

HPA axis safety of fluticasone furoate nasal spray once daily in children with perennial allergic rhinitis

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The effects of intranasal corticosteroids (INSs) on the hypothalamic–pituitary–adrenal (HPA) axis should be assessed for any to be marketed INS. The objective of this study was to assess the effects of fluticasone furoate nasal spray (FFNS) on cortisol production (as a measure of HPA axis function) following 6 wk of treatment with FFNS 110 µg once daily (QD) compared with placebo in pediatric patients with perennial allergic rhinitis (PAR). In this double-blind, parallel-group study, patients (n = 112) aged 2–11 yr with a 1-yr history of PAR (6 months for patients aged 2–3 yr) were randomized in a 1:1 ratio to either placebo or FFNS. Serum cortisol (SC) concentrations and urinary cortisol (UC) excretion were measured over a 24-h period at the randomization (baseline) and final treatment (week 6) visits for HPA axis evaluation in a domiciled environment (overnight in the clinic).

Plasma samples were collected for FFNS at several time points over the 24 h after the final dose for pharmacokinetic analyses. FFNS was non-inferior to placebo with respect to change from baseline (expressed as a ratio) in 24-h SC weighted mean. The lower limit of the two-sided 95% confidence interval (CI) for the treatment ratio was greater than the pre-specified non-inferiority margin of 0.8 (treatment ratio = 0.97, 95% CI 0.88–1.07). UC excretion over 24 h at baseline and end of treatment was similar between treatment groups; no patients had 24-h excretion levels below normal range after 6 wk of treatment. Plasma concentrations of FFNS were generally non-quantifiable (< 10 pg/ml). Results of the current study indicate that FFNS 110 µg QD has no significant effect on HPA axis function in 2- to 11-yr-old pediatric patients with PAR.

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Allergic rhinitis (AR) is a common chronic disorder with perennial AR (PAR) occurring with a greater incidence in the childhood population (1, 2). Symptoms often go unrecognized; left untreated, AR can give rise to or exacerbate a series of debilitating comorbidities, such as asthma, sinusitis and otitis media (3, 4). Antihistamines and intranasal corticosteroids (INSs) represent the cornerstone of pharmacotherapy for AR, and several INS agents have been approved for use in children (3). Indeed, INSs

have proven capacity to alleviate nasal congestion, rhinorrhea, nasal itching and sneezing episodes (5).

Despite the effectiveness of INSs (6, 7), physicians may be reluctant to prescribe long-term courses of this medication class to children. This is because of their concerns of the potential effects of steroids on the hypothalamic–pituitary–adrenal (HPA) axis and growth inhibition (3, 8, 9). Evidence suggests that such side effects are due to systemic absorption of the

corticosteroid (9). However, this does not appear to be reflective of newer high-potency corticosteroids that are applied topically to the nasal mucosa and have high first-pass hepatic metabolism (10–12).

In light of this, an INS should have low systemic bioavailability, high potency and a high binding affinity (13). Several well-designed studies have demonstrated that INSs with high potency are well-tolerated, with no measurable effects on HPA axis action in pediatric patients with PAR (7, 14–17).

Fluticasone furoate (FF) is a potent, novel, enhanced-affinity glucocorticoid, administered in a scent-free formulation using a unique, side-actuated device, designed for ease of self-administration and parent/caregiver administration to children (18). FF nasal spray (FFNS) has several beneficial properties, including low systemic bioavailability, rapid uptake and sustained pharmacological action (19, 20). In view of its pharmacological properties, it is anticipated that FFNS will be a well-tolerated treatment option with minimal adverse effects in children. This multicenter, randomized, double-blind trial was conducted to assess the effects of FFNS once daily (QD) on HPA axis function in young children aged 2–11 yr with PAR, using 24-h measurements of serum cortisol (SC) concentrations and urinary cortisol (UC) excretion obtained in a controlled, domiciled (clinical) environment.

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice, and in compliance with the requirements of the Institutional Review Board or Independent Ethics Committee. Written, informed consent was obtained from each patient's caregiver prior to commencing study-related procedures.

Male and premenarchal female patients were eligible for inclusion if they were 2–11 yr of age at the randomization visit with a 1-yr history of PAR (6 months for patients aged 2–3 yr), and a positive skin-prick test (carried out according to the individual study site's standard testing procedures and defined as wheal diameter ≥ 3 mm larger than the diluent control) for an appropriate perennial allergen during or within 12 months of the screening visit. The patient and parent/guardian of the patient were required to stay in the clinic for 24 h at the start (randomization visit) and end (final treatment

visit at week 6) of the study for collection of serum and urine samples.

Patients with any clinically significant uncontrolled disease that might interfere with clinical evaluations were ineligible for study entry, as were those showing any disorder of the ears, nose or throat; nasal polyps; chronic sinusitis; rhinitis medicamentosa; significant nasal obstruction or perforation that might affect the deposition of the study drug; asthma [with the exception of mild asthma as defined by the 1997 National Asthma Education and Prevention Program guidelines (21)] or any upper respiratory tract, sinus or ear infection.

Concomitant medications that would interfere with study evaluations were not permitted, including intranasal, inhaled or systemic corticosteroids; intranasal cromolyn; oral or intranasal decongestants; intranasal, inhaled or oral anticholinergics; antihistamines; or oral antileukotrienes. An adequate washout period prior to the screening visit was required for any patient using corticosteroids prior to study start. Patients were not allowed entry into the trial if they had a clinically abnormal electrocardiogram (ECG), laboratory test or morning SC level. Loratadine syrup (1 mg/ml) was permitted as rescue medication during the study, the use of which was recorded on diary cards.

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study (Fig. 1) performed at 10 sites in the USA. Eligible patients entered a 7- to 14-day screening period during which they were asked to score their nasal symptoms on a diary card. At randomization, patients were required to be clinically symptomatic with a daily reflective total nasal symptom score (rTNSS; the sum of individual nasal symptom scores for nasal congestion, rhinorrhea, nasal itching and sneezing; assessed in a reflective manner for the previous 12 h and recorded twice daily) of ≥ 5 (out of a total score of 12) on any four of the previous 7 days. In addition, patients were also required to have completed $\geq 80\%$ of assessments on their screening symptom diary card.

Patients meeting these criteria were randomly assigned in a 1:1 ratio to either FFNS at a dose of 110 μg QD or matching placebo nasal spray QD. To ensure adequate enrollment across age groups and treatment balance, randomization was stratified by age [2–3 yr (20%), 4–5 yr (20%) and 6–11 yr (60%)]. Patients and their parents or guardians were shown how to use the nasal spray

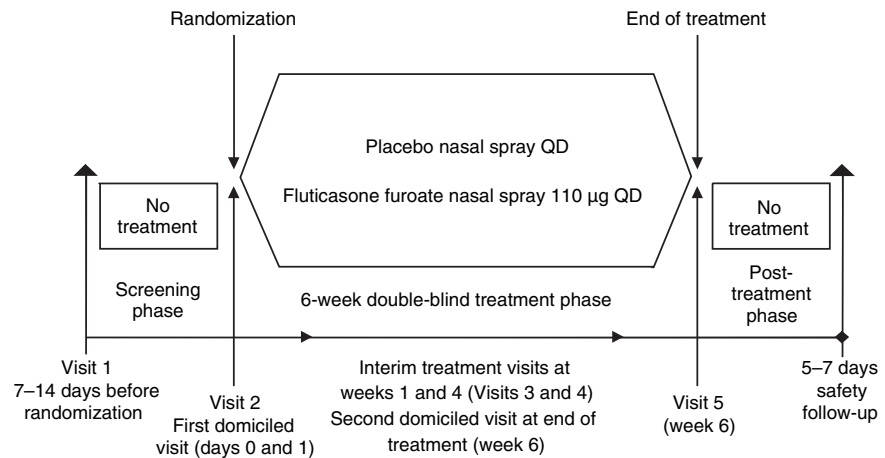


Fig. 1. Study design.

device by trained personnel who demonstrated using a placebo device. To ensure that all patients and their parents or guardians used the device correctly, administration was observed on all possible occasions by appropriately trained personnel via videophone equipment provided to each study patient or caregiver. Two sprays per nostril (27.5 µg/spray) were administered each morning. The first dose of the study drug was administered at the end of the first 24-h baseline assessments at the randomization visit; the last dose was administered at the final treatment visit (week 6). Duration of treatment was 6 wk, with treatment visits at weeks 1, 4 and 6, followed by a 5- to 7-day post-treatment safety follow-up to assess for any post-treatment adverse events.

Assessments

Serial blood samples for SC concentration were collected over 24 h at specified time points relative to the 24-h sampling start time (at 0, 2, 4, 8, 12, 16 and 24 h) at the randomization visit and following the final morning dose at the week 6 visit. Urine samples for UC excretion measurements were also collected over 24-h periods at the two visits. These data were collected in a domiciled environment, i.e. patients stayed overnight in the clinic. Blood samples for plasma level determination were collected at several time points relative to the final dose (pre-dose and at 0.5, 1, 2 and 4 h post-dose) at the week 6 visit.

The primary end-point of the study was the change from baseline (expressed as a ratio) in 24-h SC weighted mean. Other pharmacodynamic end-points included the change from baseline in 24-h UC excretion, and in the total 24-h UC excretion and 6-β hydroxycortisol excretion. Pharmacokinetic analysis for plasma concentrations of FF were conducted using a specific and sensitive

liquid chromatography-mass spectrometry/mass spectrometry (LC-MS-MS) method with a lower limit of quantification of 10 pg/ml.

Patients and/or parents/guardians were questioned by the investigator at each study visit for evidence of adverse events; severity was graded as mild, moderate or severe. Other safety evaluations included monitoring of vital signs and performing detailed nasal examinations of the turbinates, mucosa, septum and secretions to evaluate nasal patency and the presence or site of any polyps or ulcers, physical examinations, ECGs and clinical laboratory tests.

Four different means of assessing compliance were employed in this study. Traditional methods included change in nasal symptom assessment scores, diary card recordings of compliance and the difference in nasal spray device weights before and after use. An additional novel means piloted in this study involved a contract research organization observing the daily dosing of the study medication via videophone technology and equipment. Patients and/or parents/guardians were contacted by trained personnel each morning by appointment to conduct the observational session.

Statistical analysis

The primary comparison was change from baseline (expressed as a ratio) in 24-h SC weighted mean for FFNS vs. placebo. This was derived for each patient immediately prior to randomization (baseline) and at the end of 6 wk of treatment. The weighted mean was calculated by dividing the area under the curve over the 24-h sampling interval by the time interval for sample collection. A statistical analysis was performed on log_e-transformed ratio from baseline 24-h SC weighted mean. An analysis of covariance (ANCOVA) model was fitted with log_e-transformed

baseline, center and treatment group terms in the model. Change from baseline in 24-h SC weighted mean and 24-h UC excretion was analyzed similarly using ANCOVA, adjusted for baseline and center. Treatment ratios and a corresponding two-sided 95% CI were calculated for the difference. Non-inferiority was to be demonstrated if the lower limit of the two-sided 95% CI for the geometric mean treatment ratio was greater than the predefined value of 0.80.

The sample size of approximately 100 patients was selected to ensure that at least 80 patients (approximately 40 per treatment group) completed the study. This was based on the number of patients required to demonstrate non-inferiority of FFNS compared with placebo in change from baseline (expressed as a ratio) in 24-h SC weighted mean. Assuming a standard deviation of 0.30, full data available from 40 patients on each treatment would give approximately 90% power to demonstrate non-inferiority if there was no true difference between treatment groups.

The assessment of HPA axis function was carried out on the intent-to-treat (ITT), SC and UC populations, the latter two of which were defined as ITT patients who had no confounding factors that could potentially affect the interpretation of the results, such as use of protocol-prohibited medication, two or more consecutive missing SC concentrations, insufficient urine volume or collection time interval. The SC population was the primary population. UC excretion over the 24-h period was derived for the randomization and week 6 visits by multiplying the cortisol concentration over the time interval by the total volume of the urine sample. Change from baseline in UC excretion was summarized for the UC population. Safety data were summarized based on the ITT population.

Results

Patient disposition and baseline characteristics

A total of 112 patients aged 2–11 yr were randomized to treatment, 94% ($n = 105$) of whom completed the 6-wk treatment period. Baseline demographics were generally similar between the two treatment groups (Table 1). Overall, patients had moderate symptoms, with similar severity between the two treatment groups (mean daily rTNSS = 7.6 for FFNS; 7.5 for placebo). The use of loratadine syrup rescue medication during the study period was low (0.091 vs. 0.148 teaspoons/day on average for FFNS and placebo recipients, respectively).

The number of patients withdrawing from the study was similar between the treatment groups [$n = 4$ (7%) from FFNS compared with $n = 3$ (5%) from placebo]. Two patients discontinued from treatment owing to adverse events, two owing to protocol violations and three for other reasons (Table 1). With regards to the populations analyzed, 91% and 89% of patients randomized to FFNS and placebo, respectively, comprised the SC population, while 75% of patients from each treatment group formed the UC population.

24-h SC concentration

The primary analysis was performed on the SC population comprising 101 patients aged 2–11 yr. Geometric means for SC concentration over the 24-h collection period were similar between the FFNS and placebo treatment groups at baseline (Table 2). At baseline and after 6 wk of treatment, diurnal variations in SC concentrations were similar in both treatment groups and as expected (Fig. 2). FFNS was non-inferior to placebo with respect to the ratio from baseline in 24-h SC weighted mean, adjusted for baseline and center. The lower limit of the two-sided 95% CI for the treatment ratio was greater than the pre-specified non-inferiority margin of 0.8

Table 1. Patient demographics and disposition [intent-to-treat (ITT) population]

	Number (%) of patients	
	Fluticasone furoate (FF), 110 µg ($n = 57$)	Placebo ($n = 55$)
Mean age, yr	6.1	6.4
Age group, n		
2–3 yr	11 (19)	10 (18)
4–5 yr	13 (23)	12 (22)
6–11 yr	33 (58)	33 (60)
Gender, n		
Male	25 (44)	31 (56)
Female	32 (56)	24 (44)
Race, n		
White	33 (58)	40 (73)
African-American/African heritage	23 (40)	15 (27)
Other	1 (2)	0
SC population	52 (91)	49 (89)
UC population	43 (75)	41 (75)
Completed study	53 (93)	52 (95)
Withdrawn	4 (7)	3 (5)
Adverse event	1 (2)	1 (2)
Protocol violation	2 (4)	0
Other*	1 (2)	2 (4)

*Other reasons included non-compliance, missing documentation and failure to meet inclusion criteria in terms of symptom severity.

SC, serum cortisol; UC, urinary cortisol.

Table 2. Summary of derived serum cortisol (SC) weighted mean (0–24 h; µg/dl), for the SC population

	Placebo (n = 49)	Fluticasone furoate (FF), 110 µg QD (n = 52)
Baseline		
n	48	50
Geometric mean	6.71	6.88
95% CI for geometric mean	6.20, 7.25	6.35, 7.46
Median	6.41	7.02
Min-max	3.76–14.81	3.90–12.58
Week 6		
n	48	50
Geometric mean	6.58	6.58
95% CI for geometric mean	6.11, 7.09	6.05, 7.16
Median	6.59	6.21
Min-max	3.66–15.02	3.77–17.88
Ratio from baseline		
n*	47*	48*
Geometric mean	0.979	0.935
95% CI for geometric mean	0.912, 1.052	0.860, 1.017
Median	0.972	0.989
Min-max	0.52–1.66	0.56–1.86

*Ratios were not calculated if the first (0 h) or last (24 h) sample was not collected or evaluable.

CI, confidence interval; QD, once daily.

(treatment ratio = 0.97, 95% CI 0.88–1.07; Table 3).

For the clinician's practical use, mean change from baseline in SC weighted mean (0–24 h) data are also provided here. After 6 wk of treatment, mean change from baseline in the mean SC concentrations over 24 h was –0.34 and –0.23 µg/dl for the FFNS and placebo-treated groups, respectively, with a difference of –0.11 µg/dl (95% CI –0.88, 0.66).

24-h UC excretion

An assessment of 24-h UC excretion was summarized for the UC population comprising 84 patients aged 2–11 yr. Mean 24-h UC excretion levels were similar for FFNS and placebo at baseline (FFNS = 12.19 µg/day; placebo = 11.23 µg/day). After 6 wk of treatment there was a least square mean change of 0.49 and 1.92 µg/day in the FFNS and placebo groups, respectively, with a difference of –1.43 µg/day (95% CI –5.21, 2.35). Individual changes from baseline in 24-h UC excretion levels were similar, except in three patients – one in the placebo group and two in the FFNS 110 µg group. All three patients had abnormally high values at baseline; two normalized at week 6 and the other was slightly above the normal range at week 6 (Fig. 3). At week 6, no patients had 24-h UC excretion below the normal range. Total 24-h UC

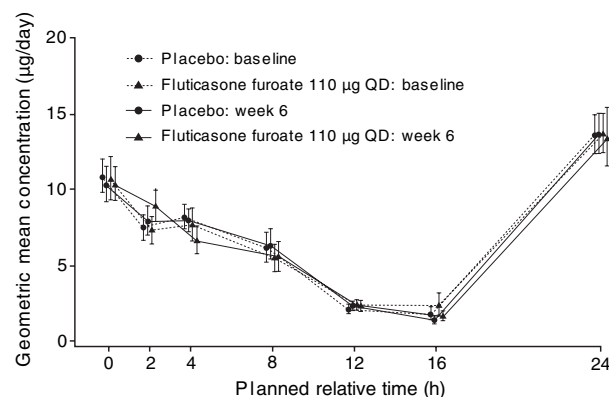


Fig. 2. Geometric mean (95% CI) serum cortisol (SC) concentration - time profile for fluticasone furoate (FF) and placebo at baseline and end of treatment (SC population).

Table 3. Summary results of statistical analysis of derived serum cortisol (SC) weighted mean (0–24 h; ratio from baseline, for the SC population)

Treatment	Comparison	LS means		Treatment ratio	95% CI
		Active	Placebo		
Fluticasone furoate (FF) 110 µg QD	vs. placebo	0.94	0.97	0.97	(0.88, 1.07)

LS, least square; QD, once daily.

and 6-β hydroxycortisol excretion data was similar to that for 24-h UC.

Plasma concentrations of fluticasone furoate

A total of 262 plasma samples were collected post-dose over a 24-h period after 6 wk of treatment from 53 patients in the FFNS 110 µg QD group. FFNS levels were generally not quantifiable (< 10 pg/ml) with the exception of six samples from four patients (all < 20 pg/ml) and, therefore, no pharmacokinetic analyses were conducted.

Treatment compliance

Efficacy results demonstrating a greater reduction in symptoms with the active treatment vs. placebo were indicative of treatment compliance; mean change in daily rTNSS over weeks 1–6 were –2.5 for FFNS vs. –1.6 for placebo (Fig. 4). Daily diary cards indicated that 96% of patients had ≥90% compliance with study medication in both treatment groups. Total usage, based on the weight of the nasal spray device at the end of treatment, was as expected and similar for both treatment groups in the ITT population. The mean and median number of daily doses

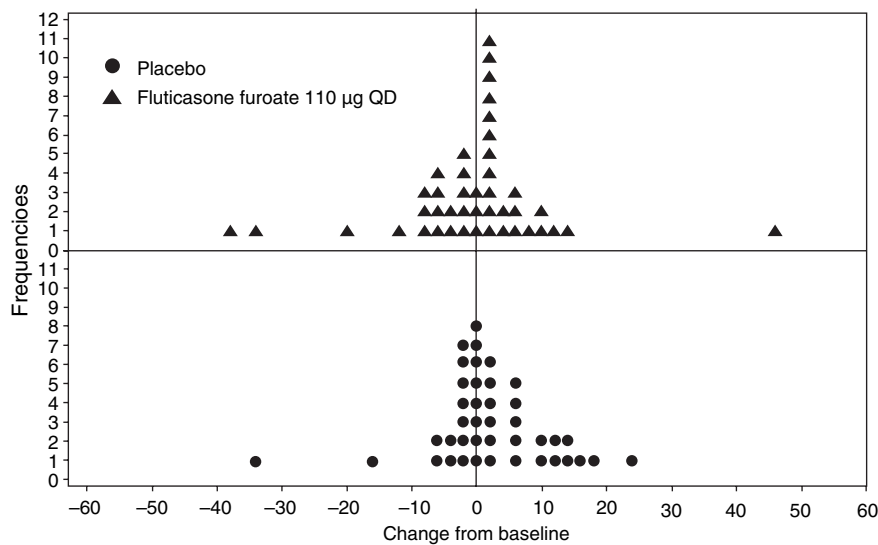


Fig. 3. Change from baseline in 24-h UC excretion ($\mu\text{g}/\text{dl}/\text{day}$) after 6 wk of treatment (UC population).

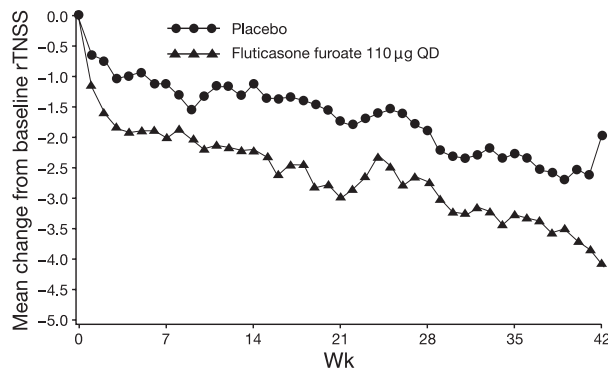


Fig. 4. Mean change from baseline in mean daily reflective total nasal symptom score (rTNSS) over 6 wk of treatment [intent-to-treat (ITT) population].

observed via videophone was similar for both groups and ranged from 85.2% to 90.7%. This compliance data was consistent with data from the other three conventional methods utilized in this study, including diary card readings, efficacy assessments and changes in bottle weight, as discussed previously.

Safety and tolerability

Treatment with both FFNS and placebo was well-tolerated, with no unexpected events. The incidence of adverse events was similar between the two treatment groups: 18% of patients receiving FFNS compared with 16% on placebo. The most common adverse event was pyrexia reported by two (4%) patients in the FFNS-treated group; neither case was deemed to be related to the study drug (Table 3). Treatment-related adverse events occurred in two patients (pruritus and urticaria in one placebo patient,

and nasal discomfort in one FFNS 110 μg patient). Adverse events leading to withdrawal included bilateral ear infection in one placebo patient and a case of pneumonia in one FFNS patient. A displaced fracture of the ulna and radius following a fall was considered serious; this event was deemed unrelated to the study drug in a patient randomized to placebo.

Findings from detailed nasal examinations were similar between the two treatment groups throughout the study for all aspects of the examination; no evidence of adverse impact to the nasal mucosa was observed in either the placebo or the FFNS group. No epistaxis was reported and there was no evidence of candidiasis during the study.

Vital signs and ECG findings, as well as clinical chemistry and hematology results, were similar between the treatment groups.

Discussion

Findings from the present randomized, double-blind, placebo-controlled trial provides evidence that QD dosing with the novel INS, FFNS 110 μg , has no impact on HPA axis function in children 2–11 yr of age with PAR following 6 wk of treatment. The lower limit of the two-sided 95% CI for the treatment ratio (FFNS/placebo) lay above the predefined bound of 0.80, indicating that FFNS was non-inferior to placebo in terms of ratio from baseline in 24-h SC weighted mean. The lack of effect of FFNS on the HPA axis compared with placebo was confirmed by the 24-h UC excretion data, which also indicated similarities between the treatment groups. Supportive of these findings, plasma concentrations of FFNS were generally not quantifiable, thereby

indicating that systemic absorption and bioavailability of this INS were negligible.

These data contribute to the existing evidence that suggests that low bioavailability of INSs may be attributed to low aqueous solubility and extensive first-pass metabolism (22). This means that only a negligible amount of drug crosses the nasal mucosa to enter the bloodstream; most is cleared from the nose or swallowed and excreted. Any drug absorbed through the intestine is subject to extensive first-pass metabolism, resulting in low systemic absorption (13).

While investigating the amount of drug that enters systemic circulation is important, its actual systemic effects may be of more value. Therefore, measuring serum and urinary cortisol levels over a 24-h period, as carried out in this study, is considered to be a more realistic reflection of the systemic effect of an INS on HPA axis function (23). The reported findings are further substantiated by the robustness of the study design; collection of blood and urine samples over 24 h in an in-patient setting at the randomization and week 6 visits ensured that samples were collected in a standardized and complete manner. Moreover, this domiciled method of collection provided a sensitive method for detecting any changes in diurnal variations in cortisol production arising as a result of systemic corticosteroid exposure. The controlled and comprehensive design of this study strengthens the significance of these findings. With regards to limitations of the study, considering that accepted normal and abnormal values for 24-h SC production do not exist, inclusion of a positive control may have been helpful. However, a control was not included owing to ethical concerns surrounding administration of a corticosteroid dose sufficient to suppress cortisol production in this young, healthy pediatric population (2–11 yr) with only AR.

Successful administration of the study medication and, thereafter, compliance with therapy can be a potential area of concern in pediatric registration studies. However, the inclusion of multiple assessments in this study helped to overcome this issue, and demonstrate that patients remained compliant with their dosing regimen over the 6-wk treatment period. Assurance of compliance via conventional assessments of efficacy as well as daily diary card recordings of treatment administration was confirmed by changes in the weight of the nasal delivery device pre- and post-dose. Videophone equipment used to observe patients actually taking their daily medication dose provided a

novel and successful method with which to further substantiate compliance.

Although none of the pediatric INS studies reported to date have involved domiciled collections of 24-h serial serum and urine for cortisol assessments before and after 6 wk of treatment, coupled with daily videophone observations of treatment compliance, several of these studies have evaluated adrenal function in pediatric patients, with similar findings.

The results of these pediatric studies of INSs with low systemic bioavailabilities (<1%) have demonstrated that QD INSs are as safe as placebo for the treatment of pediatric patients as young as 2 yr with SAR and PAR. In a study by Brannan et al., assessment of morning plasma cortisol concentrations and 24-h UC was conducted in patients aged 6–12 yr with AR treated for 7 days with mometasone furoate nasal spray (MFNS) QD or placebo. In the younger patient group (3–5 yr), treated with MFNS for 14 days, plasma cortisol concentrations were also evaluated 30 min after stimulation with a synthetic adrenocorticotrophic hormone (cosyntropin). There were no significant differences in mean plasma cortisol levels or 24-h UC levels between the MFNS and placebo recipients (14). In a further study, HPA axis function in children aged 3–9 yr with PAR following treatment with MFNS QD was evaluated. Responses to cosyntropin stimulation were normal in all patients at all measured time points and there was no evidence of HPA axis suppression (16). The effects of fluticasone propionate nasal spray (FPNS) QD on HPA axis function in children aged 2–3 yr with AR were examined by Galant et al. At the end of the 6-wk treatment period, no statistically significant difference was observed in the mean change from baseline in 12-h creatinine-corrected UC concentrations between FPNS and placebo recipients (15). Nayak et al. investigated the adrenal function in patients aged 6–12 yr with AR, randomized to receive triamcinolone acetonide nasal spray (220 or 440 µg) or placebo QD. There were no significant differences in plasma cortisol levels after cosyntropin stimulation (measured at baseline and at the end of the 6 wk treatment period) between the active drug treatment groups and the placebo group (17).

In conclusion, the results of this multicenter, domiciled, randomized, double-blind placebo-controlled trial demonstrate that FFNS 110 µg QD is well-tolerated, with no significant suppression of HPA axis function compared with placebo in young children aged 2–11 yr. This finding is of clinical relevance as a new treatment

option for the management of the bothersome symptoms of PAR in children.

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