
Comparison of patient preference for sensory attributes of fluticasone furoate or fluticasone propionate in adults with seasonal allergic rhinitis: a randomized, placebo-controlled, double-blind study

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Background: Intranasal corticosteroids are first-line treatment for moderate-to-severe seasonal allergic rhinitis (AR).

Objectives: To compare preferences for fluticasone furoate and fluticasone propionate nasal sprays after 1 week of treatment in patients with symptomatic seasonal AR.

Methods: Patients with seasonal AR were enrolled ($n = 360$) and randomized 1:1 to active treatment (fluticasone furoate, 110 μg , or fluticasone propionate, 200 μg , followed by crossover treatment for 1 week each) or matched placebo sequence with a 1-week washout before crossover dosing. Fluticasone furoate and fluticasone propionate efficacy was measured by change from baseline during 1 week in daily reflective total nasal symptom score (rTNSS) that assessed severity of rhinorrhea, nasal congestion, nasal itching, and sneezing. Patient preference for fluticasone furoate or fluticasone propionate was assessed at the end of the study by questionnaire.

Results: Three hundred sixty patients from 29 clinical sites in the United States were randomized and treated between August 1, 2007 and November 30, 2007. Most patients were white (73%) and female (59%), with a mean age of 38.3 years, and had had seasonal AR for at least 10 years (74%). Fluticasone furoate and fluticasone propionate each reduced the daily rTNSS compared with their respective placebos (least squares mean [SD] difference, -0.8 [0.24], $P < .001$, and -0.6 [0.24], $P = .01$, respectively). More patients ($P < .001$) preferred fluticasone furoate to fluticasone propionate based on attributes of scent or odor (58% vs 27%), aftertaste (60% vs 18%), leaking out of the nose and down the throat (59% vs 21%), and mist gentleness (57% vs 26%). No statistically significant differences were seen in preferences regarding ease of use, delivery method, or device comfort.

Conclusion: Both fluticasone furoate and fluticasone propionate significantly improved symptoms in adult patients with seasonal AR. Most patients preferred the sensory attributes of fluticasone furoate to those of fluticasone propionate after 1 week of treatment.

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Allergic rhinitis (AR) is a common chronic upper respiratory tract disorder that results from IgE-mediated immune reactions to environmental allergens.¹ Depending on the timing and type of allergen involved, AR can be either perennial or seasonal. AR is associated with a number of comorbid diseases, including conjunctivitis, sinusitis, and asthma,² and

is estimated to affect more than 40 million people in the United States.³ Direct costs for physicians' visits and medications and indirect costs of absenteeism and lost productivity are estimated to exceed \$2 billion annually in the United States.⁴ Indirect costs associated with AR exceed those of other common conditions, such as migraine, diabetes, and asthma.^{5,6}

Intranasal corticosteroids (INs) are the first-line treatment for moderate to severe seasonal and perennial AR or when nasal congestion is a major component of AR.² INs act via anti-inflammatory activity that inhibits the onset of the inflammatory responses and reduces the number of inflammatory cells and the release of inflammatory mediators. Currently available INs approved for once-daily use include those with propionate and furoate ester side chains that make the INs highly lipophilic. Pharmacologic potency studies show similar rank orders of potency for furoate and propionate INs,⁷ and clinical studies demonstrate comparable efficacy and tolerability.⁸ Although efficacy and tolerability may be comparable between INs with furoate and propi-

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onate modifications, patient perception of the sensory attributes of INSSs, including odor and taste, is different and can influence patient preference for individual INSSs.^{9,13}

Fluticasone furoate is an enhanced-affinity glucocorticoid developed as an aqueous suspension using a unique side-actuated nasal spray device for treatment of AR symptoms. Fluticasone furoate was formulated to reduce odor and nasal irritation and uses a delivery system with a shorter nose tip and lower volume per actuation than previous systems.¹⁴ Fluticasone furoate, 110 μg once daily, is approved in the United States for the treatment of symptoms of seasonal and perennial AR in patients 2 years and older and has been reported in randomized, double-blind, controlled studies to improve AR nasal symptoms¹⁵⁻¹⁸ and has an onset of action within 24 hours.^{15,16} Fluticasone propionate, 200 μg once daily, is approved in the United States for the treatment of seasonal and perennial AR and nonallergic rhinitis in adults.¹⁹ Reduction of nasal symptoms after fluticasone propionate administration occurs within 24 to 72 hours.²⁰

In a previous single-dose study comparing patient preferences, the sensory attributes of fluticasone furoate were preferred over those of fluticasone propionate by adult AR patients.²¹ The primary objectives of this randomized, double-blind, placebo-controlled, multidose study were to evaluate the preferences of patients with seasonal AR for fluticasone furoate and fluticasone propionate nasal spray sensory characteristics after treatment for 7 days.

METHODS

Patients and Study Design

Men and women 18 years and older with a clinical history of seasonal AR and nasal symptoms during each of the 2 previous fall allergy seasons were eligible if they had a positive skin test result to fall allergens appropriate to their region and had exposure to fall seasonal allergens during the study period. Study sites used a pollen sampling device (Rotorod Sampler; Multidata, Inc., Minnetonka, MN) to collect fall pollen samples 5 days each week. At the end of the study, a pollen summary (particles per cubic meter) was provided to GlaxoSmithKline for entry into a database along with a summary of rainfall (inches per day) during the study period for each site's geographic area.

Patients were screened for a minimum of 5 days. To be randomized, eligible patients had to have an average 12-hour reflective total nasal symptom score (rTNSS) in the 4 days before randomization of 6 or higher of a maximum possible score of 12 and an average 12-hour reflective nasal symptom assessment score for congestion of 2 or higher of a maximum possible score of 3.

Eligible female patients of childbearing potential were required to have a negative pregnancy test result and consent to the use of acceptable birth control methods. Exclusion criteria included any clinically significant uncontrolled medical disorder, infection, or structural abnormality of the respiratory system, recent use of allergy or other medications

that affect AR symptoms, use of intranasal corticosteroids within 4 weeks of the study, and use of oral or parenteral corticosteroids within 8 weeks of the study. Use of intranasal fluticasone propionate or fluticasone furoate within 1 year before the study was prohibited.

All patients provided written informed consent. Institutional review boards for each study site approved the protocol for this randomized, double-blind, single-dose, crossover study (protocol FFU105927; [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00539006) identifier NCT00539006).

After the screening period, eligible patients were randomized 1:1 (using a computer-generated code) to 1 of the following 4 treatment sequences: (1) fluticasone furoate, 110 μg once daily, followed by fluticasone propionate, 200 μg once daily; (2) fluticasone propionate, 200 μg once daily, followed by fluticasone furoate, 110 μg once daily; (3) fluticasone furoate placebo once daily followed by fluticasone propionate placebo once daily; or (4) fluticasone propionate placebo once daily followed by fluticasone furoate placebo once daily. The first 7-day treatment period was followed by a 7-day washout period then a second 7-day treatment period consisting of the alternate treatment in the randomized treatment sequence (Figure 1). Patients continued to meet eligibility criteria for the second treatment period. The second treatment period was followed by a telephone call within 3 to 5 days after the end of treatment to assess adverse events. Physical and nasal examinations were conducted at the beginning and end of the study.

All study personnel and patients were blinded to the treatment sequence assignments (active or placebo). The physical differences between the 2 nasal spray devices (ie, top-down vs side actuation) prevented complete blinding of the within-sequence treatment assignment (ie, fluticasone furoate device or fluticasone propionate device). Fluticasone furoate (Veramyst) and fluticasone propionate (Flonase; GlaxoSmithKline, Research Triangle Park, NC) and matching placebos were provided by GlaxoSmithKline (Research Triangle Park, NC). Matched placebos contained the same vehicle as their respective active drug counterparts. Fluticasone furoate and matching placebo contained dextrose, microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride, and disodium edetate and had a pH of 6. Each actuation delivered 27 μg of fluticasone furoate. Fluticasone propionate and matching placebo contained microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% (wt/wt) phenylethyl alcohol and had a pH between 5 and 7. Each actuation delivered 50 μg of fluticasone propionate.

Assessments

Patient preference of the nasal spray characteristics of fluticasone furoate compared with fluticasone propionate was determined through the assessment of selected product attributes using a paper questionnaire completed at the end of the study. The following questions were asked of patients:

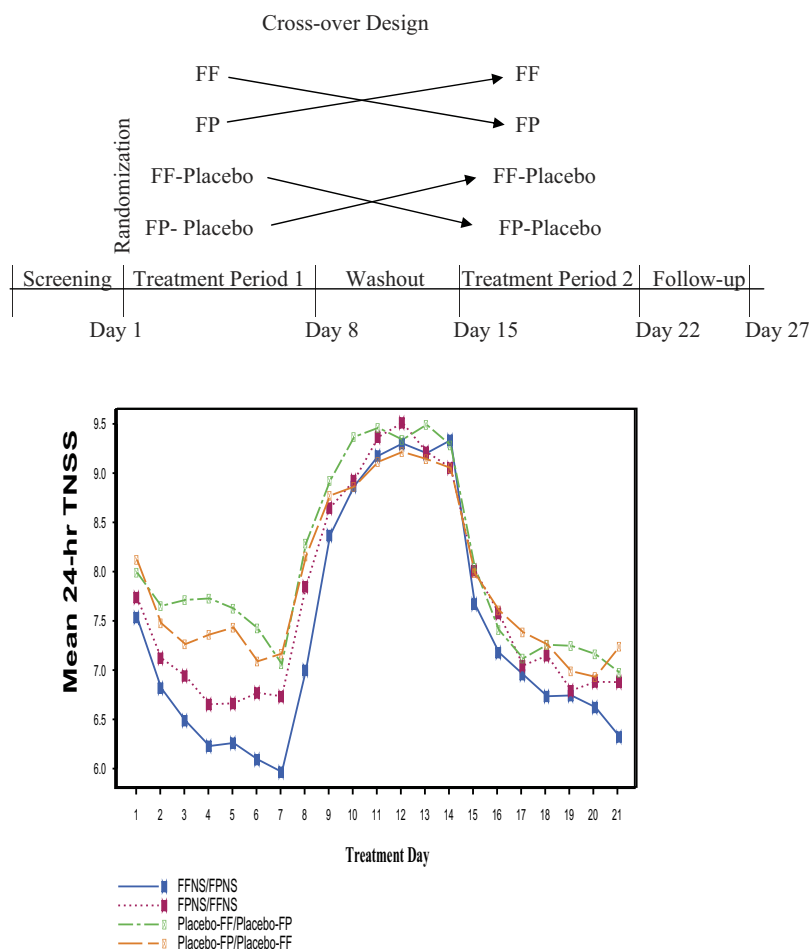


Figure 1. Timing of study events and crossover design. FF indicates fluticasone furoate; FP, fluticasone propionate; NS, nasal spray; TNSS, total nasal symptom score. Daily reflective TNSSs are shown for all groups for both treatment periods and the washout period.

1. Which product do you prefer because of its scent/odor?
2. Which product do you prefer because less of the medication it releases leaks out of your nose or down your throat?
3. Which product do you prefer because the mist that is released is gentle?
4. Which product do you prefer because it is easier to use?
5. Which product do you prefer because it is better at delivering the same amount of medication each time you use it?
6. Which product do you prefer because its nose tip is more comfortable?
7. Which product do you prefer because of the spray delivery method (ie, top-down or side-actuated)?
8. Which product do you prefer because it has less of an aftertaste?

Patients rated medication attributes by answering, “I prefer product 1” if they preferred the nasal spray used during treatment period 1 and “I prefer product 2” if they preferred the nasal spray used during treatment period 2. If the patient did not have a preference for either nasal spray, selection of “I have no preference” was allowed. With the exception of

question 7, the preference questions used in this study were selected from items tested in series of patient focus groups and one-on-one cognitive debriefing interviews.^{22,23} Question 7 was added for this study and was not pretested with patients.

The primary preference measure was patient preference for either fluticasone furoate or fluticasone propionate at the end of the second crossover period based on product scent or odor. Secondary preference end points were patient preference for either fluticasone furoate or fluticasone propionate at the end of the crossover period based on leaking out of the nose and down the throat, ease of use, and gentleness of mist. Other preference end points were delivery of the same amount of medication with each use, comfort of the nose tip, spray delivery method (ie, top-down vs side-actuation), and aftertaste.

To confirm that both treatments were effective, efficacy of each active treatment (fluticasone furoate or fluticasone propionate) was compared to its vehicle placebo during the 1-week treatment period by patient rating of nasal symptoms.

Using paper diaries, patients rated 4 nasal symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) on a 4-point (0 to 3) categorical scale as follows: 0 indicating none (symptom was not present); 1, mild (symptom was present but easily tolerated); 2, moderate (awareness of a symptom that was bothersome but tolerable); and 3, severe (hard to tolerate and caused interference with daily activities).

The sum of the 4 nasal symptom ratings was defined as the reflective total nasal symptom score (rTNSS), which represented the patient's symptoms during a 12-hour period and was assessed twice daily, before the morning treatment and 12 hours after treatment. The daytime and nighttime rTNSSs for a given 24-hour period were averaged to derive the primary efficacy measure, the daily rTNSS. Safety and tolerability were assessed from spontaneously reported adverse events, physical examinations, and nasal examinations.

Statistical Analysis

Data from each study site were pooled for analyses. The intent-to-treat population consisted of all patients who were randomized to treatment and formed the basis for all demographic and safety summaries. All patients receiving study drug were included in assessments except for 1 patient, who enrolled at 2 different investigative sites.

All tests were 2-tailed with significance levels of .05 and 95% confidence intervals. Patient preference for study medication based on sensory attributes was analyzed using a Cochran-Mantel-Haenszel test stratified by investigator. Preference results for leakage, gentleness, and ease of use were adjusted for multiplicity using the Hochberg method. The mean change from baseline in daily rTNSS between each active compound and its matched placebo was analyzed using an analysis of covariance model that included baseline daily rTNSS as a covariate with terms for investigator and treatment.

Assuming that 64% of patients indicated an overall preference for fluticasone furoate over fluticasone propionate and using a 1-group χ^2 test, a sample size of 150 patients per active treatment sequence would provide 92% power to show the assumed difference in proportions (ie, 64% favoring fluticasone furoate vs 36% favoring fluticasone propionate). This sample size also provided 91% power to detect a difference of 1.0 in the mean change from baseline during the treatment period in daily rTNSS between each active treatment and its matched placebo.

RESULTS

Patients

Three hundred sixty patients from 29 clinical sites in the United States were randomized and treated between August 1, 2007 and November 30, 2007. The disposition of patients is shown in Figure 2. One hundred eighty-one patients were assigned to 1 of the 2 active treatment sequences and 179 to 1 of the 2 placebo treatment sequences. Two hundred ninety-nine patients (83%) completed the study. Of the 61 patients who withdrew prematurely, the primary reason (38/61, 62%) was failure to meet continuation criteria. Reasons for premature withdrawal in each treatment sequence are shown in Figure 2. Demographic and patient baseline characteristics are given in Table 1 and were similar among all treatment sequences. Most patients were white (73%) and female (59%), with a mean age of 38.3 years and seasonal AR for at least 10 years (74%).

Efficacy

Mean baseline daytime rTNSSs, nighttime rTNSSs, and daily rTNSSs were similar between treatment groups (Table 1). Mean baseline scores and treatment period scores by treat-

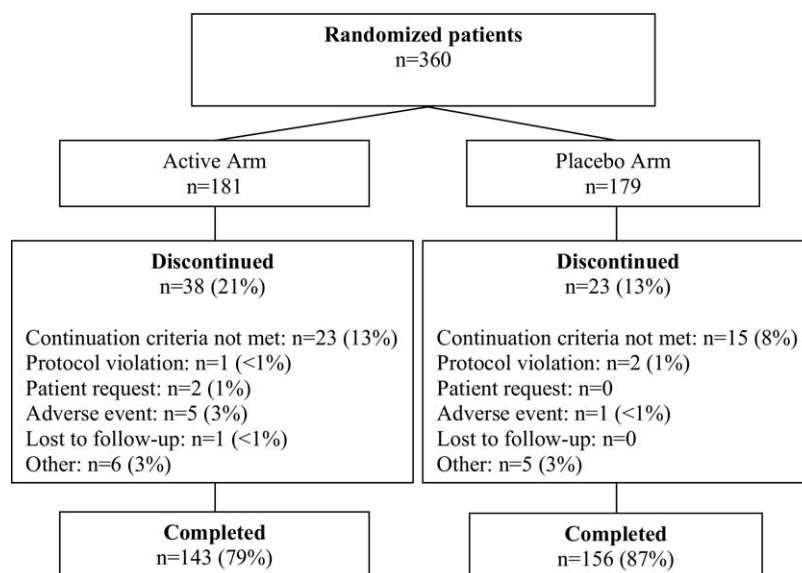


Figure 2. Disposition of patients in the study.

Table 1. Demographics and Baseline Characteristics for All Patients Enrolled in the Study (Intent-to-Treat Population)

Characteristics	Active treatment sequences (n =181)	Placebo treatment sequences (n=179)
Age, mean (SD), y	38.0 (12.4)	38.5 (11.4)
Sex, No. (%)		
Female	109 (60)	105 (59)
Male	72 (40)	74 (41)
Ethnicity, No. (%)		
White	130 (73)	130 (73)
African American	38 (21)	32 (18)
Hispanic/Latino	35 (19)	44 (25)
Other	11 (6)	15 (8)
Duration of season AR, No. (%)		
≥2 to <5 years	18 (10)	15 (8)
≥5 to <10 years	24 (13)	35 (20)
≥10 years	139 (77)	129 (72)
Baseline rTNSS, mean (SE)		
Daytime	9.3 (0.12)	9.1 (0.13)
Nighttime	9.2 (0.13)	9.1 (0.13)
Daily	9.2 (0.12)	9.1 (0.12)

Abbreviations: AR, allergic rhinitis; rTNSS, reflective total nasal symptom score.

ment sequence for daily rTNSS are given in Table 2. Results were similar for daytime rTNSS and nighttime rTNSS and are not shown. Daily rTNSSs for the 4 treatment sequences for treatment periods 1 and 2 and for the washout period are shown in Figure 1. Statistical modeling was conducted to check for carryover, and no period effect was found.

Analysis of the changes from baseline in daily rTNSS for fluticasone furoate and fluticasone propionate vs their respective placebo nasal sprays is given in Table 3. Fluticasone furoate and fluticasone propionate once daily for 1 week each significantly ($P < .001$ and $P = .01$, respectively) reduced daily rTNSS compared with its respective

Table 2. Daily Reflective Total Nasal Symptom Scores (rTNSSs) for the Baseline and Treatment Periods by Crossover Sequence

Crossover sequence	Mean (SE) Daily rTNSS		
	Baseline	Treatment period 1	Treatment period 2
Fluticasone furoate/fluticasone propionate	9.3 (0.16)	6.5 (0.28)	6.8 (0.32)
Fluticasone propionate/fluticasone furoate	9.2 (0.17)	7.0 (0.28)	7.1 (0.32)
Placebo fluticasone furoate/fluticasone propionate	9.3 (0.18)	7.6 (0.27)	7.4 (0.30)
Placebo fluticasone propionate/fluticasone furoate	8.9 (0.17)	7.4 (0.27)	7.3 (0.28)

Table 3. Analysis of Change From Baseline During 1 Week in Daily, Daytime, and Nighttime rTNSSs^a

Treatment comparison	rTNSS change from baseline		
	Daily	Daytime	Nighttime
Fluticasone furoate vs placebo			
LS mean (SD)	−0.8 (0.24)	−0.8 (0.25)	−0.8 (0.25)
difference			
95% CI	−1.3 to −0.3	−1.3 to −0.4	−1.3 to −0.3
P value	<.001	<.001	.002
Fluticasone propionate vs. placebo			
LS mean (SD)	−0.6 (0.24)	−0.6 (0.25)	−0.6 (0.25)
difference			
95% CI	−1.1 to −0.1	−1.1 to −0.1	−1.1 to −0.1
P value	.01	.02	.01

Abbreviations: CI, confidence interval; LS, least squares; rTNSS, reflective total nasal symptom score.

vehicle placebo nasal spray. Consistent with the results for daily rTNSS, both fluticasone furoate and fluticasone propionate were statistically significantly more efficacious than their respective vehicle placebo sprays in improving daytime rTNSS and nighttime rTNSS during 1 week as indicated in Table 3.

Patient Preference for Individual Medication Attributes

Preferences for fluticasone furoate or fluticasone propionate product attributes after exposure to both products are shown in Figure 3. Twice as many patients preferred fluticasone furoate compared with fluticasone propionate based on the primary preference end point of scent or odor (58% vs 27%, $P < .001$). Fifteen percent of patients had no preference for either product with respect to scent or odor. Significantly ($P < .001$) more patients preferred fluticasone furoate compared with fluticasone propionate because less medication leaked out of the nose or down the throat (59% vs 21%), because of the gentleness of the mist (57% vs 26%), and because of less aftertaste (60% vs 18%). No statistically significant differences were found in preferences for fluticasone furoate and fluticasone propionate with respect to attributes related to ease of use, consistency of medication delivered, the delivery method, or device comfort. Between 17% and 31% of patients had no preference for either fluticasone furoate or fluticasone propionate with respect to the secondary and other attributes (Figure 3).

Tolerability

The proportions of patients with any adverse event were similar among treatments. Headache was the most frequently reported adverse event and occurred in 4% of patients during fluticasone furoate treatment, 9% during fluticasone propionate treatment, and 7% during each placebo treatment. Adverse events occurring with an incidence of 1% or greater are given in Table 4. Most events were described as mild or moderate. One adverse event in the fluticasone furoate treat-

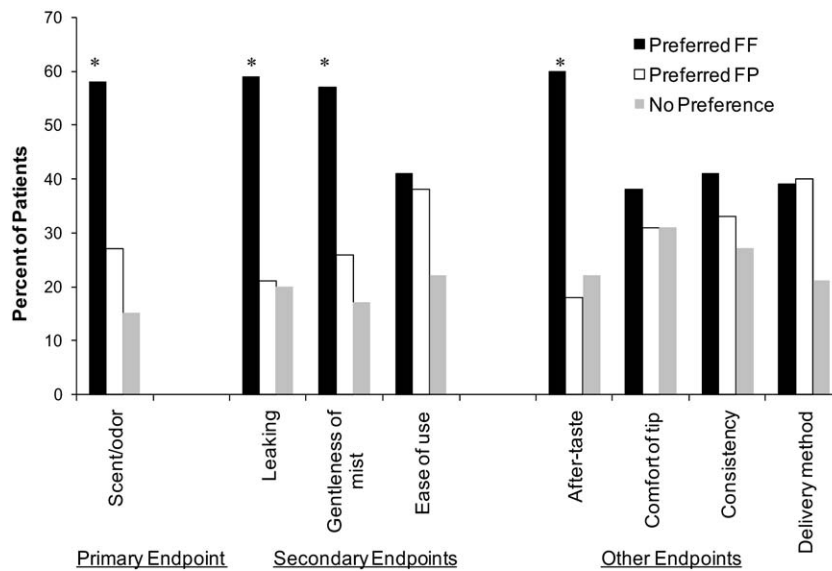


Figure 3. Proportions of patients preferring fluticasone furoate (FF) or fluticasone propionate (FP) with respect to individual product sensory attributes. Asterisk indicate $P < .001$.

ment arm, a case of sinusitis, was considered treatment related and resulted in early withdrawal. No deaths occurred during the study, and no serious adverse events were reported.

DISCUSSION

This study was designed to determine patient preferences for sensory attributes of fluticasone furoate and fluticasone propionate after administration for 1 week. Both fluticasone furoate and fluticasone propionate demonstrated statistically significant reductions from baseline in nasal allergy symptoms compared with their respective placebos. Patients preferred the scent or odor, aftertaste, and gentleness of the mist of fluticasone furoate approximately 2:1 over the same attributes of fluticasone propionate. This may be because fluticasone furoate is unscented and alcohol free in contrast to the fluticasone propionate formulation. Patients also preferred fluticasone furoate to fluticasone propionate regarding whether the nasal product leaked out of the nose or down

the throat. Fluticasone furoate is formulated in a spray device that delivers half the volume of many conventional spray devices; this formulation may minimize anterior and postnasal fluid runoff.¹⁴ Patients indicated no clear preference with regard to ease of use, delivery method, comfort of the device nose tip, or the ability to deliver medication consistently.

Because reduction in symptom severity may influence patient preference for allergy medication, the present crossover study was conducted to assess both efficacy and patient preference. Because both fluticasone furoate and fluticasone propionate were efficacious, efficacy was not a factor that would influence patient preferences for sensory attributes. These results are consistent with a previous patient preference study comparing a single-dose administration of fluticasone furoate and fluticasone propionate.²¹ In that study, significantly more patients preferred fluticasone furoate to fluticasone propionate after a single dose, and more patients stated that they would be more likely to comply with fluticasone

Table 4. Adverse Events Occurring in 1% or More of Patients

Event	No. (%) of patients			
	Fluticasone furoate (n = 166)	Fluticasone propionate (n = 159)	Fluticasone furoate placebo (n = 174)	Fluticasone propionate placebo (n = 166)
Any event	20 (12)	34 (21)	27 (16)	22 (13)
Headache	7 (4)	14 (9)	12 (7)	12 (7)
Back pain	1 (<1)	2 (1)	1 (<1)	3 (2)
Sinus headache	1 (<1)	2 (1)	2 (1)	2 (1)
Unilateral deafness	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Myalgia	1 (<1)	0	3 (2)	0
Pharyngolaryngeal pain	0	3 (2)	1 (<1)	0

furoate than with fluticasone propionate treatment. The results of this study are also consistent with data demonstrating that patient ratings of several sensory attributes were lower for fluticasone propionate than other INSs.¹⁰

Sensory attributes, such as odor, taste, and the amount of medication leakage out of the nose or down the throat, have been shown to influence patient preference when comparing INS products for treatment of AR.^{9,10,12,13} Unpleasant sensory attributes may lead to decreased patient adherence to treatment, which in turn can compromise AR management.²⁴ Therefore, sensory attributes of INS products are important considerations when optimizing INS formulations²⁵ and when making prescribing decisions regarding INS products that have comparable efficacy, tolerability, and ease of use. Patients should be provided with the information regarding patient preference for the sensory attributes of fluticasone furoate but also told that the cost per month is higher than for fluticasone propionate options. Although patients have been shown to be willing to pay more for treatments that avoid certain sensory attributes perceived as offensive,²⁶ patients should decide for themselves whether they are willing to have the higher copay or out-of-pocket cost before the prescription is written.

No significant differences in patient preferences were found for the delivery devices or assessment of comfort or ease of use. Although the fluticasone furoate delivery system was ergonomically designed for easier holding and operation, the novelty of the side-actuation delivery system and the lack of familiarity with operating this type of delivery system may have played a part in the lack of differentiation between the fluticasone propionate and fluticasone furoate devices. Considering that close to 75% of the patients had an allergy history of 10 years or longer, this finding is not surprising. Although patients were not allowed to have used either branded or generic versions of fluticasone propionate within 1 year of study participation, it is likely that most patients had previously used conventional top-down INSs and therefore may have responded to the more familiar delivery system.

In summary, in the present study, adult patients generally preferred the sensory attributes of fluticasone furoate to those of fluticasone propionate after 1 week of treatment, even though both INSs effectively managed seasonal AR symptoms.

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