

## Original article

# Safety and efficacy of fluticasone furoate nasal spray in Japanese children 2 to <15 years of age with perennial allergic rhinitis: A multicentre, open-label trial



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## ABSTRACT

**Background:** Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of allergic rhinitis (AR). This study aimed to assess the safety, efficacy, and systemic exposure of FFNS in Japanese children with perennial AR (PAR).

**Methods:** In this multicentre, open-label, phase 3 study, 61 children aged 2 to <15 years were treated with FFNS 55 µg, once daily for 12 weeks. Nasal and ocular symptoms were scored by parents/guardians/patients and recorded in a patient's daily diary. In addition, rhinoscopy findings, including mucosal swelling, were scored by the investigators as an efficacy measure. As a safety measure, adverse events and clinical laboratory data were evaluated.

**Results:** An adverse event was reported by 67% of patients during the treatment and follow-up period, all of which were mild in intensity. The most commonly reported adverse events were nasopharyngitis and acute sinusitis (acute rhinosinusitis). There were no serious adverse events. FFNS 55 µg improved nasal symptom scores and rhinoscopy findings compared with the baseline. Ocular symptom scores were also improved compared with the baseline in FFNS 55 µg in a sub-group of patients with any ocular symptoms at baseline. FFNS 55 µg was shown to be well tolerated over the 12-week treatment period. Majority of patients receiving FFNS 55 µg had unquantifiable plasma levels of fluticasone furoate (FF).

**Conclusions:** Twelve-week treatment with FFNS 55 µg, once daily, is well tolerated and effective with low systemic exposure in Japanese children aged 2 to <15 years with PAR.

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## Introduction

Allergic rhinitis (AR) is the most common chronic condition in children, and its prevalence has been increasing in most countries.<sup>1</sup> The prevalence of AR in children in Japan is approximately 30%,<sup>2,3</sup> which is similar to that in adults. In younger age children, aged 0–4 years, prevalence of AR is low but significant proportion, especially in perennial AR (PAR) (i.e., 4.0%). AR is characterized by symptoms of sneezing, rhinorrhea, nasal congestion, and nasal itching,<sup>2,3</sup> and is often associated with ocular symptoms.<sup>1</sup> According to the allergic rhinitis and its impact on asthma (ARIA) guidelines,<sup>1</sup> AR is intermittent or persistent in duration and mild or

moderate/severe in intensity. The Japanese guidelines<sup>2,3</sup> classify AR as PAR or seasonal AR (SAR) depending on the timing and duration of symptoms. Common allergens of PAR include dust mites, animal dander, molds, and cockroaches, and allergens of SAR include Japanese cedar pollens, ragweed, and orchard grass.<sup>4</sup> The Japanese guidelines use a unique scoring system based on frequency of symptoms in a day, including episodes of paroxysmal sneezing and episodes of nose blowing, to rate AR severity (mild, moderate, severe, and most severe).<sup>2,3</sup> 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 performance.<sup>5</sup> Cognitive dysfunction related to AR itself can impair the performance of school children with AR.<sup>6</sup> Some studies have shown that ocular symptoms also deteriorate patients' QOL, and some patients consider ocular symptoms to be more annoying than nasal symptoms.<sup>7,8</sup> In addition, if left untreated, comorbid conditions associated with AR, including asthma and otitis media, can be problematic in children.<sup>9</sup>

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Another important issue associated with AR is the cost of the disease.<sup>1,10</sup> In Germany, the average annual cost of SAR is 1089 € per child or adolescent and 1543 € per adult.<sup>1</sup>

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.<sup>1</sup> The Japanese guidelines recommend INS as the most effective medication to improve symptoms of AR.<sup>2,3</sup> INS has a broad spectrum of efficacy for a range of nasal symptoms, including congestion, rhinorrhea, and sneezing.<sup>1–3</sup> In addition, INS has been reported to improve eye symptoms accompanying AR.<sup>11,12</sup>

Fluticasone furoate nasal spray (FFNS) is a glucocorticoid developed for the treatment of AR, and is administered using a unique, side-actuated device.<sup>13</sup> This delivery system was designed for ease of self-administration, as well as for convenient parent or caregiver administration to children.<sup>14</sup> As a treatment for AR, FFNS is currently approved for use in more than 100 countries including Europe and United States. FFNS is approved for use in patients as young as 2 years of age with AR in the United States and 6 years of age in Europe.

Although well studied in healthy volunteers and patients with AR, including non-Japanese children aged 2–11 years with PAR or SAR,<sup>15,16</sup> the clinical efficacy, safety, and systemic exposure of FFNS in Asian children, including Japanese children, have, to our knowledge, not been investigated. Therefore, we conducted two clinical studies to evaluate the efficacy and safety of FFNS 55 µg in Japanese children. One study was a two-week, randomized, phase III study to assess the efficacy and safety of once-daily FFNS 55 µg compared with placebo in Japanese children aged 6 to <15 years with PAR, which has been reported in this journal.<sup>17</sup> (The ClinicalTrials.gov Identifier: NCT01630135, GlaxoSmithKline protocol number: FFR116364.) In this article, we report the results of the other study, a twelve-week, open-label, phase III 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.

## Methods

### Study design

This phase 3, multicenter, open-label study was conducted in 6 centers in Japan. Eligible patients entered a 1–2-week screening period and those meeting the criteria were assigned to the treatment, FFNS 55 µg. Treatment was administered once daily in the morning for 12 weeks, and patients attended a clinic every 4 weeks. A follow-up visit/phone call was scheduled one week after the end of the treatment. Patients who completed all of their visits including the follow-up were deemed to have completed the study. Patients who were assigned to a treatment and discontinued study before the completion had early withdrawal visit to assess safety and efficacy at the end the treatment.

### Patients

Eligible patients were aged 2 to <15 years with ≥6 months history of PAR, and had positive specific immunoglobulin E (IgE) antibody tests to PAR allergens (i.e., positive to at least one house dust mite or house dust allergen), elevated nasal eosinophil counts, and a 3 total nasal symptom scores (3TNSS) of ≥3 at baseline.

Patients were excluded from the study if they had symptoms of SAR due to pollen present in their geographic area during the study participation, had a co-morbid disorder that could affect the result of the study (e.g., acute/chronic sinusitis, nasal polyps, upper respiratory or eye infection), had a co-morbid disease that could

threaten their safety (e.g., tuberculosis, infection without effective antibacterials, serious hepatic/renal/cardiac/pulmonary dysfunction or hematopoietic disorder, uncontrolled hypertension/diabetes mellitus, or asthma [except for mild intermittent cases]), or used medications that could affect the efficacy outcome of the study (e.g., systemic corticosteroids within 8 weeks of the study).

Use of any medication for allergic rhinitis, other than the study medication, and any concomitant medication that could affect the efficacy outcome of the study (e.g., corticosteroids) was prohibited during the screening and treatment periods.

### Safety assessments

The primary safety endpoints were frequency and severity of adverse events. Adverse events were monitored during the treatment and follow up periods. Safety of FFNS was also assessed by laboratory tests (hematology and clinical chemistry). Blood samples (e.g. hematology, clinical chemistry, IgE) were analyzed at central laboratories. Treatment compliance was assessed through patient diary cards.

### Efficacy assessments

Efficacy values included 3TNSS, 4TNSS, total ocular symptom scores (TOSS), individual nasal and ocular symptom scores, troubles with daily life score, rhinoscopy findings, and overall evaluation of response to therapy. Parents/guardians/patients were instructed to record patients' symptom scores (individual nasal and ocular symptoms and troubles with daily life) in a diary every day during the screening and treatment periods. Each baseline value was an average of values obtained on 4 consecutive days prior to randomization. Investigators scored rhinoscopy findings at baseline (randomization) and at each visit during the treatment period. Parents/guardians/patients and investigators evaluated the overall response to therapy at the end of the treatment period.

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

rhinoscopy findings were scored based on the criteria of the Practical Guideline for the Management of Allergic Rhinitis in Japan.<sup>2,3</sup>

#### Pharmacokinetic assessments

Pharmacokinetic analysis of blood samples collected at 0.5–2 h after the last dose (end of the treatment period) was undertaken to determine plasma concentrations of fluticasone furoate (FF). Plasma concentration of FF was determined by liquid chromatography with tandem mass spectrometry analysis at a central laboratory. FF was extracted from human plasma by solid phase extraction using an isotopically labeled internal standard. The lower limit of quantification for FF was 10 pg/mL.

#### Statistical analyses

Sample size of 59 patients can detect an adverse event rate of 5% with statistical power of 95%. To obtain 59 evaluable patients, 60 patients was planned to be assigned to the treatment.

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

Efficacy analyses were performed in patients who were assigned to the treatment, received at least one dose of the study medication, and completed at least one diary assessment of 3TNSS after taking the study medication (the full analysis set [FAS]). The efficacy data are expressed as mean and standard deviation (SD) or as frequency distributions. For TOSS, analysis was performed for the sub-group of patients with baseline TOSS >0.

Pharmacokinetic (PK) analyses were performed in patients whose blood sample were taken for pharmacokinetic analyses and measured (PK concentration population).

To investigate the safety and efficacy of FFNS in younger age group (2 to <6 years), sub-group analysis (2 to <6 years and 6 to <15 years) was performed for efficacy measure of 3TNSS and rhinoscopy findings, safety measure of frequency and severity of adverse events, and pharmacokinetic analysis.

#### Ethical approval and clinical trial registration

The study was conducted in accordance with the Declaration of Helsinki (2008) and Good Clinical Practice guidelines. The institutional review boards of each center approved the protocol of this study. Written informed consent was obtained from parents or guardian of all participating children. Assent was obtained from all children aged 12 years and above. All children under 12 years old were provided with information about the study depending on their understandings and assent was obtained where appropriate. The ClinicalTrials.gov Identifier is NCT01622231. GlaxoSmithKline protocol number is FFR116365.

**Table 1**  
Subject demographics (SP).

|                        |                | FFNS 55 µg<br>(N = 61) |
|------------------------|----------------|------------------------|
| Age (years)            | Mean ± SD      | 8.0 ± 3.59             |
|                        | Min–Max        | 2–14                   |
| Gender, n (%)          | Male           | 42 (69%)               |
|                        | Female         | 19 (31%)               |
| Race, n (%)            | Japanese       | 61 (100%)              |
| Duration of PAR, n (%) | <2 years       | 14 (23%)               |
|                        | ≥2 to <5 years | 26 (43%)               |
|                        | ≥5 years       | 21 (34%)               |

SP, safety population; FFNS, fluticasone furoate nasal spray; PAR, perennial allergic rhinitis.

## Results

#### Study population

Of the 72 patients screened in the study, 61 patients received FFNS 55 µg. All of the 61 patients were included in the analysis of safety and efficacy (SP and FAS). Of the 61 patients treated, 59 patients (97%) completed the study and 2 patients prematurely withdrawn from the study. The reasons for withdrawal were withdrawal of consent and investigator discretion.

The demographic and baseline characteristics for the SP are summarized in Table 1. All patients were of Japanese heritage. Average age was 8.0 years. Duration of PAR was at least two years in 77% of patients. In the IgE test, all patients were positive for all of the four PAR allergens, two house dust mite allergens and two house dust allergens stated in the inclusion criterion. Mean baseline 3TNSS was 4.5, indicating that the study population consisted mainly of moderate cases. The mean compliance to study treatment was 98.34%.

#### Safety and tolerability

Safety and tolerability analyses were conducted in the SP comprising 61 patients aged 2 to <15 years. Treatment with FFNS 55 µg was well tolerated over the 12-week treatment period. All adverse events reported during the study were mild in intensity. The proportion of patients with at least one adverse event was 67% (n = 41) and of similar frequency across the two age groups, 2 to <6 years (74%, 14/19 subjects) and 6 to <15 years (64%, 27/42 subjects). The most frequently reported adverse events observed in this study were nasopharyngitis and acute sinusitis (acute rhinosinusitis). There was no serious adverse event and no reports of death. No patient withdrew as a result of a drug-related or drug-unrelated adverse event. A drug-related adverse event was reported by one (2%) patient, who developed dysphonia (hoarseness) during the treatment period (day 76). This event was reported in a male subject aged 11 years, was mild in intensity, and resolved two days after the end of the treatment. Adverse events reported with ≥3% incidence are listed in Table 2. Clinical laboratory results did not show any findings of clinical concern for clinical chemistry or hematology.

#### Efficacy

Efficacy analyses were performed in the FAS population of 61 patients aged 2 to <15 years. FFNS 55 µg improved nasal symptoms

**Table 2**

Adverse events with ≥3% incidence in total during the treatment and follow-up periods (SP).

|                                        | Number of patients (%)    |                           |                   |
|----------------------------------------|---------------------------|---------------------------|-------------------|
|                                        | FFNS 55 µg                |                           |                   |
|                                        | Age: <6 years<br>(N = 19) | Age: ≥6 years<br>(N = 42) | Total<br>(N = 61) |
| Nasopharyngitis                        | 5 (26%)                   | 10 (24%)                  | 15 (25%)          |
| Acute sinusitis (acute rhinosinusitis) | 5 (26%)                   | 3 (7%)                    | 8 (13%)           |
| Bronchitis                             | 1 (5%)                    | 2 (5%)                    | 3 (5%)            |
| Streptococcal infection                | 2 (11%)                   | 1 (2%)                    | 3 (5%)            |
| Otitis externa                         | 1 (5%)                    | 1 (2%)                    | 2 (3%)            |
| Eczema                                 | 0                         | 2 (5%)                    | 2 (3%)            |
| Heat rash                              | 2 (11%)                   | 0                         | 2 (3%)            |
| Arthropod sting                        | 0                         | 2 (5%)                    | 2 (3%)            |
| Pyrexia                                | 1 (5%)                    | 2 (5%)                    | 3 (5%)            |

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

**Table 3**

Mean change from baseline in 3TNSS and 4TNSS (FAS).

|                         |                  | FFNS 55 µg                |                           |                          | 4TNSS                    |
|-------------------------|------------------|---------------------------|---------------------------|--------------------------|--------------------------|
|                         |                  | 3TNSS                     |                           |                          | Total                    |
|                         |                  | Age: <6 years<br>(N = 19) | Age: ≥6 years<br>(N = 42) | Total<br>(N = 61)        | (N = 61)                 |
| Baseline                | Mean (SD)        | 4.1 (1.07)                | 4.7 (1.26)                | 4.5 (1.22)               | 5.3 (1.53)               |
| Entire treatment period | Mean change (SD) | –2.1 (1.33)               | –2.2 (1.78)               | –2.2 (1.65)              | –2.6 (2.01)              |
| Week 3–4                | Mean change (SD) | –2.4 (1.51)               | –2.5 (1.99)               | –2.5 (1.84)              | –2.9 (2.26)              |
| Week 7–8                | Mean change (SD) | –2.4 (1.51)               | –2.3 (2.02) <sup>†</sup>  | –2.4 (1.86) <sup>‡</sup> | –2.8 (2.26) <sup>‡</sup> |
| Week 11–12              | Mean change (SD) | –1.8 (1.68)               | –2.1 (2.24) <sup>†</sup>  | –2.0 (2.07) <sup>‡</sup> | –2.3 (2.50) <sup>‡</sup> |

3TNSS, three total nasal symptom score; 4TNSS, four total nasal symptom score; FAS, full analysis set; FFNS, fluticasone furoate nasal spray.

<sup>†</sup> n = 41.<sup>‡</sup> n = 60.

compared with the baseline; the mean change from the baseline over the entire treatment period in 3TNSS was –2.2 (Table 3). In addition, decrease from baseline in 3TNSS was observed in FFNS 55 µg in Weeks 3–4, 7–8, and 11–12 (Table 3). The decrease from baseline in 3TNSS was first observed on day 1 and persisted throughout the 12-week treatment period. Decrease in 4TNSS and all of the four nasal symptoms were also observed in FFNS 55 µg compared with the baseline in Weeks 3–4, 7–8, and 11–12, and over the entire treatment period (Tables 3 and 4).

Efficacy analyses of 3TNSS were performed in sub-groups divided by age (2 to <6 years and 6 to <15 years), and demonstrated a similar decrease from baseline over the entire treatment period in both groups (2 to <6 years: –2.1, 6 to <15 years: –2.2).

The rhinoscopy findings of swelling of the inferior turbinate mucosa (Fig. 1A) and quantity of nasal discharge (Fig. 1B) demonstrated improvement in FFNS 55 µg compared with the baseline. The proportion of patients who scored '3' (impossible to see middle turbinate) on swelling of inferior turbinate mucosa score decreased from baseline: 23% at the baseline, 2% on Week 4, 0% on Week 8, 2% on Week 12/early withdrawal. The proportion of patients who scored '0' (None) on quantity of nasal discharge score increased from baseline: 7% at the baseline, 50% on Week 4, 48% on Week 8, and 56% on Week 12/early withdrawal.

Efficacy analyses of rhinoscopy findings were also performed in sub-groups divided by age (2 to <6 years and 6 to <15 years), and demonstrated a similar improvement from baseline in both groups (data not shown).

Efficacy analyses of ocular symptoms were performed in sub-group of patients with baseline TOSS >0 (36 patients). Mean baseline TOSS was 1.2, indicating that the study population consisted mainly of patients with mild ocular symptoms. TOSS was reduced from the baseline in Weeks 3–4, 7–8, 11–12, and over the entire treatment period in FFNS 55 µg (Table 5).

Quality of life (QOL) assessment was performed using the troubles with daily life score. The troubles with daily life score over the entire treatment period decreased from baseline in FFNS 55 µg (baseline: 1.1, entire treatment period decreased: 0.6).

**Table 4**

Mean change from baseline in each individual symptom score over the entire treatment period (FAS).

|                         |                  | FFNS 55 µg (N = 61) |                  |             |               |
|-------------------------|------------------|---------------------|------------------|-------------|---------------|
|                         |                  | Rhinorrhea          | Nasal congestion | Sneezing    | Nasal itching |
| Baseline                | Mean (SD)        | 1.6 (0.58)          | 1.4 (0.74)       | 1.5 (0.55)  | 0.8 (0.61)    |
| Entire treatment period | Mean change (SD) | –0.8 (0.65)         | –0.8 (0.66)      | –0.7 (0.74) | –0.4 (0.58)   |

FAS, full analysis set; FFNS, fluticasone furoate nasal spray.

The overall response to therapy was assessed by parents/guardians/patients and investigators. Most parents/guardians/patients (92%) and investigators (92%) rated the overall response to therapy as improved (i.e., “significantly improved”, “moderately improved” or “mildly improved”).

### Pharmacokinetics

Plasma samples were collected 0.5–2 h post-dose at the end of the 12-week treatment period and analyzed from 59 patients who completed the study. Pharmacokinetic assessment showed that the majority of patients receiving FFNS 55 µg did not have quantifiable (lower limit of quantification: LLQ = 10 pg/mL) plasma levels of FF (2 to <6 years [89.5%], 6 to <15 years [92.5%]; Table 6). Plasma concentrations of FF in patients with quantifiable levels were 10.9 and 13.1 pg/mL in the 2 to <6 years group, and 14.9–23.7 pg/mL in the 6 to <15 years group.

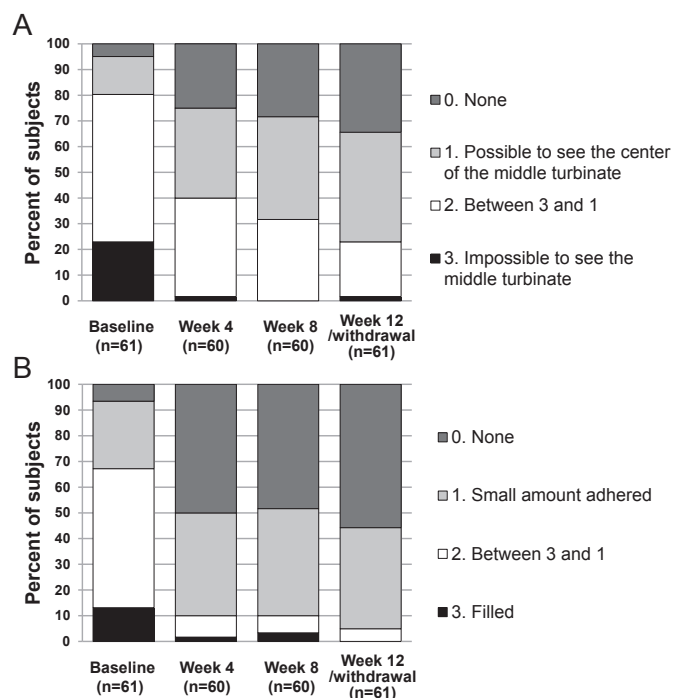


**Fig. 1.** Change in Rhinoscopy findings (FAS). A, Swelling of the inferior turbinate mucosa. B, Quantity of nasal discharge. FFNS, fluticasone furoate nasal spray; FAS, full analysis set.

**Table 5**

Mean change from baseline in TOSS (sub-group analysis in FAS: baseline TOSS &gt; 0).

|                         |                  | FFNS 55 µg<br>(N = 36)   |
|-------------------------|------------------|--------------------------|
| Baseline                | Mean (SD)        | 1.2 (1.06)               |
| Entire treatment period | Mean change (SD) | −0.5 (1.21)              |
| Week 3–4                | Mean change (SD) | −0.4 (1.26)              |
| Week 7–8                | Mean change (SD) | −0.4 (1.52) <sup>†</sup> |
| Week 11–12              | Mean change (SD) | −0.6 (1.27) <sup>†</sup> |

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

<sup>†</sup> n = 35.

## Discussion

The objectives of this multicentre open-label clinical study were to evaluate primarily the safety of FFNS 55 µg, once daily over a period of 12 weeks, and secondarily the efficacy and systemic exposure of FFNS in Japanese pediatric subjects aged 2 to <15 years with PAR.

The safety findings of this study show that FFNS 55 µg, once daily, was well tolerated in Japanese children aged 2 to <15 years old, with no adverse events of moderate to severe intensity. An event of dysphonia was considered by an investigator to be an adverse event related to FFNS 55 µg. Although mild local nasal reactions including mild irritation and epistaxis are well-known common side effects of INS, these events were not reported in this study. The adverse events observed in the 2–5 years group were all mild in intensity and were not considered to be related to FFNS 55 µg, indicating that FFNS 55 µg was well tolerated in children as young as 2 years. In clinical studies in non-Japanese children aged 2 to <12 years, FFNS 55 and 110 µg had similar AE profiles to the placebo.<sup>15,16</sup> In these studies FFNS 55 and 110 µg were reported to be well tolerated, which is consistent with the results in this study. The absence of quantifiable plasma levels of FF in most patients 0.5–2 h after the last dose in the 12-week treatment period demonstrates low systemic exposure of FFNS 55 µg. The percentage of patients with quantifiable plasma levels of FF in the 2–5 years group was low and comparable to that in the 6–14 years group, indicating low systemic exposure both in older and younger children as young as 2 years. The absence of quantifiable plasma levels of FF in most children after 2 or 12 weeks of FFNS 55 and 110 µg was reported in a clinical study in non-Japanese children,<sup>15,16</sup> which is consistent with the results in this study. In adult non-Japanese healthy male and female volunteers, bioavailability of FFNS was assessed as low, 0.5%. The pharmacokinetic results in this study are of value in view of the limited reports assessing systemic exposure of recently developed INS in patients with AR in Asia including Japan.

INS is known to have a broad spectrum of efficacy for a range of nasal symptoms, including congestion, rhinorrhea, and sneezing, and is recommended for both sneezing and rhinorrhea type and

nasal blockage/combined type in the Japanese guideline.<sup>2,3</sup> In this study, FFNS 55 µg, once daily over a 12-week treatment period improved 3TNSS, 4TNSS, and all of the four nasal symptoms of sneezing, rhinorrhea, nasal congestion, and nasal itching compared with the baseline. The reduction in 3TNSS in the 2–5 years group was similar to that in the 6–14 years group, indicating that FFNS 55 µg is effective both in older and younger children as young as 2 years. Our finding of improvement in nasal symptoms in FFNS 55 µg is in agreement with previous findings in non-Japanese children with PAR where reduction in reflective total nasal symptom scores (rTNSS) was significantly greater in FFNS 55 µg compared with placebo.<sup>15</sup>

Many global studies have investigated the efficacy of INS using patient-rated symptom scores but not investigator-rated symptom scores. In this study, both patient/parent/guardian-rated subjective nasal symptoms and investigator-rated objective rhinoscopy findings were assessed. Rhinoscopy scores are mentioned in the Japanese guideline<sup>2,3</sup>: swelling of the inferior turbinate mucosa, quantity of nasal discharge, color of the inferior turbinate mucosa, and quality of nasal discharge. Of these four scores, swelling of inferior turbinate mucosa and quantity of nasal discharge scores can be used to assess changes in severity. This study showed a reduction in rhinoscopy scores of mucosal swelling and nasal discharge compared with the baseline, which is consistent with the reduction noted in patient/parent/guardian-rated scores of nasal congestion and rhinorrhea. In clinical studies in Japanese adults, FFNS 110 µg improved both patient-rated symptom scores and investigator-rated objective nasal symptom scores.<sup>18</sup>

AR is often associated with ocular symptoms.<sup>1</sup> INS is reported to be effective in improving ocular symptoms associated with AR in adolescents and adults.<sup>11,12</sup> In children, studies investigating the effects of INS on ocular symptoms are limited, especially in PAR.<sup>19–21</sup> In this study, TOSS was reduced in FFNS 55 µg compared with the baseline in a sub-group analysis in Japanese children with PAR who had baseline TOSS >0. This is the first study investigating the efficacy of FFNS for ocular symptoms in children aged ≥2 years with PAR in 12 weeks treatment. We have reported the efficacy of FFNS for ocular symptoms in children aged ≥6 years with PAR in 2 weeks treatment.<sup>17</sup> Further study is needed to confirm the efficacy of FFNS for ocular symptoms in children with PAR.

In this study, the troubles with daily life score as QOL assessment, and the overall response to therapy by parents/guardians/patients and investigators showed improvements in FFNS 55 µg. It is considered that improvements in nasal and ocular symptoms resulted in improvements in these scores.

Limitations of the present study include its single-arm, open-label design, which can affect endpoints including patient/parent/guardian-rated and investigator-rated nasal symptom scores. In addition, sample size, 60 subjects, is too small to detect infrequent adverse events, and the lack of placebo or comparator does not permit comparison of the frequency of adverse events. Also, the baseline TOSS value was not considered as an inclusion criterion and the baseline TOSS value was small, which made it difficult to evaluate efficacy of FFNS on the basis of TOSS.

In conclusion, the results of this multicentre, open-label study suggested that FFNS 55 µg, once daily, was well tolerated and effective with low systemic exposure for the treatment of PAR in Japanese children aged 2 to <15 years old.

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**Table 6**

Plasma concentration of FF at 0.5–2 h after the last dose (PK concentration population).

|                 | Number of patients (%)    |                           |
|-----------------|---------------------------|---------------------------|
|                 | FFNS 55 µg                |                           |
|                 | Age: <6 years<br>(N = 19) | Age: ≥6 years<br>(N = 40) |
| NQ (<10 pg/mL)  | 17 (89.5%)                | 37 (92.5%)                |
| 10 to <20 pg/mL | 2 (10.5%)                 | 2 (5.0%)                  |
| 20 to <30 pg/mL | 0                         | 1 (2.5%)                  |
| ≥30 pg/mL       | 0                         | 0                         |

FF, fluticasone furoate; FFNS, fluticasone furoate nasal spray; NQ, not quantifiable.

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#### Authors' contributions

KO gave advice on the study design, conduct of the study and interpretation of the data. AO and MK contributed to the concept and study design, conduct of the study, analysis and interpretation of the data. GH contributed to the analysis of the data.

#### Conflict of interest

KO has received lecture fees from GlaxoSmithKline K.K. AO, GH and MK are employees of GlaxoSmithKline K.K.

#### References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 (in collaboration with the World Health Organization, GA (2) LEN and AllerGen). *Allergy* 2008;**63**(Suppl. 86): 8–160.
2. [Practical Guideline for the Management of Allergic Rhinitis in Japan <PG-MAR>], 7th ed. Tokyo: Life Science, 2013 (in Japanese).
3. Okubo K, Kuroki Y, Fujieda S, Ogino S, Uchio E, Odajima H, et al. Japanese guideline for allergic rhinitis. *Allergol Int* 2011;**60**:171–89.
4. Sakashita M, Hirota T, Harada M, Nakamichi R, Tsunoda T, Osawa Y, et al. Prevalence of allergic rhinitis and sensitization to common aeroallergens in a Japanese population. *Int Arch Allergy Immunol* 2010;**151**:255–61.
5. Meltzer EO, Nathan R, Derebery J, Stang PE, Campbell UB, Yeh WS, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the burden of rhinitis in America survey. *J Allergy Asthma Proc* 2009;**30**:244–54.
6. Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. *Allergy Asthma Proc* 2000;**21**:7–13.
7. Blaiss MS. Evolving paradigm in the management of allergic rhinitis-associated ocular symptoms: role of intranasal corticosteroids. *Curr Med Res Opin* 2008;**24**:821–36.
8. Mullol J. A survey of the burden of allergic rhinitis in Spain. *J Invest Allergol Clin Immunol* 2009;**19**:27–34.
9. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. *J Allergy Clin Immunol* 2000;**105**:S616–21.
10. Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc* 2010;**31**:375–80.
11. Rodrigo GJ, Neff H. Efficacy of fluticasone furoate nasal spray vs. placebo for the treatment of ocular and nasal symptoms of allergic rhinitis: a systematic review. *Clin Exp Allergy* 2011;**41**:160–70.
12. Vasar M, Houle PA, Douglass JA, Meltzer EO, Silvey M, Wu W, et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. *Allergy Asthma Proc* 2008;**29**:313–21.
13. Salter M, Biggadike K, Matthews JL, West MR, Haase MV, Farrow SN, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol* 2007;**293**:L660–7.
14. Berger WE, Godfrey JW, Slater AL. Intranasal corticosteroids: the development of a drug delivery device for fluticasone furoate as a potential step toward improved compliance. *Expert Opin Drug Deliv* 2007;**4**:689–701.
15. Máspero JF, Rosenblut A, Finn Jr A, Lim J, Wu W, Philpot E. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. *Otolaryngol Head Neck Surg* 2008;**138**:30–7.
16. Meltzer EO, Lee J, Tripathy I, Lim J, Ellsworth A, Philpot E. Efficacy and safety of once-daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. *Pediatr Allergy Immunol* 2009;**20**:279–86.
17. Okubo K, Okamasa A, Honma G, Komatsubara M. Efficacy and safety of fluticasone furoate nasal spray in Japanese children with perennial allergic rhinitis: a multicentre, randomized, double-blind, placebo-controlled trial. *Allergol Int* 2014 Jul 25. Epub.
18. Okubo K, Nakashima M, Miyake N, Uchida J, Okuda M. Dose-ranging study of fluticasone furoate nasal spray for Japanese patients with perennial allergic rhinitis. *Curr Med Res Opin* 2008;**24**:3393–403.
19. Baena-Cagnani CE, Patel P. Efficacy and long-term safety of mometasone furoate nasal spray in children with perennial allergic rhinitis. *Curr Med Res Opin* 2010;**26**:2047–55.
20. Can D, Tanaç R, Demir E, Gülen F, Veral A. Is the usage of intranasal glucocorticosteroids alone in allergic rhinitis sufficient? *Allergy Asthma Proc* 2006;**27**:248–53.
21. Prael P, Wilken-Jensen K, Mygind N. Beclomethasone dipropionate aerosol in treatment of hay fever in children. *Arch Dis Child* 1975;**50**:875–8.