

Efficacy and Safety of Fluticasone Furoate Nasal Spray in Japanese Children with Perennial Allergic Rhinitis: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of allergic rhinitis (AR). This is the first randomized clinical trial to assess the efficacy and safety of FFNS in Japanese children with perennial AR (PAR).

Methods: In this multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III study, 261 children aged 6 to <15 years were treated with FFNS 55 µg, once daily or placebo for two weeks. Nasal and ocular symptoms were rated by parents/guardians/patients in the patient daily diary. The primary endpoint was the mean change from baseline in the three total nasal symptom score (3TNSS). In addition, rhinoscopic findings were rated by the investigators as an efficacy measure. As a safety measure, adverse events and clinical chemistry and hematology were evaluated.

Results: Mean change from baseline over the entire treatment period in 3TNSS was greater in the FFNS 55 µg group compared with placebo, and the difference was statistically significant ($p < 0.001$). Significant improvements in rhinoscopic findings of swelling of inferior turbinate mucosa and quantity of nasal discharge were also observed. The total ocular symptom score (TOSS) was reduced significantly in the FFNS 55 µg group, compared with placebo, in the second week in a subgroup of patients with baseline TOSS > 0. The incidence of adverse events was similar between FFNS 55 µg (18%) and placebo (19%).

Conclusions: Two-week treatment with FFNS 55 µg, once daily is effective and tolerable in Japanese children aged 6 to <15 years with PAR.

KEY WORDS

children, double-blind, fluticasone furoate, perennial allergic rhinitis, placebo-controlled

INTRODUCTION

Allergic rhinitis (AR) is a highly prevalent chronic disease, affecting approximately 30% of the children in Japan.^{1,2} The prevalence varies worldwide and is increasing in most countries.^{3,4} AR is characterized

by the three major symptoms of paroxysmal and recurrent sneezing, watery rhinorrhea, and nasal congestion.^{1,2} In the Practical Guideline for the Management of Allergic Rhinitis in Japan, AR has been classified as perennial AR (PAR) or seasonal AR (SAR) depending on the timing and duration of symptoms.^{1,2}

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Conflict of interest: KO has received lecture fees from GlaxoSmithKline K.K.. AO, GH and MK are employees of Glaxo-

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Common allergens for PAR include dust mites, animal dander, molds and cockroaches, and allergens for SAR include Japanese cedar pollens, ragweed and orchard grass.^{5,6} Severity of AR is classified as mild, moderate, severe (and most severe) using a unique scoring system based on frequency of symptoms in a day, including episodes of paroxysmal sneezing and episodes of nose blowing.^{1,2} This scoring system was used as an efficacy measure in this study.

AR in children has a significant impact on the quality of life (QOL), sleep and school productivity.⁷⁻⁹ The performance of children with AR at school can be impaired by cognitive dysfunction related to the AR.¹⁰ In addition, if left untreated, comorbid conditions associated with AR, including asthma and otitis media, can be problematic in children.^{11,12} Moreover, AR is reported to be associated with a significant economic burden.^{3,13,14}

AR is often associated with ocular symptoms.³ Some patients consider ocular symptoms to be more annoying than nasal symptoms, and some studies have shown that ocular symptoms also impair patients' QOL.¹⁵⁻¹⁷

Corticosteroids constitute a well established anti-inflammatory therapy that effectively controls the nasal symptoms of AR, and international guidelines recommend intranasal corticosteroids (INS) as first-line therapy for patients with moderate-to-severe or persistent disease.³ In the Japanese guideline, INS are recommended as the most effective medications to improve symptoms of AR.^{1,2} INS have a broad spectrum of efficacy for a range of nasal symptoms, including congestion, rhinorrhea and sneezing.¹⁻³ In addition, INS have been reported to improve eye symptoms that accompany AR.¹⁸⁻²¹

Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of AR, and is administered in a unique, side-actuated device.^{22,23} This delivery system was designed for ease of self-administration, as well as for convenient parent/caregiver administration to children.²⁴ As a treatment for AR, FFNS is currently approved in more than 100 countries and used both in adults and children in many countries including Europe and America. Although well studied in healthy volunteers and adult patients with AR and approved for the use in adults, the clinical efficacy and safety of FFNS has not been investigated in children with AR in Asia including Japan. In Japanese children, few studies evaluated efficacy and safety of INS in double-blind design. In addition, to our knowledge, no study has evaluated the efficacy of FFNS on ocular symptoms associated with PAR in children.

We conducted two clinical studies to evaluate the efficacy and safety of FFNS 55 µg in Japanese children. One study was a twelve-week, open study to assess the safety, efficacy and systemic exposure of once-daily FFNS 55 µg in Japanese children aged 2 to

<15 years with PAR, which is reported elsewhere. (ClinicalTrials.gov Identifier: NCT01622231, GlaxoSmithKline protocol number: FFR116365.) The other study was a two-week, randomized, phase III study to assess the efficacy on nasal and ocular symptoms, and safety of once-daily FFNS 55 µg compared with placebo in Japanese children aged 6 to <15 years with PAR, which we report in this article.

METHODS

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study was conducted at 22 centers in Japan.

Eligible patients entered a one to two-week screening period. Patients meeting the randomization criteria were randomly assigned to one of the two treatment groups, FFNS 55 µg or placebo, in a 1 : 1 ratio. The vehicle placebo contained the following: purified water, glucose anhydrous, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 80, benzalkonium chloride, and edentate disodium. Patients were treated once daily in the morning for two weeks and had a clinic visit every week. A follow up visit/phone call was scheduled one week after the end of the treatment to confirm the safety. Patients who completed all of the visits including the follow up are deemed to have completed the study.

PATIENTS

Eligible patients were aged 6 to <15 years with a history of PAR for one year or more, and positive for both a specific immunoglobulin E (IgE) antibody test to a PAR allergen (house dust mite or house dust) and nasal eosinophil counts, and with the three total nasal symptom score (3TNSS) of 4 to <8 at baseline.

Patients were excluded from the study if they had SAR symptoms attributable to pollen which would be present in their geographic area during study participation, had an co-morbid disorder which might affect the result of the study (e.g. acute/chronic sinusitis, nasal polyps, upper respiratory or eye infection), or had a co-morbid disease where inclusion in the study would have been inappropriate based on safety concerns (e.g. tuberculosis, infection without effective antibacterials, serious hepatic/renal/cardiac/pulmonary dysfunction or a hematopoietic disorder, uncontrolled hypertension/diabetes mellitus, or asthma [except for mild intermittent cases]). Patients were also excluded if they had used medications which might affect the efficacy assessment of the study (e.g. systemic corticosteroids within eight weeks of study initiation).

Use of any treatment for allergic rhinitis, excluding the study medication, and any concomitant medication which might affect the efficacy assessments of the study (e.g. corticosteroids) were prohibited during the screening and treatment periods.

EFFICACY ASSESSMENTS

The primary efficacy endpoint was the mean change from baseline in 3TNSS over the entire treatment period. The 3TNSS is a common endpoint used for assessment in clinical studies of allergic rhinitis in Japan. Parents/guardians/patients were instructed to record patients' symptom scores (individual nasal and ocular symptoms and troubles with daily life) in the patient diary every day during the screening and treatment periods. The baseline values were the average score during the four consecutive days prior to randomization. Secondary efficacy values include 3 TNSS, the four total nasal symptom score (4TNSS), the total ocular symptom score (TOSS), individual nasal and ocular symptom scores, score for troubles with daily life, the rhinoscopic findings score, and overall evaluation of the response to therapy. Investigators scored rhinoscopic findings at baseline (randomization) and at each visit during the treatment period. Parents/guardians/patients and investigators scored overall evaluation of the response to therapy at the end of the treatment period.

The 3TNSS is the sum of individual four-point scores for sneezing (number of episodes of paroxysmal sneezing in a day; ≥ 11 times: 3, 10-6 times: 2, 5-1 times: 1, none: 0), rhinorrhea (number of episodes of nose blowing in a day; ≥ 11 times: 3, 10-6 times: 2, 5-1 times: 1, none: 0), and nasal congestion (a severe nasal congestion causing prolonged oral breathing in a day: 3, severe nasal congestion causing occasional oral breathing in a day: 2, nasal congestion without oral breathing: 1, none: 0). The 4TNSS is the sum of individual four-point scores for sneezing, rhinorrhea, nasal congestion, and nasal itching (severe symptom that causes interference with activities of daily living: 3, definite awareness of symptom that is tolerable [intermediate between 3 and 1]: 2, minimal awareness of symptom: 1, none: 0). TOSS is the sum of individual four-point scores for eye itching, tearing and eye redness, all of which are assessed as follows: severe symptom that causes interference with activities of daily living: 3, definite awareness of symptom that is tolerable (intermediate between 3 and 1): 2, minimal awareness of symptom: 1, none: 0. Score for troubles with daily life is a four-point score assessed as: painful and complicating daily life: 3, intermediate between 3 and 1: 2, few troubles with daily life: 1, no troubles: 0. Rhinoscopic findings were assessed based on four-point scores of swelling of inferior turbinate mucosa (impossible to see middle turbinate: 3, intermediate between 3 and 1: 2, possible to see center of the middle turbinate: 1, none: 0) and quantity of nasal discharge (filled: 3, intermediate between 3 and 1: 2, small amount adhered: 1, none: 0). Overall evaluation of response to therapy was assessed using seven-point scores: significantly improved: 0, no change: 4, significantly worse: 7. The individual nasal symptoms of sneezing, rhinorrhea, nasal congestion, and rhino-

scopic findings are based on the Japanese guideline.^{1,2}

SAFETY ASSESSMENTS

Safety of FFNS was assessed by frequency and severity of adverse events and laboratory tests (clinical chemistry and hematology). Adverse events were monitored during the treatment and follow up period. Treatment compliance was assessed through patient diary card recording.

STATISTICAL ANALYSES

To verify the superiority of FFNS 55 μ g over placebo as the primary endpoint, a sample size of 250 patients (125 patients per group) was required to provide statistical power of 90% at a two-tailed level of significance of 5%, assuming a treatment difference of 0.7 and a standard deviation of 1.7, based on our previous study.²⁵ In order to have 250 evaluable patients, it was planned to randomize 260 patients.

Efficacy analyses were performed for the full analysis set (FAS) of patients who were randomized to a treatment, received at least one dose of the study medication and completed at least one diary assessment of 3TNSS after dosing with the study medication. The primary analysis was a two-sided comparison of the two treatment groups, FFNS 55 μ g and placebo, using analysis of covariance (ANCOVA) with adjustments for baseline value, age and gender. For the secondary efficacy endpoints of rhinoscopic findings (swelling of inferior turbinate mucosa and quantity of nasal discharge) and overall evaluation of response to therapy, differences between the two treatment groups were assessed by pairwise comparison, using the Wilcoxon two-sample test. For the other secondary efficacy endpoints, differences between the two treatment groups were assessed in the same way as the primary analysis.

Safety analyses were performed for the safety population (SP) of patients who received at least one dose of the study medication.

ETHICAL APPROVAL AND CLINICAL TRIAL REGISTRATION

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards at each center approved the protocol of this study. Written informed consent was obtained from a parent or a guardian of each child participating in the study. Assent was taken from all children aged twelve years and older. All children under twelve years were informed depending on their understanding, and assent was taken if appropriate. The ClinicalTrials.gov Identifier is NCT01630135. The GlaxoSmithKline protocol number is FFR116364.

Table 1 Subject demographics (FAS)

	Placebo (N = 130)	FFNS 55 µg (N = 131)	Total (N = 261)
Age (years)			
Mean ± SD	10.1 ± 2.22	10.0 ± 2.32	10.1 ± 2.26
Min-Max	6-14	6-14	6-14
Gender, n (%)			
Male	79 (61%)	85 (65%)	164 (63%)
Female	51 (39%)	46 (35%)	97 (37%)
Duration of PAR, n (%)			
<2 years	16 (12%)	14 (11%)	30 (11%)
≥2 to <5 years	49 (38%)	49 (37%)	98 (38%)
≥5 years	65 (50%)	68 (52%)	133 (51%)

FAS, full analysis set; FFNS, fluticasone furoate nasal spray; PAR, perennial allergic rhinitis.

Table 2 Mean change from baseline in 3TNSS (FAS)

		Placebo (N = 130)	FFNS 55 µg (N = 131)
Baseline	Mean (SD)	5.2 (1.06)	5.0 (0.94)
Entire treatment period	LS mean change (SE)	-0.89 (0.12)	-1.98 (0.12)
	LS mean difference †	-	-1.089
	p-value vs. placebo	-	<0.001
Week 1	LS mean change (SE)	-0.70 (0.12)	-1.60 (0.12)
	LS mean difference †	-	-0.894
	p-value vs. placebo	-	<0.001
Week 2	LS mean change (SE)	-1.10 (0.13)‡	-2.38 (0.13)
	LS mean difference †	-	-1.279
	p-value vs. placebo	-	<0.001

3TNSS, three total nasal symptom score; FAS, full analysis set; FFNS, fluticasone furoate nasal spray; LS, least square.

† LS mean difference = LS mean change in FFNS 55 µg minus LS mean change in placebo.

‡ n = 128.

RESULTS

STUDY POPULATION

Of the 307 patients screened in the study, 261 patients were randomized to one of the two treatment groups; 131 patients in the FFNS 55 µg group and 130 patients in the placebo group. All of the 261 patients were included in the analysis of efficacy and safety (FAS and SP). Of the 261 patients randomized, 259 patients (>99%) completed the study and two patients in the placebo group were withdrawn from the study due to a protocol deviation based on the exclusion criterion, but included in the analysis.

The demographic and baseline characteristics for the FAS population were similar between the two treatment groups and are summarized in Table 1. All patients were of Japanese ethnicity. Average age was 10.1 years in the placebo group and 10.0 years in the FFNS 55 µg group. Duration of PAR was at least two years in 89% of patients. All patients were positive for one of the PAR allergens (house dust mite or house dust constituted an inclusion criterion) and positive in nasal eosinophil counts. The percentage of patients with a positive IgE test for each allergens was high

(98-100%) and similar in the two treatment groups. Mean baseline 3TNSS was approximately 5 (placebo: 5.2, FFNS 55 µg: 5.0) for the two treatment groups, indicating that the study population consisted mainly of moderate cases. The mean rate of treatment compliance was also similar among the two treatment groups (placebo: 99.34%, FFNS 55 µg: 99.03%).

EFFICACY

Primary efficacy analyses were performed in the FAS population of 261 patients aged 6 to <15 years. FFNS 55 µg significantly improved nasal symptoms; the least square (LS) mean change from baseline over the entire treatment period in 3TNSS was greater for FFNS 55 µg (-1.98) than for placebo (-0.89), and the difference (-1.089) was statistically significant ($p < 0.001$, Table 2). FFNS 55 µg also showed significantly greater improvements compared with placebo with respect to the LS mean change from baseline in 3 TNSS in Weeks 1 and 2 (Table 2). The mean change from the baseline in 3TNSS over the two weeks of the treatment period is presented in Figure 1. A significant treatment difference in mean change from baseline for 3TNSS was first observed on day 2 ($p < 0.001$)

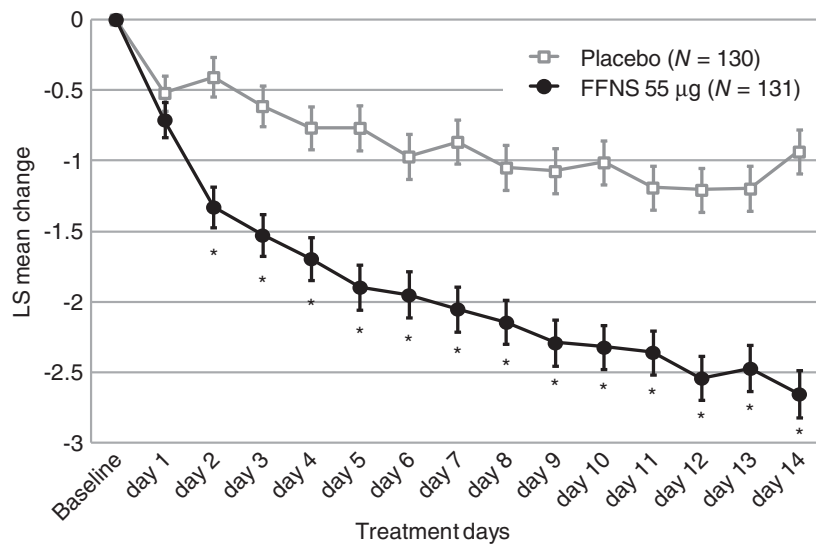


Fig. 1 Mean change from baseline in 3TNSS (FAS). * $p < 0.001$. Pairwise (two-sided) comparison using an analysis of covariance (ANCOVA) (FFNS 55 µg vs. Placebo). No adjustments for multiplicity. 3TNSS, three total nasal symptom score; FFNS, fluticasone furoate nasal spray; LS, least square; FAS, full analysis set.

for FFNS 55 µg compared with placebo and was maintained throughout the treatment period. FFNS 55 µg significantly improved all four individual nasal symptoms assessed and the 4TNSS compared with placebo in terms of the LS mean change from baseline in Weeks 1, 2 and over the entire treatment period (Table 3).

Significant improvements in rhinoscopic findings, swelling of inferior turbinate mucosa (Fig. 2A) and quantity of nasal discharge (Fig. 2B) were observed in FFNS 55 µg compared with placebo. For the rhinoscopy score of swelling of inferior turbinate mucosa, the proportion of patients rated '3' (impossible to see middle turbinate) decreased with FFNS 55 µg: 39% at baseline, 18% at week 1, 10% at week 2/early withdrawal (EW). For the rhinoscopy score of quantity of nasal discharge, the proportion of patients rated '0' (None) increased with FFNS 55 µg; 6% at baseline, 29% at week 1, 48% at week 2/EW.

Efficacy analyses of ocular symptoms were performed in a subgroup of patients with a baseline TOSS > 0 (191 patients). Mean baseline TOSS was approximately 2 (placebo: 2.3, FFNS 55 µg: 2.1) for the two treatment groups, indicating that the study population consisted mainly of cases with mild ocular symptoms. TOSS was reduced significantly in FFNS 55 µg compared with placebo in the second week and reduced numerically but not significantly in the first week (Table 4).

QOL assessment was performed using the score for troubles with daily life. A significantly greater decrease in the mean change from baseline over the entire treatment period with respect to the score for

troubles with daily life was observed in FFNS 55 µg compared with placebo (LS mean difference: -0.302, 95%CI: -0.42, -0.19, $p < 0.001$).

Treatment differences, determined by overall response to therapy were significant for FFNS 55 µg compared with placebo ($p < 0.001$) both in parent/guardian/patient assessment and investigator assessment. A greater percentage of patients receiving FFNS 55 µg (parent/guardian/patient: 21%, investigator: 24%) rated the overall response to therapy as "significantly improved" compared with patients receiving placebo (parent/guardian/patient: 2%, investigator: 9%).

SAFETY AND TOLERABILITY

Safety and tolerability analyses were conducted in the SP, comprising 261 patients aged 6 to <15 years. Treatment with FFNS 55 µg was well tolerated over the two-week treatment period. Adverse events reported during the study were of mild or moderate intensity and of similar type and frequency across the two treatment groups. The proportion of patients with at least one adverse event was similar across the groups (placebo: 19%, FFNS 55 µg: 18%). The most frequently reported adverse events observed in this study were nasopharyngitis and epistaxis (Table 5). There were no serious adverse events and no deaths. No patients withdrew as a result of drug-related or drug-unrelated adverse events. Drug-related adverse events was reported by six (4%) patients in the placebo group and by one (<1%) patient in FFNS 55 µg group. The drug-related adverse event reported with FFNS 55 µg was a case of nasal discomfort. Clinical

Table 3 Mean change from baseline in 4TNSS and each individual symptom score over the entire treatment period (FAS)

		Placebo (N = 130)	FFNS 55 µg (N = 131)
4TNSS			
Baseline	Mean (SD)	6.1 (1.58)	6.0 (1.34)
Entire treatment period	LS mean change (SE)	-1.01 (0.15)	-2.4 (0.15)
	LS mean difference [†]	-	-1.393
	p-value vs. placebo	-	<0.001
Rhinorrhea			
Baseline	Mean (SD)	1.9 (0.60)	1.8 (0.56)
Entire treatment period	LS mean change (SE)	-0.31 (0.05)	-0.69 (0.05)
	LS mean difference [†]	-	-0.383
	p-value vs. placebo	-	<0.001
Nasal congestion			
Baseline	Mean (SD)	1.7 (0.62)	1.5 (0.66)
Entire treatment period	LS mean change (SE)	-0.36 (0.05)	-0.70 (0.05)
	LS mean difference [†]	-	-0.339
	p-value vs. placebo	-	<0.001
Sneezing			
Baseline	Mean (SD)	1.6 (0.61)	1.7 (0.60)
Entire treatment period	LS mean change (SE)	-0.21 (0.04)	-0.60 (0.04)
	LS mean difference [†]	-	-0.391
	p-value vs. placebo	-	<0.001
Nasal itching			
Baseline	Mean (SD)	1.0 (0.76)	1.0 (0.72)
Entire treatment period	LS mean change (SE)	-0.12 (0.04)	-0.41 (0.04)
	LS mean difference [†]	-	-0.292
	p-value vs. placebo	-	<0.001

4TNSS, three total nasal symptom score; FAS, full analysis set; FFNS, fluticasone furoate nasal spray; LS, least square.

[†] LS mean difference = LS mean change in FFNS 55 µg minus LS mean change in placebo.

chemistry and hematology results did not show any findings of clinical concern.

DISCUSSION

This is the first randomized clinical study of FFNS in Japanese children, first study in Asian children as well. The objective of this study was to evaluate efficacy and safety of FFNS 55 µg, given once daily over a period of two weeks, compared with placebo, in Japanese children aged 6 to <15 years with PAR.

The primary endpoint in this study is 3TNSS, which is a common primary endpoint in Japan. With regard to the mean change from baseline in 3TNSS over the entire treatment period, the change in 3TNSS was significantly greater in the FFNS 55 µg, once daily group compared with placebo. INS has been shown to be effective for all three of the typical nasal symptoms, sneezing, rhinorrhea and nasal congestion, and is recommended for both types, sneezing and rhinorrhea type, and nasal blockage/combined type in the Japanese guideline.^{1,2} The results of this study show that FFNS 55 µg significantly improved all of the individual nasal symptoms assessed: sneezing, rhinorrhea, nasal congestion and nasal itching, compared with placebo. Findings in nasal symp-

toms in this study add important information to the evidence for the efficacy of INS in Japanese children with AR, as few placebo-controlled studies have been conducted in Japanese children.

4TNSS, which is a common primary endpoint in global studies, was also evaluated in this study. The mean change in 4TNSS from baseline was significantly greater in the FFNS 55 µg group compared with placebo. Máspero *et al.* reported that FFNS 55 µg showed significantly greater reduction in rTNSS, the sum of four individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing scored in a reflective manner, in non-Japanese children (white: 73%, black: 4%) aged 6 to <12 years with PAR,²⁶ which is consistent with the results in our study. In addition, Máspero *et al.* reported that FFNS 55 µg showed significantly greater reduction in each four individual nasal symptom scores, which is also consistent with the results in our study. In our study, three of the four nasal symptom scores: sneezing, rhinorrhea and nasal congestion, were evaluated based on the Japanese guideline.^{1,2} The scoring of sneezing and rhinorrhea in the Japanese guideline is based on the frequencies of sneezing and nose-blowing, which is different from the measures used in the study re-

FFNS in Japanese Children with PAR

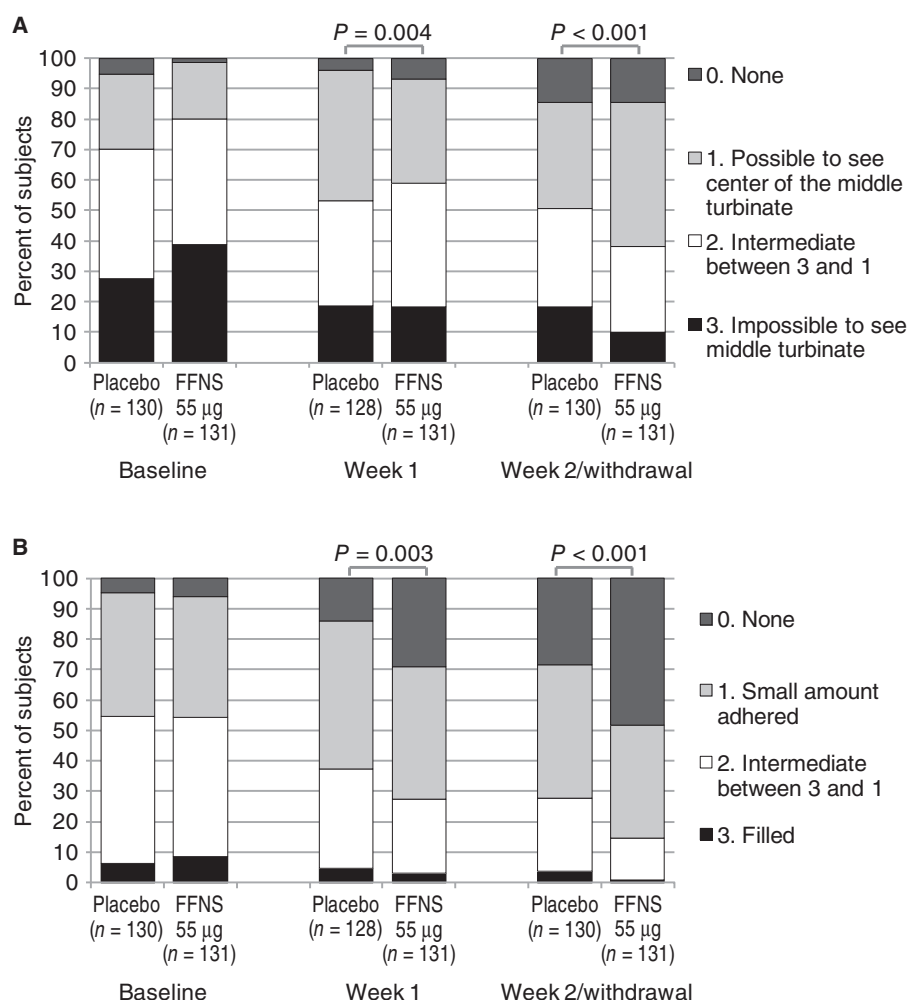


Fig. 2 Change in Rhinoscopic findings (FAS). **A**, Swelling of inferior turbinate mucosa. **B**, Quantity of nasal discharge. *P*-value: Comparison of score change from baseline in individual subjects (FFNS 55 µg vs. Placebo, Wilcoxon's 2-sample test). No adjustments for multiplicity. FFNS, fluticasone furoate nasal spray; FAS, full analysis set.

Table 4 Mean change from baseline in TOSS (sub-group analysis in FAS: baseline TOSS > 0)

		Placebo (<i>N</i> = 92)	FFNS 55 µg (<i>N</i> = 99)
Baseline	Mean (SD)	2.3 (1.78)	2.1 (1.62)
Entire treatment period	LS mean change (SE)	-0.47 (0.11)	-0.77 (0.11)
	LS mean difference [†]	-	-0.302
	<i>p</i> -value vs. placebo	-	0.056
Week 1	LS mean change (SE)	-0.35 (0.11)	-0.56 (0.11)
	LS mean difference [†]	-	-0.207
	<i>p</i> -value vs. placebo	-	0.185
Week 2	LS mean change (SE)	-0.56 (0.13) [‡]	-0.99 (0.13)
	LS mean difference [†]	-	-0.428
	<i>p</i> -value vs. placebo	-	0.020

TOSS, total ocular symptom score; FAS, full analysis set; FFNS, fluticasone furoate nasal spray; LS, least square.

[†]LS mean difference = LS mean change in FFNS 55 µg minus LS mean change in placebo.

[‡]*n* = 90.

Table 5 Adverse events with $\geq 2\%$ incidence during the treatment and follow-up periods (SP)

	Number of patients (%)	
	Placebo (N = 130)	FFNS 55 μg (N = 131)
Nasopharyngitis	3 (2%)	6 (5%)
Epistaxis	3 (2%)	2 (2%)
Alanine aminotransferase increased	2 (2%)	0
Aspartate aminotransferase increased	2 (2%)	0
Conjunctivitis allergic	0	2 (2%)
Headache	2 (2%)	0

SP, safety population; FFNS, fluticasone furoate nasal spray.

ported by Máspero *et al.* In the previous reports including Máspero's, nasal symptom scores were evaluated based on the guidance for industry on allergic rhinitis issued by the Food and Drug Administration (FDA). Consistent results with different measuring systems strengthen evidence for the efficacy of FFNS.

Rhinoscopy scores are investigator-rated objective nasal symptoms scores, providing additional information to the parent/guardian/patient-rated subjective score. This is the first study assessing efficacy of FFNS using rhinoscopy scores in children with AR, and shows a significant reduction in rhinoscopy scores of mucosal swelling and nasal discharge compared with placebo. These objective findings, which are consistent with the results of parent/guardian/patient-rated subjective scores, further support the efficacy of FFNS.

Studies in adults and adolescents have shown the efficacy of INS in improving ocular symptoms associated with AR,^{18,20,21} and several mechanisms of action have been proposed to explain the effects of INS on these symptoms, including improvements due to modulation of the naso-ocular reflex.²⁷ In children, however, few studies have examined the efficacy of INS on ocular symptoms associated with AR, especially in PAR.²⁸⁻³⁰ Here we report that, in a subgroup analysis in Japanese children with PAR with a baseline TOSS > 0, TOSS was reduced significantly in the FFNS 55 μg group compared with placebo in the second week and reduced numerically but not significantly in the first week. One of the reasons for non-significance in the first week might be the smaller numbers in the evaluated population. To our knowledge, however, this is the first study that shows the efficacy of INS in improving ocular symptoms in children with PAR compared with placebo. Further study is needed to confirm the efficacy of INS on ocular symptoms in children with AR.

The safety findings of this study show that FFNS 55 μg , once daily were well tolerated in Japanese children aged 6 to <15 years, with the incidence of adverse events observed being similar to that of placebo. Safety results in this study are consistent with

previous reports in non-Japanese children where FFNS 55 and 110 μg were reported to be well tolerated.^{26,31} Máspero *et al.* reported that adverse events reported were of similar type and frequency between FFNS 55 μg and placebo groups (FFNS 55 μg : 56%, placebo: 59%) in non-Japanese children aged 2 to <12 years with PAR.²⁶ Common adverse events observed include pharyngolaryngeal pain, epistaxis, and pyrexia. Common drug-related adverse event observed was epistaxis.

Limitations of this study include the treatment period of two weeks which may be too short to evaluate the safety of FFNS in real-life settings. Safety in longer term-use was assessed in a 12-weeks study of FFNS 55 μg in Japanese children aged 2 to <15 years with PAR, which is reported elsewhere. (ClinicalTrials.gov Identifier: NCT01622231, GlaxoSmithKline protocol number: FFR116365.) Another limitation is that the baseline TOSS value was not included as an inclusion criterion and some participants in the study had no ocular symptoms at baseline.

In conclusion, the results in this randomized, placebo-controlled study suggested that FFNS 55 μg , once daily was effective and tolerable for the treatment of PAR in Japanese children aged 6 to <15 years.

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