

Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis

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ABSTRACT

Fluticasone furoate nasal spray (FFNS) is a novel, enhanced-affinity glucocorticoid administered in a unique side-actuated device for the treatment of allergic rhinitis. No previous clinical studies have compared the efficacy of FFNS with another intranasal steroid. The purpose of this study was to compare the efficacy and safety of FFNS, 110 µg/day, once daily with fluticasone propionate nasal spray (FPNS), 200 µg/day, twice daily in patients with Japanese cedar pollinosis to support the regulatory filing in Japan. In this multicenter, randomized, placebo-controlled, double-blind, parallel-group study, patients (≥16 years old) were randomized to receive 2 weeks of treatment with FFNS (n = 151), FFNS placebo (n = 72), FPNS (n = 148), or FPNS placebo (n = 75). FFNS once daily was noninferior to FPNS twice daily in mean change from baseline in three total nasal symptom scores (3TNSS; sneezing, rhinorrhea, and nasal congestion; -1.23 ± 0.140 and -1.06 ± 0.142 , respectively). Compared with placebo, FFNS was superior in reducing 3TNSS ($p < 0.001$). Both FFNS and FPNS showed similar mean changes from baseline in 4TNSS (3TNSS and nasal itching) and individual nasal symptom scores. The onset of action for FFNS was observed from the 1st day of treatment, whereas in the FPNS group it was observed on the 2nd day. There were similar improvements in rhinoscopy findings, activity of daily life interference, and patient-rated overall evaluation to therapy in the FFNS and FPNS groups. FFNS was well tolerated. Treatment with once-daily FFNS was effective and noninferior to twice-daily FPNS in reducing nasal symptoms. Faster onset of action for FFNS was observed.

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Key words: Allergic rhinitis, clinical trial, corticosteroid, fluticasone furoate, fluticasone propionate, intranasal, nasal spray, placebo controlled, safety, steroid

Allergic rhinitis (AR), the most common form of noninfectious rhinitis, is characterized by the three major symptoms of paroxysmal and recurrent sneezing, watery rhinorrhea, and nasal congestion.¹ Depending on the time to exposure to allergens and the duration of symptoms, AR has been classified as perennial AR (PAR) or seasonal AR (SAR).^{2,3} Patients with SAR experience symptomatic exacerbations primarily during the pollen season, which in Japan is often caused by cedar pollen in spring.⁴ Although SAR is not life-threatening, SAR is regarded as an important respiratory disease because it has a considerable im-

pact on patients' quality of life, daytime performance and productivity, and economic impact.^{5–9}

The prevalence of cedar pollen allergy in Japan is ~20%,⁴ and it is estimated that >10 million people suffer from this disease. The area of cedar vegetation has reached 18% of the entire country, and the amount of pollen released is greater and the duration of pollen season is longer compared with those in the United States and Europe. Therefore, it is assumed that the disease condition is likely to be more severe. In addition, it has been a social issue because the incidence of cedar pollen allergy increases especially during the period from February to April, which is the end of the academic or business year when school entrance examinations or annual events take place. Moreover, it has been reported that the total medical cost for cedar pollen allergy is ~200 billion yen (~US\$2 billion) per year. Hence, it has become a problem in terms of medical economics as well.¹

Several classes of medications are available to treat AR; however, only intranasal corticosteroids (INS) have proven anti-inflammatory activity against pathophysiological aspects of both early and late-phase allergic reactions¹⁰ and have a broad spectrum of efficacy for the range of nasal symptoms including congestion, rhinorrhea, sneezing, and nasal itching.¹ The Allergic

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Rhinitis and its Impact on Asthmas Workshop Report in 2007 stated that INS were the most effective drugs for the treatment of AR and are recommended for its treatment in adults and children.¹¹ According to the Practical Guideline for the Management of Allergic Rhinitis in Japan (PG-MARJ), INS are recommended primarily for moderate to severe AR.¹ The guidelines also note that INS characteristically have few systemic adverse effects even with chronic use over a year or longer because absorption is negligible and they are immediately metabolized.

Fluticasone furoate (FF) nasal spray (FFNS) is a novel enhanced-affinity glucocorticoid administered to the nose in a unique side-actuated device. This ergonomically designed drug delivery system allows for improved handling and comfort during use and shows consistent dose-delivery characteristics across a wide patient population.¹² A preclinical study in human lung glucocorticoid receptors has shown that the relative receptor affinity of FF exceeds that of clinically available corticosteroids, including fluticasone propionate (FP) and mometasone furoate.¹³ FF also has potent pharmacologic actions including acceleration of transcription *via* the glucocorticoid response element, inhibition of activation of transcription factors including NF κ B, and inhibition of antigen-induced eosinophil infiltration in lungs in sensitized rats.¹⁴ These results may contribute to prolonged duration and highly efficacious profile for FF as a topical treatment for AR.

The clinical benefits of FFNS in reducing the nasal symptoms of AR have been shown in clinical studies in the United States, Europe, and Japan. In a 2-week dose-ranging study in SAR, once-daily doses of FF, 55–440 μ g, were well tolerated and significantly more effective than placebo, with FF, 110 μ g, selected as the optimal dose.¹⁵ In a 2-week dose-ranging study in PAR, FF, 110 μ g, was also selected as the optimal dose.¹⁶ Data from phase III trials indicated that FFNS, 110 μ g, once daily showed significantly greater improvement than placebo in the treatment of SAR and PAR.^{17–20} In addition, in a 12-month study of FFNS in PAR, the adverse-event profile was typical of the INS class, with no evidence of clinically relevant systemic corticoid exposure.²¹ However, no previous clinical studies have compared FFNS with another INS. This phase III study was conducted to show that the clinical effects of the FFNS, 110 μ g/day, once daily were non-inferior to those of FP nasal spray (FPNS), 200 μ g/day, twice daily in patients with Japanese cedar pollinosis to support the regulatory filing in Japan (GSK protocol number FFR100652). Therefore, this is the first study to compare FFNS with FPNS, which is widely used in current clinical practice.

METHODS

Study Design

This multicenter, randomized, placebo-controlled, double-blind, parallel-group study was conducted in patients with Japanese cedar pollinosis. The study protocol was approved by the appropriate local ethics committees, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before participation.

This study was conducted in seven study sites in Tokyo, Saitama, and Osaka during the 2005 cedar allergy season. Pollen counts were monitored by the use of Durham's pollen trap method for each area before and throughout the study. All patients were randomized after local pollen levels indicated that the cedar pollen season had started (the first 2 consecutive days when ≥ 1 grain/cm² were counted).

The efficacy and safety of FFNS were evaluated in patients with Japanese cedar pollinosis who received 2 weeks' treatment with once-daily FFNS, 110 μ g; once-daily FFNS placebo; twice-daily FP, 200 μ g; or twice-daily FPNS placebo. The FFNS, 110 μ g, versus FFNS placebo groups were double blinded, and FPNS versus FPNS placebo groups were also double blinded. However, the FFNS, 110 μ g, or FFNS placebo groups versus FPNS or FPNS placebo groups were only blinded to the investigators. Complete blinding with a double-dummy method with those placebos would dilute the drug at the site of administration and wash off the active drugs. Additionally, it would make it difficult for patients to keep good compliance because of the complicated regimen. Therefore, a double-dummy method was considered not appropriate for the present study.

Patients

Male or female patients with a history (>2 years) of SAR (Japanese cedar pollinosis) aged ≥ 16 years old were eligible for inclusion if they had a positive skin-prick test to Japanese cedar pollen or a positive *in vitro* test for specific IgE antibody. Diagnosis was confirmed by either a positive nasal challenge test (disk method²²) or nasal eosinophil counting (the choice was made by the investigators based on their experience of either methodology). To perform nasal eosinophil counting, a nasal smear was collected, stained, and then the number of eosinophils was counted.²³ Patients were also required to be symptomatic at baseline during the Japanese cedar pollen season. The patients who were confirmed to have SAR and met the symptom requirements and who also had PAR were still eligible for enrollment.

Patients were excluded if they had an existing nasal disorder that might interfere with evaluation (*e.g.*,

acute/chronic sinusitis, nasal polypsis, vasomotor rhinitis, or drug-induced rhinitis) or a coexisting disease (*e.g.*, serious hepatic/renal, cardiac, or pulmonary dysfunction; tuberculous diseases; systemic mycosis; hypertension; diabetes mellitus; nasal or oropharynx candidiasis; asthma [except mild intermittent asthma]; glaucoma; cataract; herpes simplex ophthalmic; or recurrent epistaxis). Patients were also excluded if they were pregnant or lactating. Furthermore, patients were excluded if they had received a corticosteroid within 8 weeks of the screening period or any other medication that could affect efficacy assessment.

Study Assessment and Procedures

The study consisted of three periods: a 1- to 2-week screening period, a 2-week treatment period, and a 1-week posttreatment observation period during which time adverse events were assessed. Patients were required to make up to five visits: screening (visit 1, 4–14 days), randomization (visit 2), midtreatment efficacy and safety evaluation (visit 3), and the end of the treatment period (visit 4). On the completion day of the posttreatment observation period, patients were asked at the visit (visit 5) or by telephone call whether they had experienced any adverse events.

Patients underwent tests during the screening period to confirm whether they met requirements to enter the treatment period. Patients were randomized in a 1:1:0.5:0.5 ratio to receive FFNS, FPNS, FFNS placebo, or FPNS placebo for 2 weeks. During both the screening and the treatment periods, patients rated the severity of nasal symptoms (sneezing, rhinorrhea, nasal congestion, and nasal itching [only for the four total nasal symptom scores {4TNSS}]) on a 4-point categorical scale (0 = none and 3 = severe)^{1,24} using an allergy diary. Patients who were judged to be able to write the diary correctly at visit 2 were eligible for randomization. The investigators instructed the patients to bring the diary at each visit, confirmed the details of the entries, and instructed them to fill out the diary appropriately as needed. Patients were randomized to treatment if they had an average of 3TNSS (for sneezing, rhinorrhea, and nasal congestion) of ≥ 4.0 in the consecutive 4 days before visit for randomization (visit 2). Patients also rated the severity of overall interference in activity of daily living (ADL; including overall interference of work, study, housework, and sleep) on a 4-point categorical scale (0 = no interference and 3 = activities were impossible).

The investigators examined nasal findings, including mucosal swelling of inferior turbinate mucosa and watery secretion volume by rhinoscopy on the 1st day of the treatment (visit 2), post-1-week treatment (visit 3), and post-2-week treatment (visit 4), and scored them using a 4-point scale (0 = none and 3 = severe). At the

end of the treatment period, patients rated their impression of the treatment efficacy using the 7-point categorical scale (markedly improved, moderately improved, slightly improved, no change, slightly worse, moderately worse, or markedly worse).

Safety and tolerability were assessed by adverse-event monitoring and clinical laboratory tests (hematology and clinical chemistry) and adrenocorticoid function test (serum cortisol levels determined using only blood samples taken between 8 A.M. and 10 A.M.). Treatment compliance was assessed through patient allergy diary recording.

End Points

The primary efficacy end point was the mean change from baseline over the entire treatment period in 3TNSS, defined as the sum (0–9) of three individual symptom scores for sneezing, rhinorrhea, and nasal congestion where each symptom was scored on a scale of 0–3 in the allergy diary. According to PG-MARJ (Japanese guideline), these three symptoms are considered to be the major symptoms of AR.^{1,24}

The secondary efficacy end points included mean change from baseline over the entire treatment period in 4TNSS (sum of scores for sneezing, rhinorrhea, nasal congestion, and nasal itching) and mean change in the 3TNSS and 4TNSS in weeks 1 and 2. Mean change from baseline over the entire treatment period in individual nasal symptom scores and change from baseline in the individual nasal examination (rhinoscopy) score were also assessed. Patients' impression of the treatment effect, the number of days until onset of action, based on the significant change in 3TNSS compared with placebo and change in the mean ADL interference scores over the treatment period were also evaluated in this study.

Statistical Analyses

The target sample size was set at a total of 420 patients, including 140 patients each in the FFNS, 110 μg , and FPNS groups and 70 patients each in the placebo groups. The mean treatment difference between the FFNS, 110 μg , and FPNS groups and standard deviation were assumed to be 0 and 1.8, respectively, based on the results of the U.S. study.¹⁵ Assuming that one-half of the difference between the FFNS, 110 μg , and placebo groups in the US study (GSK protocol number FFR20001) study¹⁵ (*i.e.*, 0.75) is an equivalence limit for noninferiority and assuming a one-sided significance level of 2.5% and a 90% power, 122 patients per group were required.

As the secondary objectives, the study aimed to test the superiority of FFNS, 110 μg , and FPNS compared with each placebo. The sample size of placebo groups was to be one-half of the active groups (*i.e.*, 61 patients

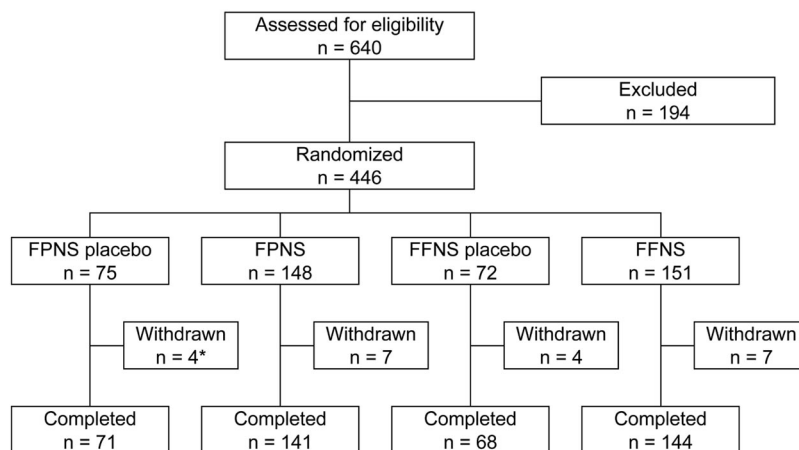


Figure 1. Disposition of patients. FPNS, fluticasone propionate nasal spray; FFNS, fluticasone furoate nasal spray. *Including one patient receiving no investigational product.

for each of the FFNS placebo and FPNS placebo groups). In addition, assuming a percentage of withdrawals after randomization and patients excluded from the per protocol set (PPS) is 10%; 140 and 70 patients were required for the active and placebo groups, respectively.

The PPS included all patients who entered the treatment period except those who did not receive any dose of study medication, those who did not have 3TNSS after treatment initiation (*i.e.*, who had only baseline data), and those who were not included in the efficacy analysis because of deviations from the protocol. Because the primary objective of the present study was to compare the efficacy of FFNS with FPNS, the primary efficacy analysis population was the PPS. The safety population included all patients who received at least one dose of study medication. The primary comparison for testing noninferiority of primary end point in the FFNS, 110 μ g, and FPNS groups was performed by a one-sided test at a significance level of 2.5% (97.5% one-sided confidence interval).

Mean change from baseline over the entire treatment period in 3TNSS was compared between the FFNS, 110 μ g, group and the FPNS group using the analysis of covariance (ANCOVA) in which study center, baseline value, age, and gender were adjusted. In each summary table, sample size, adjusted mean, standard error, adjusted mean difference, and two-sided 95% confidence intervals were calculated.

Statistical analyses for most secondary end points were conducted in the same manner as those used for the primary end point. For individual nasal rhinoscopy scores and patients' overall evaluation of treatment, differences between active and placebo groups were tested using the Wilcoxon two-sample test.

The comparisons for testing superiority in the active groups compared with the placebo groups were made by a two-sided test at a significance level of 5%. The

comparisons between the active groups and the comparison between the placebo groups were performed with a 95% two-sided confidence interval.

RESULTS

Study Population

Of the 640 patients who enrolled in this study, 446 were randomized, and 194 were withdrawn during the screening period and thus excluded. The major reason for discontinuation during the screening period was not satisfying the inclusion criteria. Disposition of patients in this study is shown in Fig. 1.

Of the 446 patients who were randomized, 433 patients (147 patients in the FFNS group, 70 patients in the FFNS placebo group, 144 patients in the FPNS group, and 72 patients in the FPNS placebo group) were included in the PPS, and 8 patients were excluded because of deviations from the protocol, 2 due to double enrollment, 2 for lost allergy diary, and 1 patient did not receive the investigational product. All the randomized patients met the inclusion criteria with regard to the allergy test.

The safety population comprised 443 of 446 randomized patients (149 patients in the FFNS group, 72 patients in the FFNS placebo group, 148 patients in the FPNS group, and 74 patients in the FPNS placebo group); exclusions were for receiving no investigational product ($n = 1$) and double enrollment ($n = 2$).

The patient characteristics were similar among the treatment groups (Table 1) with the ratio of males/females at $\sim 50\%$ and a mean age of 30.6–32.5 years. Duration of Japanese cedar pollinosis was 10 years or longer in about one-half of the patients in each treatment group (43–52%). All patients had a clinical history (>2 years) of Japanese cedar pollinosis with seasonal onset and offset of nasal symptoms during the Japanese cedar pollen season. The number of patients

Table 1 Patient characteristics (per protocol set)

	FPNS Placebo (n = 72)	FPNS (n = 144)	FFNS Placebo (n = 70)	FFNS (n = 147)	Total (n = 433)
Gender, n (%)					
Female	37 (51%)	78 (54%)	34 (49%)	76 (52%)	225 (52%)
Male	35 (49%)	66 (46%)	36 (51%)	71 (48%)	208 (48%)
Age (yr)					
Mean $\pm$ SD	30.6 $\pm$ 10.22	32.1 $\pm$ 10.27	32.5 $\pm$ 11.48	32.4 $\pm$ 10.98	32.0 $\pm$ 10.69
Range	20–66	19–69	20–60	20–69	19–69
Ethnicity, n (%)					
East/Southeast Asians	72 (100%)	144 (100%)	70 (100%)	147 (100%)	433 (100%)
Duration of Japanese cedar pollinosis, n (%)					
2–5 yr	13 (18%)	17 (12%)	10 (14%)	21 (14%)	61 (14%)
5–10 yr	23 (32%)	53 (37%)	30 (43%)	50 (34%)	156 (36%)
≥ 10 yr	36 (50%)	74 (51%)	30 (43%)	76 (52%)	216 (50%)

FPNS = fluticasone propionate nasal spray; FFNS = fluticasone furoate nasal spray; SD = standard deviation.

who also had PAR was 86 (21% for FFNS, 20% for FFNS placebo, 17% for FPNS, and 24% for FPNS placebo). Patients with non-AR were not enrolled. The mean treatment compliance rate was at least 99% in all treatment groups in the PPS. Only 1 case in the FPNS group reported <70% treatment compliance rate and was excluded from the PPS.

EFFICACY

Three Total Nasal Symptom Scores

For the primary efficacy end point (mean change from baseline in the 3TNSS over the entire treatment period), score reduction was similar in the FFNS and FPNS groups (Table 2). The upper limit of the two-sided 95% confidence interval for the adjusted mean difference between the two groups was 0.17. Because this value was lower than the noninferiority margin of 0.75, the noninferiority of FFNS to FPNS was verified.

The mean change from baseline in 3TNSS over the entire treatment period was significantly greater for FFNS than for FFNS placebo (–1.27 and 0.42, respectively; adjusted mean difference, –1.689; $p < 0.001$; Table 3). A significant decrease in 3TNSS was also observed in the FPNS group compared with the FPNS placebo group (–1.01 and 0.45, respectively; adjusted mean difference, –1.501; $p < 0.001$).

The significant reduction in 3TNSS against placebo was observed from the 1st day (day 1) of treatment in the FFNS group ($p = 0.003$), whereas in the FPNS group the first significant reduction was observed on day 2 ($p < 0.001$), indicating the faster onset of action of FFNS (*post hoc* statistical analysis). The difference in mean changes from baseline in 3TNSS was –0.784 (adjusted mean) on day 1 between the FFNS and FFNS placebo groups (Fig. 2).

Four Total Nasal Symptom Scores

As with the 3TNSS, there were similar mean changes from baseline in 4TNSS for all treatment periods in the FFNS and FPNS groups (difference of adjusted means; week 1, –0.245; week 2, –0.279; over the entire treatment period, –0.249). In addition, between FFNS and FFNS placebo, mean changes from baseline in 4TNSS for each of the treatment periods showed significant differences (adjusted means; week 1, –1.880; week 2, –2.732; and the entire treatment period, –2.298; $p < 0.001$, respectively).

Individual Nasal Symptom Score

There were similar mean changes from baseline in individual nasal symptom scores (sneezing, rhinorrhea, nasal congestion, and nasal itching) in the FFNS and FPNS groups from baseline (adjusted mean) for each of the treatment periods (week 1, week 2, and the entire treatment period; Fig. 3). There was a significant decrease in all symptom scores with FFNS compared with FFNS placebo ($p < 0.001$; Fig. 4).

Rhinoscopy Findings

Rhinoscopy findings, such as mucosal swelling of the inferior turbinate and amount of watery rhinorrhea showed similar frequency distributions for symptom score changes in the FFNS and the FPNS groups, with a shift to milder severity (Fig. 5, A and B). When FFNS and FFNS placebo groups were compared, there were significant changes in mucosal swelling ($p = 0.005$) and watery rhinorrhea ($p < 0.001$) at week 2, suggesting improvement of the symptoms.

Table 2 Mean change from baseline in 3TNSS (per protocol set), FFNS vs FPNS

	FPNS	FFNS
Baseline		
<i>n</i>	144	147
Mean $\pm$ SD	5.9 $\pm$ 1.43	5.8 $\pm$ 1.33
Mean change from baseline in 3TNSS		
1 wk after treatment initiation		
<i>n</i>	144	147
Adjusted mean $\pm$ SE	-1.17 $\pm$ 0.147	-1.31 $\pm$ 0.145
Adjusted mean difference from FPNS	—	-0.139
95% CI (two-sided)	—	-0.49, 0.21
2 wk after treatment initiation		
<i>n</i>	142	146
Adjusted mean $\pm$ SE	-0.95 $\pm$ 0.171	-1.17 $\pm$ 0.169
Adjusted mean difference from FPNS	—	-0.226
95% CI (two-sided)	—	-0.63, 0.18
Entire treatment period		
<i>n</i>	144	147
Adjusted mean $\pm$ SE	-1.06 $\pm$ 0.142	-1.23 $\pm$ 0.140
Adjusted mean difference from FPNS	—	-0.173
95% CI (two-sided)	—	-0.51, 0.17

CI = confidence interval; TNSS = total nasal symptom score; FPNS = fluticasone propionate nasal spray; FFNS = fluticasone furoate nasal spray; SD = standard deviation; SE = standard error.

Activities of Daily Living

The mean changes from baseline (adjusted mean) of the ADL interference score were similar in the FFNS, 110 μ g, and FPNS groups for each of the treatment periods (week 1, week 2, and the entire treatment period). When the changes were compared between the FFNS, 110 μ g, group and the FFNS placebo group, a significant decrease was observed for all of the treatment periods (week 1, -0.536; week 2, -0.757; the entire treatment period, -0.645; all $p < 0.001$).

Patients' Impression of the Treatment Effect

After 2 weeks of treatment, the number of cases who felt "improved (improved, remarkably improved)" was highest with FFNS (50%), followed by FPNS (45%), FPNS placebo (14%), and then FFNS placebo (10%). There was a significant difference between the FFNS and FFNS placebo groups ($p < 0.001$), suggesting improvement of ADL in the patients treated with FFNS.

SAFETY

Once-daily treatment with FFNS, 110 μ g, was well tolerated. The overall incidence of adverse events was comparable across the treatment groups (17% for FFNS, 21% for FFNS placebo, 18% for FPNS, and 19% for FPNS placebo). The incidence of drug-related adverse events was 6, 4, 5, and 9% for FFNS, FFNS placebo, FPNS, and FPNS placebo, respectively. Headache and nasopharyngitis (common

cold) were the most common reported adverse events (headache, 3% for FFNS, 4% for FFNS placebo, 3% for FPNS, and 1% for FPNS placebo; nasopharyngitis, 3% for FFNS, 1% for FFNS placebo, 3% for FPNS, and 3% for FPNS placebo). Of note, there were no cases of epistaxis in the FFNS group (1% for FFNS placebo, 2% for FPNS, and 4% for FPNS placebo). No serious adverse events were reported after treatment with FFNS or in any other group and many adverse events were mild in severity. Withdrawal due to adverse events was low and similar in each group (one patient for FFNS, two patients for FFNS placebo, two patients for FPNS, and one patient for FPNS placebo.) One patient receiving FFNS withdrew from the study because of moderate nasopharyngitis (common cold), and this was judged to be drug unrelated. No laboratory parameters showed changes specific to the active treatment groups or specific to the FFNS group. The mean changes from baseline in adrenocortical function test, as measured by morning serum cortisol level, were -1.15, -2.03, -0.89, and -1.37 μ g/dL in the FFNS, FFNS placebo, FPNS, and FPNS placebo groups, respectively, showing no evidence of a decrease in serum cortisol level after FFNS treatment.

DISCUSSION

The number of SAR patients has been increasing every year in Japan, and it is considered as a social

Table 3 Mean change from baseline in 3TNSS (per protocol set), FFNS vs FFNS placebo

	FFNS Placebo	FFNS
Baseline		
<i>n</i>	70	147
Mean $\pm$ SD	5.9 $\pm$ 1.28	5.8 $\pm$ 1.33
Mean change from baseline in 3TNSSs		
1 wk after treatment initiation		
<i>n</i>	70	147
Adjusted mean $\pm$ SE	-0.08 $\pm$ 0.209	-1.41 $\pm$ 0.157
Adjusted mean difference from placebo	—	-1.330
95% CI (two-sided)	—	-1.79, -0.87
<i>P</i> Value	—	<0.001
2 wk after treatment initiation		
<i>n</i>	68	146
Adjusted mean $\pm$ SE	0.91 $\pm$ 0.235	-1.15 $\pm$ 0.178
Adjusted mean difference from placebo	—	-2.061
95% CI (two-sided)	—	-2.57, -1.55
<i>P</i> Value	—	<0.001
Entire treatment period		
<i>n</i>	70	147
Adjusted mean $\pm$ SE	0.42 $\pm$ 0.201	-1.27 $\pm$ 0.151
Adjusted mean difference from placebo	—	-1.689
95% CI (two-sided)	—	-2.13, -1.25
<i>P</i> Value	—	<0.001

CI = confidence interval; TNSS = total nasal symptom score; FFNS = fluticasone furoate nasal spray; SD = standard deviation; SE = standard error.

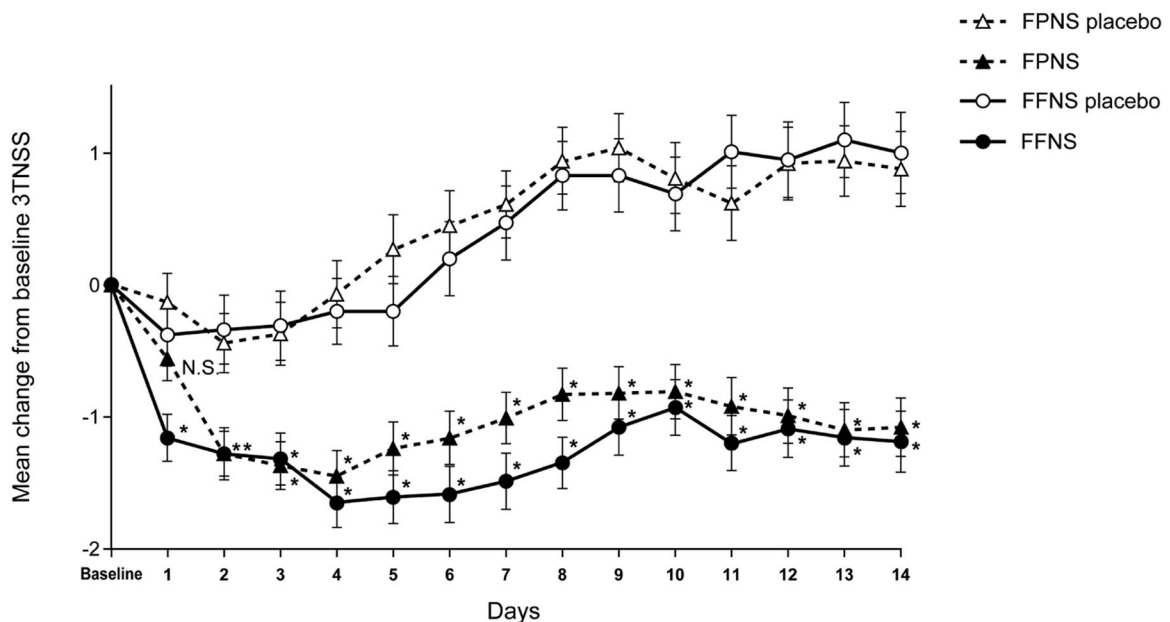


Figure 2. Mean change from baseline in daily 3TNSS (per protocol set). TNSS, total nasal symptom score; FPNS, fluticasone propionate nasal spray; FFNS, fluticasone furoate nasal spray. **p* < 0.005, compared with each placebo group.

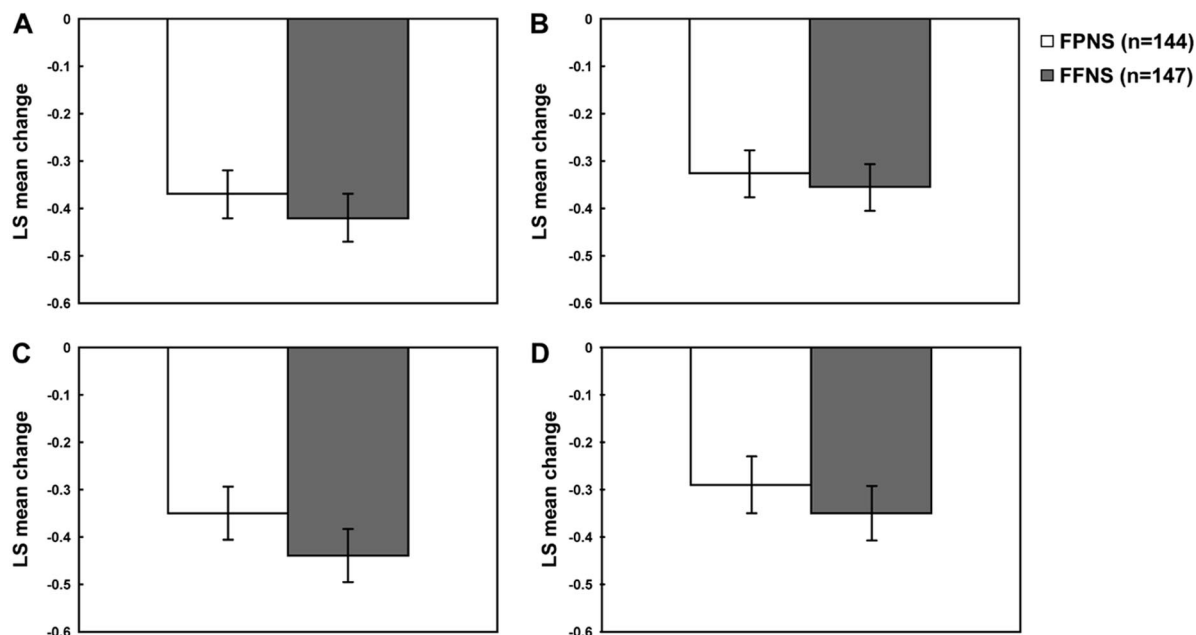


Figure 3. Mean changes from baseline in individual nasal symptom scores (per protocol set, FFNS versus FPNS). (A) Sneezing, (B) rhinorrhea, (C) nasal congestion, and (D) nasal itching. FPNS, fluticasone propionate nasal spray; FFNS, fluticasone furoate nasal spray; LS, least squares.

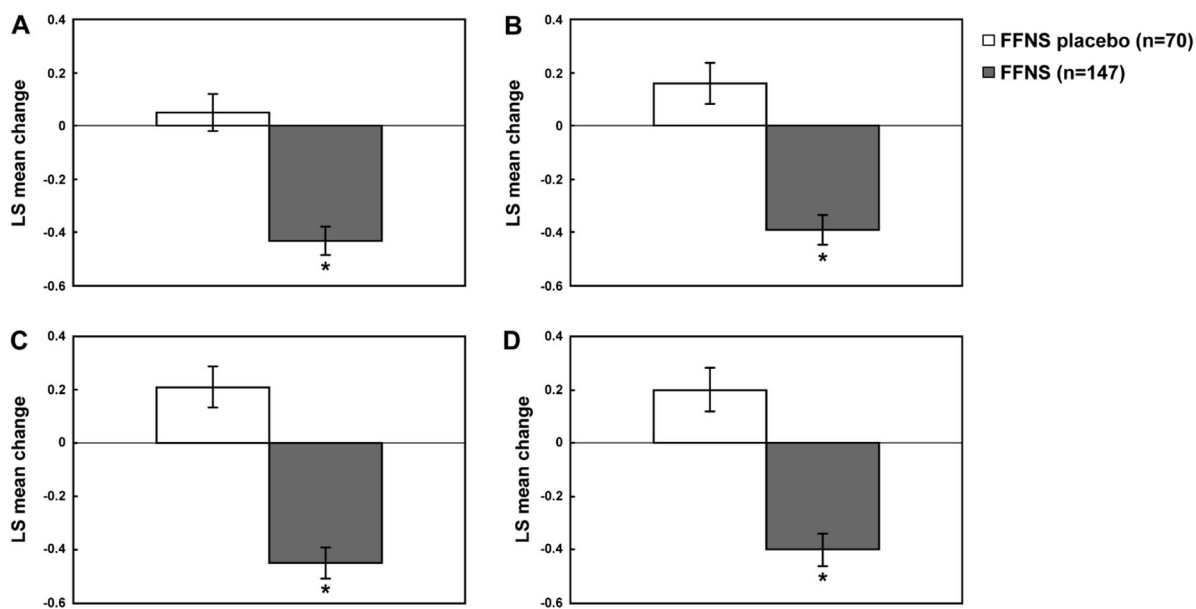


Figure 4. Mean changes from baseline in individual nasal symptom scores (per protocol set, FFNS versus FFNS placebo; $p < 0.001$ for all comparisons). (A) sneezing, (B) rhinorrhea, (C) nasal congestion, and (D) nasal itching. FPNS, fluticasone propionate nasal spray; FFNS, fluticasone furoate nasal spray; LS, least squares.

issue due to the high morbidity and the effects on quality of life.¹ However, patients tend to prefer taking oral drugs. INS, which are considered more effective,²⁵ are not used as often as doctors expect.

This is the first clinical study to compare the efficacy of FFNS against FPNS, the most commonly used INS, in the treatment of AR in Japan. The noninferiority of FFNS to FPNS was shown by the similar reduction in

3TNSS with the two treatments. As expected, statistically significant difference between FFNS to FPNS was not established in this study. This study was designed to show noninferiority of FFNS to FPNS; therefore, the patient sample size was small and detection power was insufficient to show superiority of FFNS to FPNS. The efficacy of FFNS placebo was comparable with that of FPNS placebo, and the efficacy of both FFNS and FPNS

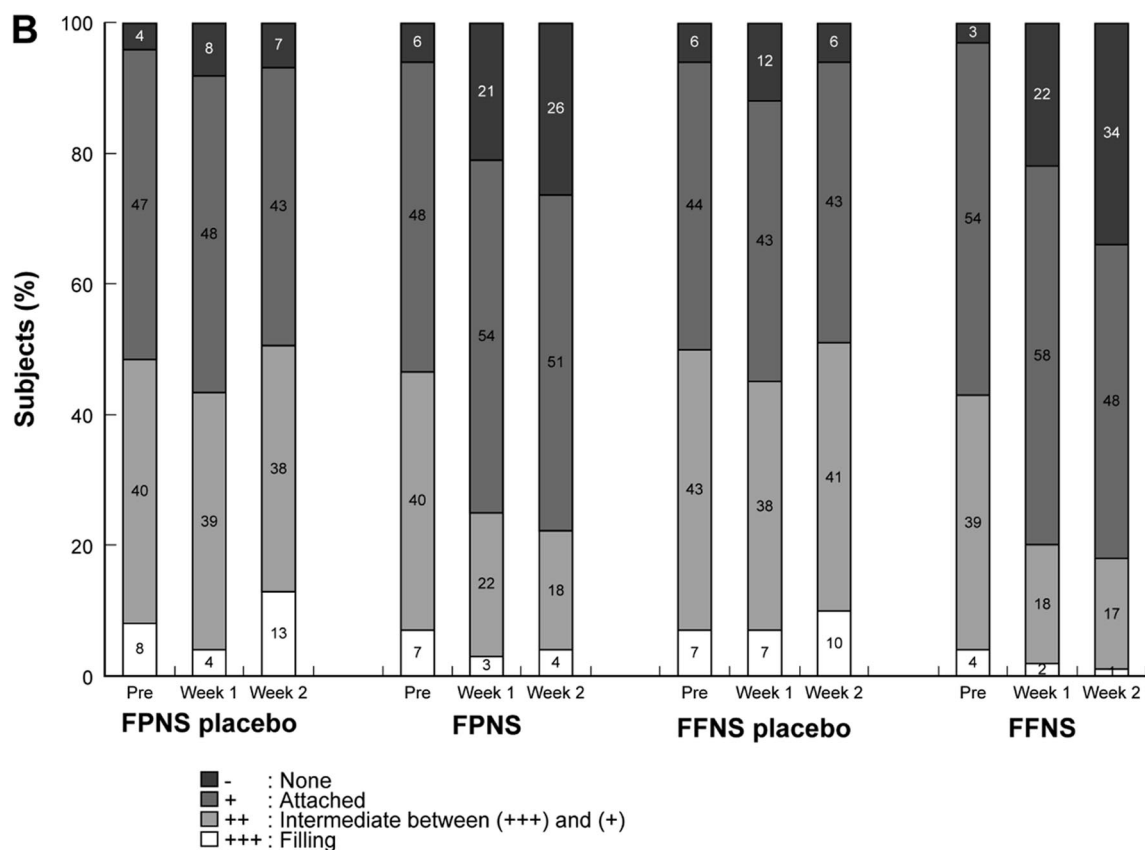
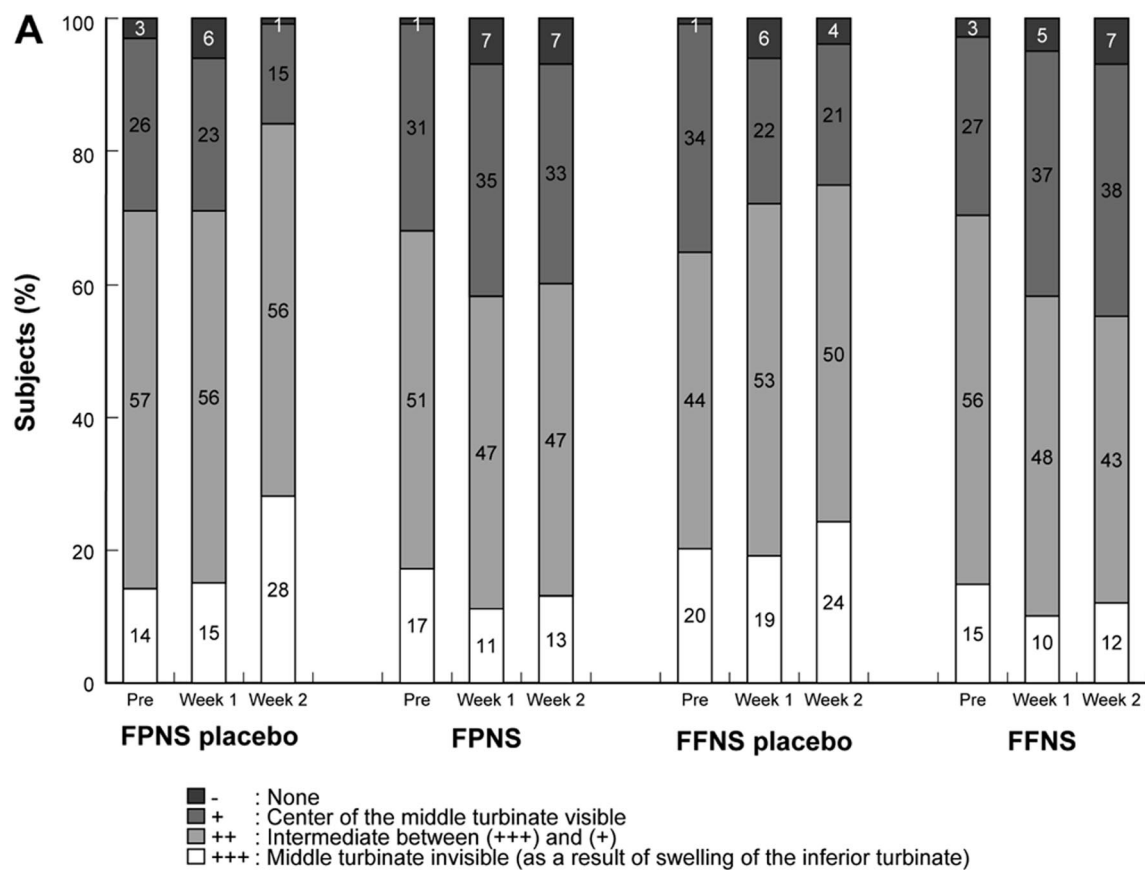


Figure 5. Nasal rhinoscopy findings (per protocol set, stacked percentage bar graph). (A) Mucosal swelling of the inferior turbinate. (B) Amount of watery rhinorrhea. FPNS, fluticasone propionate nasal spray; FFNS, fluticasone furoate nasal spray.

was superior to that of the respective placebos. As seen in the results that the symptoms worsened in each placebo group, it was a difficult season for the patients with Japanese cedar pollinosis, because a large amount of cedar pollen were released in 2005. However, we consider it significant that efficacy was observed with FFNS against SAR in this study.

In Japan, FPNS is administered twice daily (200 $\mu\text{g}/\text{day}$) in the treatment of AR. The present study showed that the efficacy of FFNS once daily (110 $\mu\text{g}/\text{day}$) was as effective as that of FPNS twice daily (200 $\mu\text{g}/\text{day}$). This suggests that the once-daily administration of FFNS, compared with the twice-daily administration of FPNS, will be more convenient for patients because there is no need to take the drug as often as before. Moreover, it is expected to result in an improvement with drug compliance.

In an *in vitro* study, FF was shown to have a very fast and extensive association with the human lung glucocorticoid receptor, with a relative receptor affinity significantly higher than for any other glucocorticoid, including FP.¹³ Other studies using human lung epithelial cells showed that FF causes rapid translocation of glucocorticoid receptor into the nucleus and exhibits approximately two times greater affinity for these cells compared with FP. In addition, no instability or chemical modification of FF was observed in lung tissue.¹⁴ These advantageous data of FFNS may contribute to a highly efficacious profile as a topical treatment for AR and support the results of this study.

The time to the onset of treatment effect (*i.e.*, the number of days to the initial day on which significant difference was observed in the active treatment group when compared with the matching placebo group) was 1 day in the once-daily FFNS group and 2 days in the twice-daily FPNS group. Thus, despite the less frequent dosing regimen, an earlier onset of treatment effect was confirmed for FFNS compared with FPNS. Indeed, some studies have reported that the onset of the efficacy of FFNS is ~ 8 hours after administration.^{15,17} For those patients suffering from the symptoms of AR, it is important to relieve the symptoms as quickly as possible. Also, if patients realize that the symptoms have been relieved quickly because of the earlier onset of efficacy, they are more likely to continue treatment, and hence patients' adherence to treatment may be improved.

The present study indicated that, like other INS, FFNS was effective for all four symptoms of Japanese cedar pollinosis (rhinorrhea, sneezing, nasal itching, and nasal congestion), indicating its usefulness in the treatment of SAR. This is in contrast to oral antihistamines, which have some efficacy against the three histamine-mediated symptoms (rhinorrhea, sneezing, and nasal itching) of SAR, but are less effective for nasal congestion.²⁶

INS have a well-known safety profile.^{2,27} The present study showed that FFNS has a well-tolerated and similar profile to FPNS. Nasopharyngitis and headache were the most common adverse events, occurring with the same incidence in both groups (3%). Withdrawal due to adverse events was low and similar in each group and no serious adverse events were reported after administration. No laboratory parameters showed changes specific to the active treatment groups. Moreover, FFNS had little effect on adrenocortical function. These data suggest that FFNS has a favorable safety and tolerable profile in agreement with the safety profile of other INS.

INS are useful drugs that are strongly effective against each symptom of AR. On the other hand, according to PG-MARJ, INS are considered to induce less systemic adverse reactions because they are hardly absorbed and, even if they are, are easily metabolized.¹ The bioavailability of FFNS is as low as 0.5%,²⁸ and the blood concentration was lower than the detectable value in most patients in many studies.¹⁵ The safety of long-term FFNS administration has been confirmed by the results of a placebo-controlled study conducted for 1 year.²¹ In addition, according to the results of a comparative study with oral prednisone regarding the effect on adrenal cortical function, it has been reported that it does not affect the adrenal cortical system.²⁹ Considering the finding of the present study and the aforementioned study results, it can be concluded that FFNS is a drug that shows efficacy against AR but is well tolerated with a good safety profile.

To complement the development of FFNS, a new delivery device has also been produced. It has a side-actuation system and a short delivery nozzle. It is considered that the use of the side-actuation system would make it easier for elderly and juvenile patients to spray and for third persons to administer the drug. In addition, by adopting the short delivery nozzle, it is expected that the feeling of invasiveness will be removed and the risk for pain or nasal bleeding will be reduced. Moreover, there is less concern for dripping from the nostril because the amount of fluid sprayed at a time is 50 μL , which is smaller than that of FPNS (100 μL).¹² A clinical study to assess the preferences of AR patients has shown that the sensory attributes (*e.g.*, overall product preference, scent/odor, immediate taste, and after taste) of FFNS were superior to those of FPNS.³⁰ It is anticipated that, because of these features, the FFNS system will aid in improving compliance with medication in individuals affected by AR, which in turn should aid in the long-term management of the symptoms of AR.

In conclusion, once-daily treatment of FFNS, 110 μg , was effective in improving nasal symptoms of SAR and noninferior to twice-daily FPNS. It also showed faster onset of action than FPNS. In addition, FFNS was

well-tolerated and the safety profile was similar to that of existing INS, indicating the usefulness of FFNS in the treatment of AR.

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