

Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk

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The objective of this study was to evaluate the efficacy and safety of fluticasone furoate (FF) nasal spray 55 and 110 µg once daily in children with seasonal allergic rhinitis (SAR). Patients (n = 554) received placebo nasal spray or FF, administered using a unique side-actuated device, in a 2-wk, randomized, double-blind study. Symptoms were evaluated by patients using a 4-point categorical scale. Efficacy assessments included reflective and instantaneous total nasal symptom scores (r/iTNSS). Primary analyses were conducted in patients aged 6–11 yr in the intent-to-treat population (ITT); the 2–11 yr group provided supportive analyses. In patients aged 6–11 yr, FF 110 µg once daily significantly improved the daily rTNSS compared with placebo. FF 55 µg once daily was only numerically better for rTNSS and iTNSS. Secondary pre-dose iTNSS and overall response to therapy were significant with FF 110 µg. The significant findings for FF 110 µg were supported by analyses in the entire ITT population of 2–11 yr olds. Both doses of FF were well tolerated. These study results suggest that FF nasal spray administered once daily for 2 wk is well tolerated and effective for the treatment of SAR symptoms in children aged 2–11 yr.

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Allergic rhinitis (AR) is the most common chronic condition in children, with a varying prevalence worldwide (1, 2). Clinically defined as an immunoglobulin E (IgE)-mediated inflammatory disease of the upper airways, AR occurs following exposure of the nasal membranes to allergens to which the patient is sensitized (3). Patients with AR present with symptoms of nasal congestion, rhinorrhea, nasal itching, and sneezing episodes. With seasonal allergic rhinitis (SAR), commonly referred to as 'hay fever', patients show periodic exacerbations of symptoms that occur primarily during pollinating seasons; usually, spring for trees, spring and summer for grasses, and fall for weeds (4).

The impact of poorly controlled AR on children's quality of life, psychologic well-being and capacity to function in activities of daily living can be significant (5). Children with AR

are more likely to exhibit shyness, depression, anxiety, and fearfulness than those without the condition (1, 5, 6). In addition, children with AR miss 2 million school days each year in the USA and, even when at school, their performance can be impaired by cognitive dysfunction related to the AR itself (7). This detrimental impact was observed in examination performances of UK adolescents, who showed a 50% increase in the risk of dropping an examination grade between winter and summer (8). As well as these psychosocial and performance difficulties, if left untreated, AR appears to increase the risk of developing potentially problematic co-morbid conditions, including asthma, sinusitis, and otitis media (1, 3).

Anti-inflammatory therapy with corticosteroids to effectively control the nasal symptoms of AR is well established, and international

guidelines recommend intranasal corticosteroids (INS) as first-line therapy for patients with all but the mildest symptoms (3, 9, 10). In particular, the American Academy of Allergy, Asthma and Immunology (AAAAI) recommends INS as first-line therapy when nasal congestion is a major component of the patient's AR (11). Although the exact pharmacologic mechanism of these agents remains unknown, INS have been shown to reduce vascular permeability and edema of the nasal mucosa through inhibitory effects on inflammatory cells and inflammatory mediator activity (12).

Fluticasone furoate (FF) nasal spray is a new enhanced-affinity glucocorticoid developed for the treatment of AR that is administered in a unique, side-actuated device. This delivery system was designed for ease of self-administration, as well as for convenient parent/caregiver administration to children. Preclinical studies have demonstrated that FF has a higher affinity for the glucocorticoid receptor, compared with several currently available INS (13), although the clinical relevance of this is unknown. A dose-ranging study in adults and adolescents showed that FF doses between 55 and 440 μg once daily were well tolerated and effective in treating the symptoms of SAR, with 110 μg being the optimal dose in this population (14). In view of the importance of treating SAR in children, it is reasonable to assess the effectiveness of FF nasal spray in pediatric patients. In this study, 110 μg was chosen as the higher dose because it was found to be the optimal dose in adults in terms of its risk–benefit ratio. The 55 μg dose was chosen as the lower dose because it showed efficacy in the aforementioned dose-ranging study, and because data from previous studies with other INS have demonstrated that half of the adult dose is often adequate for controlling the symptoms of AR in children (15, 16).

The primary objective of the present study was to assess the efficacy and safety of FF nasal spray 55 and 110 μg once daily compared with placebo nasal spray once daily, and to determine the optimal dose of FF in children aged 2–11 yr with SAR.

Methods

Study design

This 2-wk, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 57 centers in the USA. The study was carried out in compliance with good clinical practice in accordance with the Declaration of Helsinki.

Patients, where appropriate, and parents/guardians of all patients provided written informed consent before patients took part in the study.

To be eligible for inclusion, patients had to be 2–11 yr of age at randomization, male or premenarchal females of non-childbearing potential. Patients must have had seasonal allergy symptoms during the last allergy season and a positive skin-prick test (wheal ≥ 3 mm larger than control) or *in vitro* test for a specific IgE within the past 12 months. Eligible patients must also have had adequate exposure to seasonal (spring/summer/fall) allergens prevalent to the geographic area and have had no intention of traveling outside the geographic region for more than 48 h during the study period.

Patients were excluded if they had significant concomitant medical conditions, including recent respiratory conditions, any conditions likely to be adversely affected by glucocorticoid use, or a history of use of any corticosteroid or other allergy medications or treatments that could affect the signs and symptoms of AR or the effectiveness of the study drug. General exclusion conditions included clinically significant uncontrolled disease in the body as a whole (e.g., tuberculosis, psychologic disorders, eczema). Children with asthma were also excluded, except those with mild intermittent asthma.

Patients meeting the inclusion criteria entered a 5- to 21-day screening period to determine the severity and frequency of their SAR symptoms. To be randomized at visit 2, the average of the last eight reflective total nasal symptom score (rTNSS) assessments over the four 24-h periods prior to randomization must have been ≥ 6 (out of a score of 12), and the average of the last eight rTNSS assessments for congestion must have been ≥ 2 (out of a score of 3; four morning and four evening assessments) prior to randomization. In addition, patients were required to have completed $\geq 80\%$ of assessments on the screening symptom diary card.

During the screening period, patients were not allowed to take any anti-allergy or anti-rhinitis medication. Patients and/or parents/guardians were also required to note any medical conditions and use of concomitant medications. Patients aged 6–11 yr did not receive rescue medication; patients aged 2 to <6 yr were provided with loratadine syrup (1 mg/ml), an over-the-counter antihistamine, for use only on an as-needed basis.

Patients meeting the randomization criteria received study medication – FF nasal spray 55 μg once daily or 110 μg once daily, or vehicle placebo nasal spray once daily – in a 1:1:1 ratio

for 2 wk. Patients in the placebo group received two placebo devices; patients in the FF nasal spray 55 µg group received one placebo device and one active device; and patients in the FF nasal spray 110 µg group received two active devices. During the 2-wk treatment period, patients (either on their own or with assistance from a parent/guardian) were asked to administer one spray into each nostril (27.5 µg/spray) from the first device, followed by one spray into each nostril (27.5 µg/spray) from the second device. Administration took place in the morning following pre-dose symptom assessment. Study drug administration was documented on daily treatment diary cards.

Assessments

Four clinic visits were scheduled (Fig. 1) and, for the duration of the study, patients recorded their allergy symptoms on two types of diary cards: a screening diary card, used during the screening period, and a daily treatment diary card, used from the first day of study medication administration (visit 2) and throughout the remainder of the study. In both diary cards, the same 4-point categorical scale was used: 0 (none), sign/symptom not evident; 1 (mild), sign/symptom clearly present but causing minimal awareness and easily tolerated; 2 (moderate), definite awareness of sign/symptom that is bothersome but tolerable; and 3 (severe), sign/symptom that is hard to tolerate and causes interference with activities of daily living and/or sleeping.

The rTNSS, scored approximately 12 h after treatment in a reflective manner, was summed from the individual nasal symptom scores for nasal congestion, rhinorrhea, nasal itching, and sneezing to provide rTNSS at AM and PM time points. The daily rTNSS for the entire 24-h dosing interval was calculated as the average of the AM and PM assessments.

The mean change from baseline over the entire treatment period in AM pre-dose instantaneous TNSS (iTNSS) in patients 6–11 yr of age was used to assess the treatment effect at the end of the dosing interval. The AM pre-dose iTNSS, summed from the four individual nasal symptom score assessments, was performed immediately prior to taking the daily dose, where each symptom was scored on the 4-point scale previously described.

At the final study visit, patients and/or parents/guardians were asked to evaluate the patient's overall response to therapy over the entire treatment period using a 7-point categorical scale. Patients rated their perception of the change or lack of change in their allergic symptoms 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?' They were then asked to respond by selecting one of the following categories: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse.

The primary efficacy end-point was the mean change from baseline over the entire treatment period in daily rTNSS. Key secondary efficacy end-points were the mean change from baseline over the entire treatment period in AM pre-dose iTNSS, and the overall evaluation of response to therapy.

The safety end-points assessed were frequency and type of clinical adverse events (AEs), clinical laboratory tests (hematology and clinical chemistry), nasal examinations, vital signs (systolic and diastolic blood pressure, heart rate), and 12-lead electrocardiograms (ECG).

Pharmacokinetic assessments in this study included plasma concentrations of FF, as well as pharmacokinetic parameters (AUC, C_{max} , T_{max}).

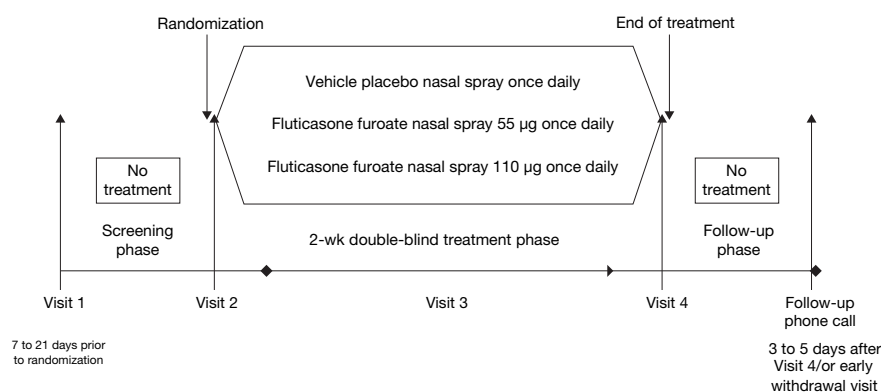


Fig. 1. Schematic study design.

Statistical analyses

The analyses of the efficacy data were performed for patients in the intent-to-treat (ITT) population who were 6–11 yr of age at the time of randomization. A total of 576 patients were required for this study, with 192 patients [approximately 48 (25%) patients 2 to <6 yr of age and 144 (75%) patients 6–11 yr of age] in each of the three treatment groups. The sample size was selected to provide 90% power to detect a difference of 1.0 between active treatment and placebo for mean change in daily rTNSS in children aged 6–11 yr, using a two-sample *t*-test with a 0.05 two-sided significance level and a standard deviation of 2.6.

The ITT population was defined as all patients who were randomized and received at least one dose of study drug. Unless otherwise specified, analyses based on the ITT population included all available data for those patients. Considering the difficulty in assessing subjective symptoms in children, particularly in those of very young age, the primary analyses of efficacy data were performed for patients in the ITT population who were 6–11 yr of age at the time of randomization. Primary and key secondary efficacy end-points were analyzed for the entire ITT population of patients 2–11 yr of age to provide supportive data. The entire ITT population was also the basis for analyses of safety data.

The primary analysis method was the pairwise comparison of the treatment groups (FF nasal spray 110 µg once daily vs. vehicle placebo nasal spray once daily, and FF nasal spray 55 µg once daily vs. vehicle placebo nasal spray once daily) using an analysis of covariance (ANCOVA) adjusting for baseline rTNSS, region, age, gender, and season (spring or fall). The key secondary efficacy end-point for nasal symptoms was analyzed in a way similar to the primary analysis. Overall evaluation of response to therapy was analyzed using logistic regression adjusted for age, gender, season, region, and treatment. Multiplicity adjustments were made on the results from the primary efficacy analyses only. Multiple comparisons between each of the two active doses and placebo were performed sequentially, first with FF nasal spray 110 µg vs. vehicle placebo, then with FF nasal spray 55 µg vs. vehicle placebo.

Results

Patient population and baseline characteristics

The ITT population comprised 554 patients who were 2–11 yr of age and received at least one dose

Table 1. Demographic and baseline characteristics

	Fluticasone furoate			Total (n = 554)
	Placebo (n = 186)	55 µg (n = 184)	110 µg (n = 184)	
Age (yr)				
Mean (s.d.)	8.0 (2.55)	8.2 (2.43)	8.0 (2.54)	8.1 (2.50)
Age group, n (%)				
2–5 yr	35 (19)	32 (17)	38 (21)	105 (19)
6–11 yr	150 (81)	152 (83)	146 (79)	448 (81)
≥12 yr	1 (<1)	0	0	1 (<1)
Female/male	42/58	43/57	40/60	42/58
Race*				
White	80	85	76	80
Black	16	12	14	14
Other	4	3	10	6
Duration of SAR, n (%)				
≥6 months to <1 yr	7 (4)	2 (1)	11 (6)	20 (4)
≥1 to <2 yr	25 (13)	22 (12)	28 (15)	75 (14)
≥2 to <5 yr	94 (51)	85 (46)	74 (40)	253 (46)
≥5 to <10 yr	55 (30)	70 (38)	65 (35)	190 (34)
≥10 yr	5 (3)	4 (2)	5 (3)	14 (3)

SAR, seasonal allergic rhinitis; s.d., standard deviation.

*White, Arabic/North African heritage or White/Caucasian/European heritage; Black, African/African American heritage only; Other, all other races indicated in case report form (CRF).

of study medication: 184 received 55 µg FF once daily, 184 received FF 110 µg once daily, and 186 received vehicle placebo once daily. Patient enrollment was stratified by age: 448 patients were 6–11 yr of age, 105 were 2 to <6 yr of age, and one patient turned 12 yr of age during the screening period (prior to randomization). Ninety-seven percent of patients completed the study. The early withdrawal rate was low for each treatment group; the primary reason for withdrawal was the experience of AEs (10 patients, 2%). The demographic and baseline characteristics for the ITT population were similar between the three treatment groups and are summarized in Table 1. Mean scores over the four 24-h periods prior to randomization for TNSS and nasal congestion were similar among treatment groups. The mean rate of treatment compliance was also similar among the three treatment groups (placebo, 87.1%; FF 55 µg, 85.8%; and FF 110 µg, 86.4%). Overall, 82–85% of patients in all treatment groups had ≥80% compliance.

Efficacy

Primary efficacy analyses were performed in the ITT population of 448 patients aged 6–11 yr. FF 110 µg significantly improved nasal symptoms; the least squares (LS) mean change from baseline over the entire treatment period in daily rTNSS

Table 2. Mean change from baseline in symptom scores [intent-to-treat (ITT) population: patients aged 6–11 yr]

	Placebo (n = 150)	Fluticasone furoate	
		55 µg (n = 152)	110 µg (n = 146)
<i>Daily rTNSS</i>			
Baseline (s.e.)	8.4 (0.14)	8.6 (0.15)	8.5 (0.14)
Δ from baseline (weeks 1–2)			
LS mean Δ (s.e.)	−2.54 (0.21)	−2.71 (0.20)	−3.16 (0.21)
LS mean difference	−	−0.161	−0.616
p-value vs. placebo	−	0.553	0.025
95% CI	−	−0.69, 0.37	−1.15, −0.08
<i>AM pre-dose iTNSS</i>			
Baseline (s.e.)	8.4 (0.17)	8.4 (0.17)	8.3 (0.15)
Δ from baseline weeks 1–2			
LS mean Δ (s.e.)	−2.13 (0.21)	−2.37 (0.20)	−2.80 (0.21)
LS mean difference	−	−0.234	−0.668
p-value vs. placebo	−	0.389	0.015
95% CI	−	−0.77, 0.30	−1.21, −0.13

CI, confidence interval; iTNSS, instantaneous total nasal symptom score; LS, least squares; rTNSS, reflective total nasal symptom scores; s.e., standard error.

was greater for FF 110 µg (–3.16) than for placebo (–2.54), and the difference (–0.616) was statistically significant ($p = 0.025$). A significant treatment difference in mean change from baseline for rTNSS was first observed on day 4 ($p = 0.046$) for FF 110 µg and was maintained throughout the treatment period, except for days 5, 9, 10, and 14. Patients receiving FF 55 µg demonstrated a numerically greater LS mean change in daily rTNSS than those receiving placebo (–2.71 vs. –2.54), although this was not statistically significant (LS mean difference: –0.161, $p = 0.553$) (Table 2; Fig. 2).

Secondary efficacy analysis for LS mean change from baseline over the entire treatment

period in AM pre-dose iTNSS was also performed in the 6–11 yr age group. LS mean change was greater for FF 110 µg (–2.80) than for placebo (–2.13), and the mean difference was significant (–0.668, $p = 0.015$) (Fig. 3; Table 2). A significant treatment difference in mean change from baseline for AM pre-dose iTNSS was first observed on day 6 ($p = 0.035$) for FF 110 µg; this was maintained ($p \leq 0.044$) throughout the treatment period, except for day 14 ($p = 0.184$). No significant difference (–0.234, $p = 0.389$) was observed between FF 55 µg and placebo, although there was a numerical difference.

To reconfirm findings from the 6–11 yr age group, primary efficacy analyses were conducted in the entire ITT population of 554 patients aged 2–11 yr. At the end of the 2-wk treatment period, the LS mean difference from baseline in daily rTNSS was statistically significant for FF 110 µg (–0.609; $p = 0.012$) vs. placebo in those aged 2–11 yr; however, the LS mean difference for FF 55 µg was not statistically different from placebo (–0.030; $p = 0.900$). Over the 2-wk treatment period, LS mean difference from baseline in AM pre-dose iTNSS compared with placebo was significant for FF 110 µg (–0.647; $p = 0.008$), but was not significant for FF 55 µg (0.080; $p = 0.743$).

Overall evaluation of response to therapy

For the 6–11 yr age group, the treatment difference in the overall response to therapy was significant for FF 110 µg compared with placebo ($p < 0.001$), but was not significant for FF 55 µg ($p = 0.083$). Patient assessment of overall response to therapy was rated as ‘significantly

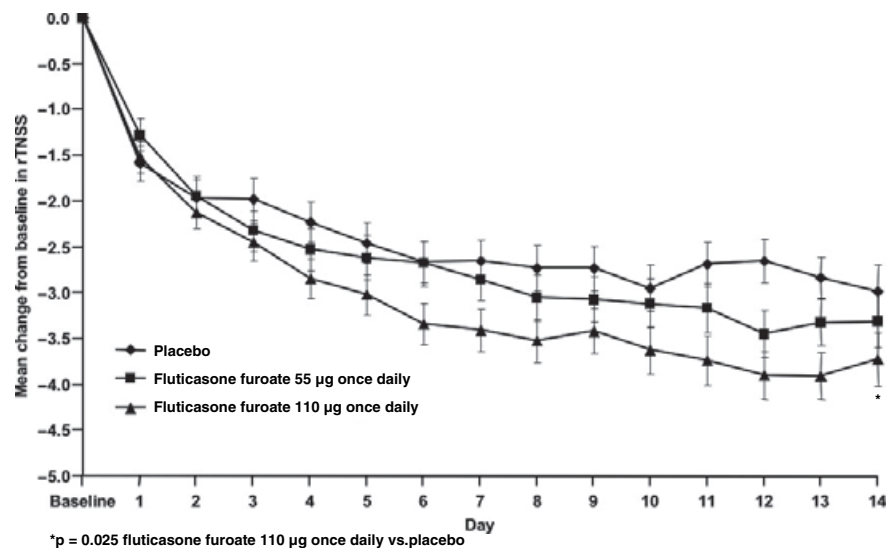


Fig. 2. Mean change from baseline in mean daily reflective total nasal symptom score over the entire 2-wk treatment period in the intent-to-treat population: patients aged 6–11 yr.

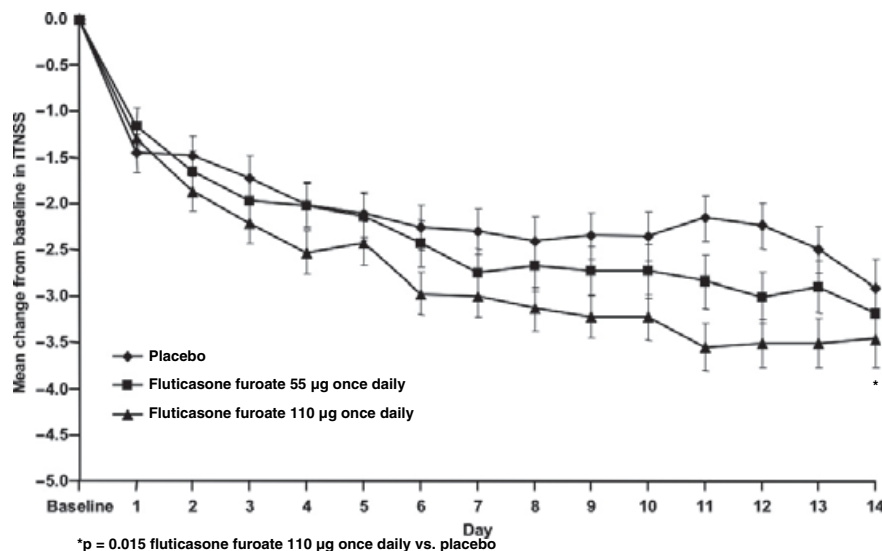


Fig. 3. Mean change from baseline in mean AM pre-dose instantaneous total nasal symptom score over the entire 2-wk treatment period in the intent-to-treat population: patients aged 6–11 yr.

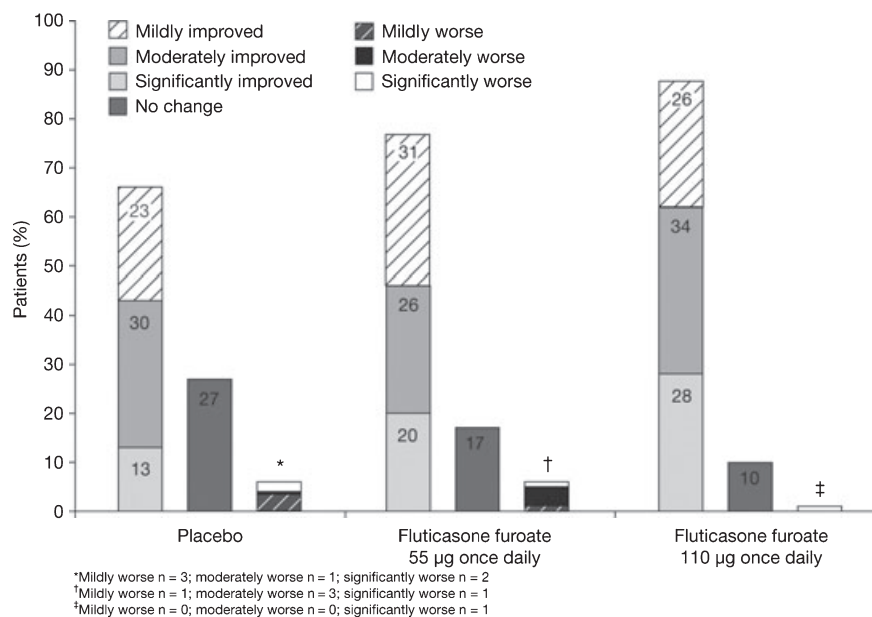


Fig. 4. Distribution of overall response to therapy in the intent-to-treat population: patients aged 6–11 yr.

improved' by a greater number of patients in the FF 110 µg (28%) and 55 µg (20%) groups than in the placebo group (13%; Fig. 4).

For the entire ITT population, overall response to therapy was significant for FF 110 µg but not for 55 µg ($p < 0.001$ and $p = 0.196$, respectively). Again, a greater percentage of patients rated their symptoms as significantly improved with FF 110 and 55 µg compared with placebo (29% and 19%, respectively, vs. 12%).

Safety and tolerability

Safety and tolerability analyses were conducted in the entire ITT population of 554 patients aged

2–11 yr. FF was well tolerated and had a good safety profile. The types of AEs were similar between the two active treatment groups but the overall incidence was higher than in the placebo group: 20% placebo, 30% FF 55 µg, and 30% FF 110 µg. The most common reported AE was headache (4% placebo, 4% FF 55 µg and 6% FF 110 µg). Nine (5%) patients receiving placebo, 11 (6%) patients receiving FF 55 µg, and nine (5%) patients receiving FF 110 µg experienced AEs that were considered by the investigator to be drug related. The most common drug-related AE, epistaxis, was reported by five (3%) patients in the FF 55 µg group and by four (2%) patients in both the FF 110 µg and placebo treatment groups.

Clinical laboratory evaluations did not show any findings of clinical concern for clinical chemistry or hematology. Findings from the nasal examinations of the turbinates, mucosa, septum, and nasal secretions were similar across the three treatment groups. Vital signs were similar among groups at baseline and at the end of the study. In addition, there were no clinically significant abnormal ECGs reported during the study.

Plasma samples were collected 1.5 h post-dose at visit 4 and analyzed from 318 patients who completed the study in the FF treatment groups. Pharmacokinetic assessment showed that the majority of patients receiving either 55 µg FF (98.1%) or 110 µg FF (86.4%) did not have quantifiable plasma levels of FF after 2 wk of dosing.

Of those patients with quantifiable plasma levels of FF, 100% of patients in the 55 µg group and 95.5% of patients in the 110 µg group had values below 30 pg/ml, which is less than three times the lower limit of quantitation (< 10 pg/ml). Median concentrations in patients with quantifiable levels were 19.9 (range 18.4–20.8 pg/ml) and 13.4 pg/ml (range 10.0–54.7 pg/ml) for the 55 and 110 µg groups, respectively.

Discussion

The primary objective of this study was to evaluate the efficacy and safety of FF as a potential treatment option in pediatric patients aged 2–11 yr with SAR. In the 6–11 yr age group, the 110 µg once-daily dose of FF consistently demonstrated greater reductions from baseline in patients' self- or parent/guardian-assessed allergy symptom scores, compared with vehicle placebo nasal spray once daily. The treatment difference in symptom reduction was significantly in favor of FF 110 µg. Notably, this result was also seen in the full ITT population comprising patients aged 2–11 yr. For FF 55 µg once daily, however, there were numerical improvements but no statistically significantly greater improvements in SAR symptoms compared with placebo for the primary and secondary end-points. An explanation for this may be that placebo nasal sprays can, in themselves, ease the symptoms of AR; therefore, the difference in scores may not be so apparent. However, a greater number of patients receiving 55 µg FF rated overall response to therapy as significantly improved compared with placebo recipients.

In pre-clinical studies, FF had a greater relative receptor affinity than other corticosteroids. Although the clinical relevance of this is

unknown, FF receptor binding studies showed a higher affinity for glucocorticoid receptors compared with other corticosteroids and, in addition, greater potency in attenuating lipopolysaccharide-induced tumor necrosis factor release from human peripheral blood monocytes (13). Further to pre-clinical study findings, FF has demonstrated efficacy in the management of symptoms of AR in adults. In a dose-ranging study in adult patients with SAR, all doses of FF tested were efficacious and well tolerated. However, when factors such as nasal symptom efficacy, onset of action, and efficacy at higher dose were taken into consideration, 110 µg was selected as the optimal dose. The 55 µg dose, although less effective in the adult dose-ranging study when compared with the full 110 µg adult dose, was included in the present study to determine its efficacy in children with SAR.

The safety findings of the present study show that both doses of FF were well tolerated in children aged 2–11 yr. Headache, the most common AE, was the only event that occurred at a greater than 3% incidence and was more common with the active drug than with placebo. No clinically relevant effects were noted from the nasal examinations or clinical laboratory tests. Additionally, the absence of quantifiable plasma levels of FF after 2 wk of dosing in most patients demonstrates the low bioavailability of this INS.

The results of this study suggest that once-daily FF nasal spray is effective and safe for the treatment of SAR in children aged 2–11 yr. Although the FF 55 µg dose showed only numerical reductions in the primary and key secondary end-points compared with placebo, the FF 110 µg dose appeared to be the optimal dose for SAR based on its demonstrated consistent statistical significance in all primary and key secondary efficacy end-points.

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