticasone furoate – Intranasal corticosteroids – *Juniperus ashei* – Mountain cedar – Nasal spray – Nasal symptoms – Ocular symptoms – Seasonal allergic rhinitis

ABSTRACT

Background: Fluticasone furoate (FF) is a novel enhanced-affinity corticosteroid for the treatment of allergic rhinitis, delivered by a unique side-actuated device. This study was designed to investigate the efficacy and safety of FF nasal spray (FFNS) 110 µg once daily compared with placebo in adults and adolescents (aged ≥12 years) with seasonal allergic rhinitis (SAR) symptoms caused by mountain cedar (*Juniperus ashei*) pollen.

Methods: This was a randomized, double-blind, placebo-controlled, parallel-group, phase III study conducted over a 2-week period (between 10 December 2004 and 19 January 2005) at seven study sites, in Austin, Texas, USA, and San Antonio, Texas, two metropolitan cities in the central Texas Hill Country located approximately 80 miles apart. Adult and adolescent patients (aged ≥12 years) with SAR, who were sensitized to mountain cedar (*Juniperus ashei*) pollen, were randomized to receive either FFNS 110 µg ($n = 152$) or placebo

($n = 150$) once daily. Patients rated the severity of each nasal symptom (rhinorrhea, nasal congestion, nasal itching, and sneezing) and ocular symptom (redness, watery eyes, itching and burning) on a 4-point categorical scale (0 = none, 3 = severe) in a reflective and instantaneous manner. Patients also rated their overall evaluation of response to therapy.

Trial registration: ClinicalTrials.gov Identifier NCT00115622

Results: FFNS significantly improved the nasal symptoms of SAR compared with placebo. The least square (LS) mean difference in the reflective total nasal symptom score (TNSS) was -0.777 ($p = 0.003$). A significant reduction in morning pre-dose instantaneous TNSS was also observed compared with placebo (LS mean difference -0.902 ; $p < 0.001$). Patients receiving FFNS had significantly greater improvements from baseline in reflective total ocular symptom scores (TOSS) than those receiving placebo (LS mean difference -0.546 ; $p = 0.008$). Significant improvements in ocular symptoms

*Data from this study were presented in abstract and poster format at the American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting, held in San Diego, CA, USA, 23–27 February 2007

with FFNS versus placebo were also observed for morning pre-dose instantaneous TOSS (LS mean difference -0.519 ; $p = 0.009$). FFNS had a favorable safety and tolerability profile: fewer adverse events occurred with FFNS (22%) than

with placebo (29%), and no serious adverse events were observed.

Conclusions: FFNS 110 μg once daily demonstrated efficacy in relieving both the nasal and ocular symptoms of SAR in adult and adolescent patients.

Introduction

Allergic rhinitis (AR) is a highly prevalent, atopic condition that affects as many as 40 million people in the USA annually¹. The disorder is characterized by nasal (congestion, sneezing, itching, and rhinorrhea) and ocular symptoms (redness, watery eyes, itching and burning) and, depending on the timing and duration of symptoms, can be classified as seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR)^{2,3}. Patients with SAR experience symptomatic exacerbations during pollen seasons. Although not life threatening, the symptoms of AR can have a detrimental impact on a patient's quality of life, affecting social activities, learning ability, exam results, and work productivity³⁻⁵.

Several treatment options for managing the symptoms of AR exist, including antihistamines, intranasal corticosteroids (INS), and antileukotrienes. The American Academy of Allergy, Asthma and Immunology (AAAAI) recommends INS as first-line therapy for AR when nasal congestion is a major component of the condition, and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend INS for patients with moderate-to-severe symptoms^{6,7}. Oral antihistamines are effective against symptoms mediated by histamine (rhinorrhea, sneezing, and nasal itching), but are less effective against nasal congestion⁸. They have also been shown to reduce ocular symptoms and can be used as an ancillary treatment with INS in patients particularly affected by ocular symptoms⁹. INS have been shown to be consistently effective in relieving nasal symptoms, particularly congestion⁹; however, significant reductions in the ocular symptoms of AR have not been consistently observed with previously studied INS⁹⁻¹².

Fluticasone furoate (FF) is a novel, enhanced-affinity corticosteroid for the treatment of AR, delivered by a unique side-actuated delivery device¹³. The device was developed based on results from market research in patients with AR and includes features such as a shorter nozzle, ergonomic design, and once-monthly priming. Preclinical studies have shown that FF exhibits enhanced affinity and selectivity for the glucocorticoid receptor, low systemic bioavailability (0.5%)¹⁴, and long duration of anti-inflammatory activity compared with other currently available INS¹⁵. FF nasal spray (FFNS) 110 μg once daily has been shown to be

significantly more effective than placebo in relieving the nasal and ocular symptoms of adult and adolescent patients sensitized to grass and ragweed pollen^{16,17}.

The current study was designed to investigate the efficacy and safety of FFNS 110 μg once daily compared with placebo in adults and adolescents (aged ≥ 12 years) with SAR symptoms caused by mountain cedar (*Juniperus ashei*) pollen. Mountain cedar trees are found in abundance in south-central Texas, USA, and produce copious amounts of pollen during the months of December through February. Studies of AR are often performed during the mountain cedar pollen season because of the very allergenic nature of the pollen and its predominance as the primary seasonal allergen at this time. Studies of 2 weeks' duration are considered ethically and scientifically appropriate for this typically intense pollen season.

Methods

Study design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted from 10 December 2004 (first screening visit) to 19 January 2005 (last treatment visit) at five centers in San Antonio, Texas, USA, and two centers in Austin, Texas, USA. Pollen samples began being collected in early December and were collected for ≥ 5 days per week during the course of the study using a Rotorod Sampler (Sampling Technologies, Inc., Minnetonka, MN, USA) located at or near the investigator's office. Sites were directed to initiate screening when pollen counts determined the onset of the cedar season in the two locales. To ensure continued exposure, patients were not permitted to travel outside their geographic region for more than 48 hours. The study was approved by the institutional review board (Coast IRB, LLC, Colorado Springs, CO, USA), and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients and/or parents/guardians provided written informed consent prior to participation.

Patients

Key inclusion and exclusion criteria

Patients aged ≥ 12 years were eligible for inclusion at each site if they had documented SAR (seasonal onset

and offset of nasal symptoms over the last two allergy seasons) and a positive skin-prick test for mountain cedar allergy (wheal ≥ 3 mm larger than the diluent control) 12 months prior to study start. Sensitivity to other allergens was not tested because mountain cedar pollen is the predominant cause of allergic symptoms at this time. Patients were required to be clinically symptomatic on the first day of treatment and to have attained a predefined minimum level of symptom severity to be eligible for randomization. Patients were excluded from the study if they had significant concomitant medical conditions or an existing nasal disorder that might interfere with the conduct of the study. Patients were excluded if they had used corticosteroids, including INS within 4 weeks of visit 1 (screening visit), or inhaled, oral, intramuscular, intravenous, ocular, and/or dermatological corticosteroids (with the exception of hydrocortisone cream/ointment 1% or less) within 8 weeks prior to visit 1. Patients who had used other allergy medications, such as short-acting prescription and over-the-counter antihistamines (within 3 days prior to visit 1), long-acting antihistamines (within 10 days prior to visit 1), intranasal antihistamines (within 2 weeks prior to visit 1), oral or intranasal decongestants, long-acting beta-agonists, intranasal, oral or inhaled anticholinergics, or oral antileukotrienes (all within 72 hours prior to visit 1), were also excluded, as were patients who were using medications that affect AR symptoms (e.g., tricyclic antidepressants, other intranasally administered medications, throat lozenges), immunosuppressive medications, and medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4 (including ritonavir and ketoconazole). Other medications were allowed provided the treatment regimen remained the same throughout the study.

Study assessments and procedures

The study consisted of a screening period and a 2-week treatment period that included four clinic visits during December 2004 to January 2005: screening (visit 1, -5 to -21 days); randomization (visit 2, day 1); mid-treatment efficacy and safety evaluation (visit 3, day 8 ± 2 days); and final efficacy and safety evaluation (visit 4, day 15 ± 1 day). Patients entered the trial at different time points during the approximately 6-week study period. During the screening and treatment periods, the severity of each patient's nasal, ocular, and throat/palatal itching symptoms was assessed in an instantaneous and reflective manner using patient diary cards. Instantaneous scores represented patients' symptoms at the time of assessment (just prior to taking the next dose each day, as a measure of 24-hour duration of action). Reflective scores

were based on the symptoms experienced by a patient during the previous 12 hours (evaluated in the morning [AM] and evening [PM]).

Patients rated the severity of each nasal, ocular and throat/palatal itching symptom on a 4-point categorical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), as recommended by the US Food and Drug Administration (FDA) and European Committee for Medicinal Products for Human Use (CHMP). The total nasal symptom score (TNSS) is the sum of the four individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing. The total ocular symptom score (TOSS) is the sum of the individual symptom scores for itching/burning eyes, tearing/watering eyes, and eye redness. Mean baseline scoring was defined as the average of the daily reflective TNSS (rTNSS) over the four consecutive 24-hour periods prior to randomization, including the assessment on the morning of randomization. Patients were randomized to treatment if they had an instantaneous TNSS (iTNS) of ≥ 6 , an instantaneous nasal symptom score for congestion of ≥ 2 on the morning of randomization; and an average score for rTNSS of ≥ 6 , reflective TOSS (rTOSS) of ≥ 4 , and a reflective nasal symptom score for congestion of ≥ 2 for the last eight pre-randomization assessments.

Randomization was achieved using a computer-generated block randomization schedule and was stratified by investigation site, ensuring that patients at each site had an equal chance of receiving FFNS or placebo. Double-blind treatment with either FFNS 110 μ g once daily or vehicle placebo nasal spray once daily for 2 weeks was assigned using an interactive voice response system, which was accessed via personal identification numbers assigned to authorized site personnel. The randomization number assigned corresponded to a particular treatment kit containing an identical FFNS or placebo nasal spray device. Compliance was determined by subject verification of daily treatment administration on the diary card. Symptom scores were recorded on a daily basis prior to morning dosing and then 12 hours later. Evaluation of iTNS took place 4, 6, 8, 10, and 12 hours after the first dose of study medication to provide data for the onset of treatment effect, and then daily thereafter. Quality of life was assessed at baseline and after 2 weeks of treatment using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), a validated, self-administered, 28-item questionnaire. Each question is scored from 0 to 6, with higher scores indicating greater impairment of quality of life. Items are grouped into seven domains: activity limitations (3 items), sleep problems (3 items), non-nose/eye symptoms (7 items), practical problems (3 items), nasal symptoms

(4 items), eye symptoms (4 items) and emotional function (4 items). An overall quality of life score was calculated from the mean score of all items.

Patients rated their overall response to therapy on a 7-point categorical scale (significantly, moderately, or mildly improved; no change; mildly, moderately, or significantly worse) by answering the question 'How would you rate the effectiveness of the double-blind study drug for relieving your AR symptoms over the entire treatment period?'

Safety and tolerability were assessed at each clinic visit by adverse event (AE) monitoring, clinical examination (including observation of vital signs, physical examination, and nasal examination), 12-lead electrocardiogram monitoring and clinical laboratory tests. All AEs were recorded from screening through the follow-up phone call, which took place 3–5 days after the final visit.

Endpoints

The primary endpoint was mean change from baseline over the entire treatment period in daily rTNSS. Key secondary endpoints included mean change from baseline over the entire treatment period in AM pre-dose iTNSS and daily rTOSS, and overall evaluation of response to therapy. Other endpoints included mean change from baseline over the entire treatment period in AM pre-dose instantaneous TOSS (iTTOSS), AM and PM rTNSS, and individual nasal symptoms, ocular symptoms, throat/palatal itching, and quality of life.

Statistical analyses

A sample size of 144 patients per treatment group (required to detect a difference of 1.0 in the primary efficacy endpoint between active treatment and placebo with a 5% two-sided significance level and 90% power) was calculated on the basis of results from a previous study¹⁸. The primary analysis method was the two-sided comparison of treatment groups (FFNS vs. placebo) using an analysis of covariance (ANCOVA) with adjustments for baseline rTNSS, investigation site, age, and gender. Secondary efficacy measures of nasal and ocular symptoms involving diary cards were analyzed using the same method. Efficacy assessments were carried out in the intent-to-treat (ITT) population (all randomized patients who had received at least one dose of the study drug). Multiplicity adjustments were made for the results from the primary and key secondary efficacy analyses and the quality of life endpoint. No adjustments for multiplicity were made for any other efficacy endpoints. To control for multiplicity, null hypothesis tests were performed in a sequential manner to control the type I error rate at 0.05.

The primary analysis of the RQLQ was the pair-wise comparison of FFNS and placebo in the mean change from baseline to endpoint for the global score. A mean change from baseline of 0.5 for the RQLQ scores is considered the minimum change that patients perceive to be beneficial (minimally important difference)¹⁹. Overall evaluation of response to therapy was analyzed using logistic regression, adjusting for age, gender, investigation site and treatment. Onset of action for the study drug was determined from the mean change from baseline in AM pre-dose iTNSS at 4, 6, 8, 10, and 12 hours after the first dose and daily thereafter, as well as the mean change from baseline in daily rTNSS from days 1 to 14. These data were analyzed using a repeated-measures model, adjusting for baseline iTNSS, age, gender, treatment, investigator, time, and treatment-by-time interaction. Demographic, tolerability and safety data were summarized using descriptive statistics.

Results

Study population

A total of 575 patients were screened, of whom 302 were considered eligible for randomization (ITT population) to receive either FFNS 110 µg once daily ($n = 152$) or placebo once daily ($n = 150$). Each study center enrolled between 3% ($n = 8$) and 20% ($n = 60$) of study participants; patients were not required to be matched for age or gender between sites. In total, 94% of patients completed the study. Withdrawal rates following randomization were low, and only patients in the placebo group withdrew because of AEs (two patients, 1%) and protocol violations (four patients, 3%). Demographic characteristics were generally similar in the treatment and placebo groups (Table 1). In total, 63% and 65% of patients receiving FFNS 110 µg once daily and placebo, respectively, reported having SAR for ≥ 10 years. As expected, pollen counts varied among the sites because of factors such as weather conditions (e.g., wind, temperature) and proximity of the Rotorod sampler to cedar trees. In general, pollen counts obtained during the study showed the onset of the season beginning in early December 2004 with declines in normal seasonal levels occurring in mid and late December following the occurrence of freezing temperatures.

Efficacy assessments

Effect of treatment on nasal symptoms

Treatment with FFNS 110 µg once daily improved rTNSS to a greater extent than placebo: the mean change from baseline in daily rTNSS over the treatment

Table 1. Demographic and baseline characteristics of 302 patients (ITT population) with SAR who were sensitized to mountain cedar pollen and received randomized, double-blind treatment with FFNS or placebo once daily for 2 weeks

Characteristic	FFNS 110 µg (n = 152)	Placebo (n = 150)	Total (n = 302)
Age (years)			
Mean (SD)	37.0 (13.9)	38.1 (13.60)	37.6 (13.74)
Min–max	12–75	13–67	12–75
Gender, n (%)			
Female	92 (61)	99 (66)	191 (63)
Male	60 (39)	51 (34)	111 (37)
Duration of SAR, n (%)			
≥2 to <5 years	24 (16)	16 (11)	40 (13)
≥5 to <10 years	32 (21)	37 (25)	69 (23)
≥10 years	96 (63)	97 (65)	193 (64)
TNSS*, mean (SD)			
Daily reflective	9.8 (1.37)	9.7 (1.30)	—
AM instantaneous	9.4 (1.59)	9.5 (1.53)	—
AM reflective	9.8 (1.43)	9.7 (1.42)	—
PM reflective	9.9 (1.48)	9.8 (1.37)	—
TOSS†, mean (SD)			
Daily reflective	6.6 (1.34)	6.5 (1.33)	—
AM instantaneous	6.3 (1.56)	6.4 (1.53)	—
AM reflective	6.6 (1.41)	6.5 (1.39)	—
PM reflective	6.7 (1.41)	6.6 (1.42)	—

*Maximum score for TNSS = 12; †maximum score for TOSS = 9

AM, morning; ITT, intent-to-treat; PM, evening; SAR, seasonal allergic rhinitis; SD, standard deviation; TNSS, total nasal symptom score; TOSS, total ocular symptom score

period was significantly greater for FFNS than for placebo (−3.03 and −2.25, respectively; least square [LS] mean difference −0.777, $p=0.003$; Figure 1A and Table 2). The LS mean difference between the two treatments was significant for all of the reflective individual nasal symptoms (rhinorrhea, $p=0.004$; nasal congestion, $p=0.012$; sneezing, $p<0.001$), with the exception of nasal itching ($p=0.063$; Table 2).

Significant improvements in AM pre-dose iTNSS were also observed with FFNS 110 µg once daily compared with placebo (−2.38 and −1.47, respectively; LS mean difference −0.902, $p<0.001$; Figure 1B). Onset of treatment effect, defined as a significant LS mean change from baseline in iTNSS compared with placebo, was observed at the end of days 1, 2 and 4 and sustained from day 6 onwards ($p\leq0.045$).

Effect of treatment on ocular symptoms

Patients receiving FFNS experienced significantly greater improvements from baseline in rTOSS than those receiving placebo. The LS mean change from baseline over the entire treatment period in daily rTOSS was −2.15 in the FFNS group versus −1.60 in the placebo group (LS mean difference −0.546, $p=0.008$; Table 3, Figure 2).

Significant improvements in ocular symptoms with FFNS versus placebo were also observed for AM pre-dose iTOSS (LS mean change from baseline: −1.57 and −1.05 in the FFNS and the placebo group; LS mean difference −0.519; $p=0.009$).

Health-related quality of life

At baseline, patients in both the FFNS and placebo groups had moderate-to-severe impairment of their rhinitis-related quality of life (Table 4). At the end of the study, patients receiving FFNS had experienced significant and clinically meaningful improvements in overall rhinitis-related quality of life (LS mean difference −0.690; $p<0.001$) and in each of the seven individual domains of the RQLQ: activities ($p=0.003$), sleep ($p=0.023$), non-hay fever symptoms ($p=0.006$), practical problems ($p<0.001$), nasal symptoms ($p<0.001$), eye symptoms ($p=0.001$) and emotional problems ($p=0.013$) compared with patients in the placebo group (Table 4).

Other endpoints

A significant mean change from baseline was observed for the AM pre-dose instantaneous exploratory

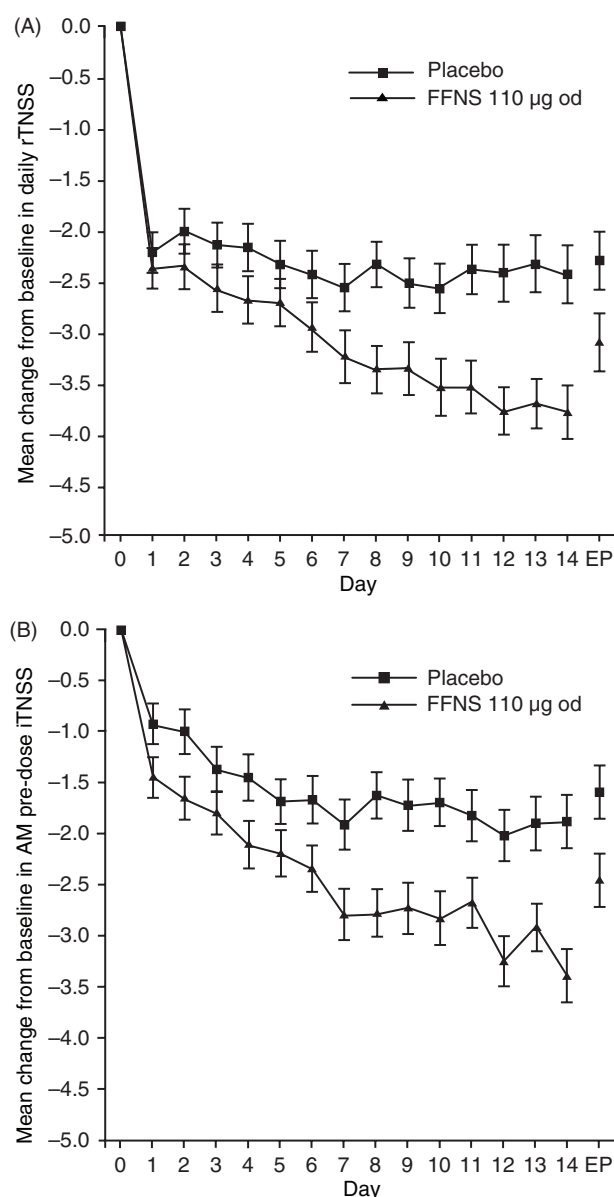


Figure 1. Mean change ($\pm$ SE) from baseline in (A) daily reflective total nasal symptom scores (rTNSS) and (B) mean change from baseline in AM pre-dose instantaneous total nasal symptom scores (iTNSS) over the treatment period (302 patients; ITT population) (EP, endpoint; ITT, intent-to-treat)

assessment of throat/palatal itching with FFNS compared with placebo ($p=0.024$). Although the daily reflective score for FFNS for this symptom achieved a numerically greater reduction versus placebo, this difference did not reach statistical significance.

Overall response to treatment was significantly better in FFNS-treated patients than in placebo-treated patients ($p < 0.001$). Overall, 48% of patients receiving FFNS noted a significant or moderate improvement in their condition, compared with 31% of patients receiving placebo. In the FFNS group, 6% of patients reported worsening of symptoms, compared with 18% of placebo recipients.

Table 2. Mean change from baseline in daily reflective total and individual nasal symptom scores for weeks 1–2 in 302 patients (ITT population) with SAR who were sensitized to mountain cedar pollen and received randomized, double-blind treatment with FFNS or placebo once daily for 2 weeks

Nasal symptoms	FFNS 110 µg (n = 152)	Placebo (n = 150)
Daily rTNSS		
LS mean change (SE)	–3.03 (0.21)	–2.25 (0.21)
LS mean difference	–0.777	
P-value	0.003	
95% CI	–1.28, –0.27	
Rhinorrhea		
LS mean change (SE)	–0.77 (0.06)	–0.56 (0.06)
LS mean difference	–0.206	
P-value	0.004	
95% CI	–0.35, –0.07	
Nasal congestion		
LS mean change (SE)	–0.75 (0.05)	–0.58 (0.05)
LS mean difference	–0.168	
P-value	0.012	
95% CI	–0.30, –0.04	
Nasal itching		
LS mean change (SE)	–0.74 (0.06)	–0.61 (0.06)
LS mean difference	–0.135	
P-value	0.063	
95% CI	–0.28, –0.01	
Sneezing		
LS mean change (SE)	–0.77 (0.06)	–0.51 (0.06)
LS mean difference	–0.264	
P-value	<0.001	
95% CI	–0.41, –0.12	

CI, confidence interval; FFNS, fluticasone furoate nasal spray; ITT, intent-to-treat; LS, least square; rTNSS, reflective total nasal symptom score; SAR, seasonal allergic rhinitis; SE, standard error

Safety and tolerability

Overall, FFNS 110 µg once daily had a favorable safety and tolerability profile. Fewer AEs occurred in the FFNS group (22%) than in the placebo group (29%; Table 5). Headache was the most commonly reported AE (5% in the FFNS group and 4% in the placebo group). The most common drug-related AE, epistaxis, occurred at an incidence of 3% in both treatment groups. All episodes were mild (four patients in each group) or moderate (one patient in each group) in intensity and resolved in all but one patient receiving placebo. There were no serious AEs. At treatment end, the condition of the nasal septum, mucosal crusting, and mucosal bleeding were similar to baseline for both groups. The incidence of laboratory abnormalities was low and similar between the two treatment groups.

Table 3. Mean change from baseline in daily reflective total and individual ocular symptom scores for weeks 1–2 in 302 patients (ITT population) with SAR who were sensitized to mountain cedar pollen and received randomized, double-blind treatment with FFNS or placebo once daily for 2 weeks

Ocular symptoms	FFNS 110 µg (n = 152)	Placebo (n = 150)
Daily rTOSS		
LS mean change (SE)	–2.15 (0.17)	–1.60 (0.17)
LS mean difference	–0.546	
p-value	0.008	
95% CI	–0.95, –0.14	
Eye itching/burning		
LS mean change (SE)	–0.70 (0.06)	–0.51 (0.06)
LS mean difference	–0.195	
p-value	0.007	
95% CI	–0.34, –0.05	
Eye tearing/watering		
LS mean change (SE)	–0.76 (0.06)	–0.60 (0.06)
LS mean difference	–0.157	
p-value	0.032	
95% CI	–0.30, –0.01	
Eye redness		
LS mean change (SE)	–0.69 (0.06)	–0.49 (0.06)
LS mean difference	–0.198	
p-value	0.006	
95% CI	–0.34, –0.06	

CI, confidence interval; FFNS, fluticasone furoate nasal spray; ITT, intent-to-treat; LS, least square; SAR, seasonal allergic rhinitis; SE, standard error; rTOSS, reflective total ocular symptom score

Discussion

Treatment with FFNS for 2 weeks was significantly more effective than placebo in improving the nasal symptoms (congestion, nasal itching, rhinorrhea, and sneezing) of SAR during the US mountain cedar allergy season (December to February) in adult and adolescent (aged ≥ 12 years) patients. In addition, FFNS was significantly more effective than placebo in the relief of ocular symptoms (watering/tearing, itching/burning, and redness) and throat/palatal itching.

In agreement with findings from the dose-ranging study¹⁸, as well as the results of two phase III studies^{16,17}, the results from this trial show that FFNS is consistently effective in reducing both the nasal and ocular symptom scores of SAR in adult and adolescent patients.

Although the ocular mechanism of action is currently unknown, it is postulated that ocular symptoms of AR

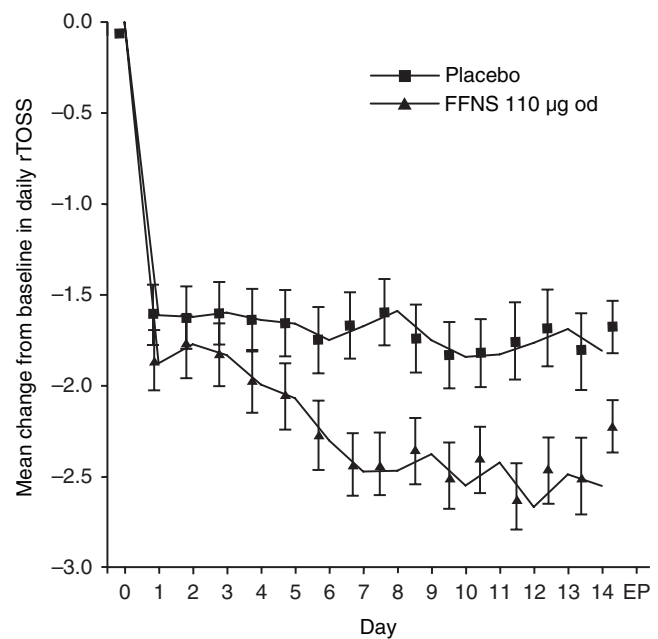


Figure 2. Mean change ($\pm$ SE) from baseline over the entire treatment period in daily reflective total ocular symptom scores (rTOSS) (n = 302 patients; ITT population) (EP, endpoint; ITT, intent-to-treat)

might be stimulated by the naso-ocular reflex, which is initiated by the release of histamine at the site of nasal allergen challenge²⁰. FFNS may reduce the strength of this reflex, and the resulting ocular symptoms, by reducing nasal inflammation. Intranasal FF has a low systemic bioavailability (0.5%) resulting from poor aqueous solubility, limited mucosal contact time with the nose, and extensive first-pass metabolism; therefore, it is unlikely that the observed effects on ocular symptoms are attributable to systemic effects¹⁴.

Duration of treatment effect over the full 24 hours was demonstrated through the significant improvements in AM pre-dose iTNSS and iTOSS for FFNS compared with placebo. Instantaneous symptom scores were recorded immediately prior to administration of each daily dose, providing a measure of efficacy at the end of the 24-hour dosing period. Unlike reflective scores, instantaneous scores provide a true measure of 24-hour efficacy, supporting the adequacy of once-daily dosing with FFNS, as also demonstrated in earlier studies^{16–18}.

Baseline symptom scores of randomized patients in this study were similar to those seen in another study of FFNS performed during a different mountain cedar season¹⁸. During the first week of treatment, although numerically greater, the overall treatment differences from placebo for rTNSS and rTOSS in patients receiving FFNS were not significant ($p = 0.098$ and $p = 0.077$, respectively). It is probable that low pollen counts related to unseasonably cold weather during the

Table 4. RQLQ scores in 302 patients (ITT population) with SAR who were sensitized to mountain cedar pollen and received randomized, double-blind treatment with FFNS or placebo once daily for 2 weeks

Quality of life	FFNS 110 µg	Placebo
Overall		
Baseline, <i>n</i>	152	150
Baseline mean (SE)	4.1 (0.9)	4.1 (0.9)
Endpoint, <i>n</i>	150	149
LS mean difference		−0.690
Activities		
Baseline, <i>n</i>	141	139
Baseline mean (SE)	4.4 (1.0)	4.5 (1.1)
Endpoint, <i>n</i>	143	142
LS mean difference		−0.720*
Sleep		
Baseline, <i>n</i>	152	149
Baseline mean (SE)	3.8 (1.3)	4.0 (1.2)
Endpoint, <i>n</i>	151	149
LS mean difference		−0.508†
Non-hay fever symptoms		
Baseline, <i>n</i>	152	150
Baseline mean (SE)	3.7 (1.1)	3.8 (1.1)
Endpoint, <i>n</i>	151	149
LS mean difference		−0.574‡
Practical problems		
Baseline, <i>n</i>	151	150
Baseline mean (SE)	4.5 (1.2)	4.4 (1.2)
Endpoint, <i>n</i>	151	149
LS mean difference		−0.919
Nasal symptoms		
Baseline, <i>n</i>	151	150
Baseline mean (SE)	4.7 (1.0)	4.6 (0.9)
Endpoint, <i>n</i>	151	149
LS mean difference		−0.943
Eye symptoms		
Baseline, <i>n</i>	150	150
Baseline mean (SE)	4.1 (1.1)	4.1 (1.2)
Endpoint, <i>n</i>	150	149
LS mean difference		−0.743§
Emotional problems		
Baseline, <i>n</i>	151	150
Baseline mean (SE)	3.6 (1.3)	3.7 (1.3)
Endpoint, <i>n</i>	150	149
LS mean difference		−0.544**

p < 0.001 for the LS mean difference, except where indicated

p* = 0.003, †*p* = 0.023, ‡*p* = 0.006, §*p* = 0.001, *p* = 0.013

FFNS, fluticasone furoate nasal spray; ITT, intent-to-treat; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SE, standard error

first few weeks of the study contributed to this result. However, from week 2, the overall treatment differences for rTNSS and rTOSS in patients receiving FFNS continued to increase relative to placebo (*p* < 0.001 and *p* = 0.003, respectively) resulting in an overall statistically significant improvement over the

Table 5. Adverse events occurring at ≥ 1% incidence and more common than placebo in 302 patients (ITT population) with SAR who were sensitized to mountain cedar pollen and received randomized, double-blind treatment with FFNS or placebo once daily for 2 weeks

Adverse event	FFNS 110 µg (<i>n</i> = 152)	Placebo (<i>n</i> = 150)
Patients with any adverse event, <i>n</i> (%)	34 (22)	43 (29)
Headache	8 (5)	6 (4)
Nasopharyngitis	3 (2)	1 (<1)
Pharyngolaryngeal pain	2 (1)	1 (<1)
Sinus headache	2 (1)	1 (<1)
Nausea	2 (1)	0

FFNS, fluticasone furoate nasal spray; ITT, intent-to-treat; SAR, seasonal allergic rhinitis

remainder of the study (*p* = 0.003 and *p* = 0.008, respectively).

The symptoms of SAR can profoundly affect a patient's quality of life; therefore, reductions in the disease burden could help to improve patient quality of life. In this study, patients experienced significant and clinically meaningful improvements in rhinitis-related quality of life (as evidenced by RQLQ scores). Improvements in RQLQ scores across all domains were paralleled by improvements in seasonal allergy symptoms. Furthermore, the significant improvements in reflective and instantaneous ocular scores were also paralleled by significant improvements in the ocular domain.

FFNS had a favorable safety and tolerability profile. The incidence of AEs was similar in both groups and all AEs were mild or moderate in intensity. Safety and tolerability results obtained were consistent with those from previously published studies^{16–18}. FFNS has also been shown to have a favorable long-term safety profile. In a study of 806 patients with PAR who received once-daily treatment with FFNS 110 µg or placebo for 12 months, the incidence of most adverse events was similar for FFNS and placebo²¹. As found in the current study, the most common adverse events were headache (incidence 31% and 34% for FFNS and placebo, respectively) and nasopharyngitis (incidence 26% and 25%, respectively)²¹.

In conclusion, once-daily treatment with FFNS 110 µg for 2 weeks was effective in alleviating the nasal symptoms of SAR. Significant improvements in ocular symptoms, and quality of life were also demonstrated. These findings, coupled with a favorable safety and tolerability profile, suggest that FFNS 110 µg once daily could represent a single treatment option for relief of SAR symptoms.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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References

1. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998;81:478-518
2. Canonica GW, Bousquet J, Mullol J, et al. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; 62(Suppl 85):17-25
3. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007;62(Suppl 85):9-16
4. Blanc PD, Trupin L, Eisner M, et al. The work impact of asthma and rhinitis: findings from a population-based survey. *J Clin Epidemiol* 2001;54:610-18
5. Walker S, Khan-Wasti S, Fletcher M, et al. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol* 2007;120:381-7
6. Task Force on Allergic Disorders. The Allergy Report. (Available at <http://www.theallergyreport.com>) Volume 1. 2000. Milwaukee, WI, American Academy of Allergy, Asthma and Immunology. Accessed 21 June 2007
7. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63:8-160
8. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: Management of allergic rhinitis. *Prim Care Respir J* 2006;15:58-70
9. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998; 317:1624-9
10. Bernstein DI, Levy AL, Hampel FC, et al. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2004;34:952-7
11. DeWester J, Philpot EE, Westlund RE, et al. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. *Allergy Asthma Proc* 2003;24:331-7
12. Bielory L, Katelaris CH, Lightman S, et al. Treating the ocular component of allergic rhinoconjunctivitis and related eye disorders. *MedGenMed* 2007;9:35
13. Berger WE, Godfrey JW, Slater AL. Intranasal corticosteroids: the development of a drug delivery device for fluticasone furoate as a potential step toward improved compliance. *Expert Opin Drug Deliv* 2007;4:689-701
14. Allen A, Down G, Newland A, et al. Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin Ther* 2007;29:1415-20
15. Salter M, Biggadike K, Matthews JL, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol* 2007; 293:660-7
16. Fokkens WJ, Jogi R, Reinartz S, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. *Allergy* 2007;62:1078-84
17. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;119:1430-7
18. Martin BG, Ratner PH, Hampel FC, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. *Allergy Asthma Proc* 2007;28:216-25
19. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994;93:413-23
20. Naclerio RM, Pinto J, deTineo M, et al. Elucidating the mechanism underlying the ocular symptoms associated with allergic rhinitis. *Allergy Asthma Proc* 2008;29:24-8
21. Rosenblut A, Bardin PG, Muller B, et al. Long-term safety of fluticasone furoate nasal spray in adults and adolescents with perennial allergic rhinitis. *Allergy* 2007;62:1071-7

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