

Efficacy and safety of fluticasone furoate nasal spray in Chinese adult and adolescent subjects with intermittent or persistent allergic rhinitis

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ABSTRACT

Fluticasone furoate nasal spray (FFNS) is a novel, enhanced-affinity intranasal corticosteroid administered for the management of allergic rhinitis (AR). Several studies have shown that FFNS at a dose of 110 µg once daily (o.p.d.) is effective in relieving nasal as well as ocular symptoms in adolescents and adults with AR. The primary objective of this study was to compare the efficacy and safety of FFNS 110 micrograms o.p.d. with matching placebo nasal spray for 2 weeks in Chinese adult and adolescent subjects with intermittent AR (IAR) or persistent AR (PAR). In this multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients (adults and adolescents aged ≥12 years with AR) received either FFNS 110 micrograms (n = 181) or placebo (n = 182) o.p.d. for 2 weeks. AR was defined according to Allergic Rhinitis and Its Impact on Asthma classification. Efficacy measures included reflective total nasal symptom score (rTNSS), rhinoscopy score, overall interference in activities of daily living (ADL) score, and reflective total ocular symptom score (rTOSS). FFNS significantly improved the mean change from baseline in daily rTNSS compared with placebo (treatment difference of -1.498, 95% confidence interval [-1.897, -1.099]; $p < 0.0001$). FFNS was also significantly more effective than placebo in decreasing rhinoscopy score (treatment difference of -1.3; $p < 0.0001$) and ADL score (treatment difference of -0.4; $p < 0.0001$). In patients with severe ocular symptoms, FFNS showed numerically better treatment effect in reducing daily rTOSS than placebo (treatment difference of -0.646; $p = 0.0853$). FFNS 110 micrograms o.p.d. was significantly more effective than placebo in improving nasal symptoms in Chinese patients with IAR and PAR. ClinicalTrials.gov registration number: NCT01231464.

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Allergic rhinitis (AR) is a chronic upper respiratory disease, which has increased in prevalence over the last few decades and currently affects over 600 million people all over the world.^{1,2} A recent study of self-reported AR in 11 major cities across mainland China showed prevalence to range between 8.7 and 24.1%.³ Moreover, 74.4% of all AR patients were diagnosed as having intermittent AR (IAR) and 25.6% as

having persistent AR (PAR), as defined according to the new Allergic Rhinitis and Its Impact on Asthma (ARIA) classification.¹ AR is an immunoglobulin E (IgE)-mediated, inflammatory disorder that leads to nasal and ocular symptoms after allergen exposure.⁴ Although the symptoms of AR are not life-threatening, they have an adverse impact on the quality of life (QoL) of affected individuals, affecting employment, learning, emotions, psychological status, and social functioning.^{5–11}

Intranasal corticosteroids (INSs) have been generally recognized as an important component in the treatment of AR. The ARIA guidelines have indicated that therapeutic or prophylactic use of INS can control most of the nasal symptoms that accompany AR and therefore recommended the use of INS as first-line therapy for severe PAR or moderate-severe IAR.¹ Fluticasone furoate nasal spray (FFNS), a novel INS administered via a unique side-actuated device, has been shown to have high glucocorticoid receptor affinity and selectivity and lower systemic bioavailability (0.5%) compared with other currently available INSs.^{12,13} Several well-controlled clinical trials have indicated that treatment for 2 weeks with FFNS 110 µg once daily (o.p.d.) significantly improved symptoms and the QoL in

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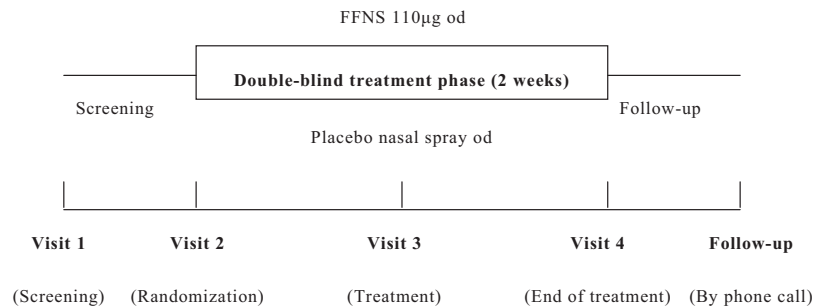
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FFNS: Fluticasone furoate nasal spray

Figure 1. Schematic study design.

adult, adolescent, and pediatric patients with seasonal AR (SAR) or perennial AR (PER).^{14–20} Indeed, an integrated analysis of data from four randomized trials of FFNS in SAR patients²¹ and a systematic review of 16 trials of FFNS in SAR and PER patients²² recently confirmed that FFNS 110 µg o.p.d. was consistently effective in relieving all nasal and ocular symptoms of AR and improving QoL in adult and adolescents with AR. The effects of FFNS, however, have mostly been investigated in white subjects with AR. The primary objective of this study was therefore to evaluate the efficacy and safety of FFNS 110 µg o.p.d. for 2 weeks in a cohort of ethnic Chinese adult and adolescent subjects with IAR and PAR.

MATERIALS AND METHODS

Patients

Clinically symptomatic subjects aged ≥ 12 years and ≤ 65 years old were eligible for enrollment, if they had a diagnosed history of IAR or PAR according to the current ARIA guidelines¹ for at least 1 year. At the screening visit, all subjects showed two or more nasal symptoms (watery rhinorrhea, nasal obstruction, nasal itching, and sneezing) and/or ocular symptoms (ocular itching, red eyes, and watery eyes). All patients additionally showed a positive skin-prick test response to a standardized allergen extract. The antigens included house-dust mite (Der f and Der p); seasonal grass pollens (giant ragweed, mugwort, lamb's quarters, *Humulus*, *Chenopodium album*, and so on); animal hair (especially dog and cat); molds (indoor and outdoor mustiness or floricultural environment), and cockroach (ALK-Abello, Hørsholm, Denmark). A positive skin-prick test result was defined as a wheal greater than or equal to one-half of the diameter of the histamine control and at least 3 mm larger than the diameter of the negative control. IAR was defined as having symptoms present < 4 days/week or for < 4 weeks and PAR was diagnosed when the symptoms were present > 4 days/week and for > 4 weeks.

Subjects with any nasal disease, vasomotor rhinitis, rhinitis with eosinophilia (nasal cytology analysis indicates $> 20\%$ eosinophils), drug-induced rhinitis, bacterial/viral infection of upper respiratory tract, any clinically significant systemic diseases, or a history of hypersensitivity to steroids were excluded from the study. Patients who had immunotherapy during the last year or any medications that significantly inhibit CYP3A4 (including ritonavir and ketoconazole) during the last 3 months and those who were unable to stop taking their normal allergy medications or other anti-allergic medications during the study period were also excluded. Similarly, pregnant and lactating women, patients with a history of alcohol and drug abuse, patients planning to travel outside their study region, patients who had participated in another clinical trial within the previous 3 months, or patients judged to be inappropriate for inclusion in any way by the investigators were also excluded.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study, conducted at seven investigational sites in six major cities (Beijing, Shanghai, Nanjing, Chengdu, Wuhan, and Hangzhou) in China. The study involved four visits: visit 1 (screening 2–14 days before randomization), visit 2 (randomization, day 1), visit 3 (treatment for 7 ± 2 days after visit 2; day 8), and visit 4 (completion of treatment after 14 ± 2 days after visit 2; day 15; Fig. 1). During the screening period, subjects were not allowed any antiallergy/antirhinitis medication, including allergy rescue medication, and recorded their nasal and ocular symptoms twice daily (in the morning and the evening) on a diary card, to determine eligibility for randomization. At the end of the screening period, patients returned to the clinic at visit 2, and all eligible subjects showing active nasal and/or ocular symptoms, mean reflective total nasal symptom score (rTNSS) of ≥ 6 , and mean reflective nasal congestion score of ≥ 2 over two consecutive

Table 1 Nasal finding score scale by rhinoscopy

Item	None (0)	Mild (1)	Moderate (2)	Severe (3)
Swelling degree of inferior turbinate	None	Can observe center of middle turbinate	Between 1 and 3	Can not observe middle turbinate
Color of inferior turbinate mucosa	Normal	Light red	Red	Pale
Watery secretion volume	None	Only adhesion	Between 1 and 3	Fullness
Description of rhinorrhea	None	Purulent	Viscous	Aqueous

24-hour periods, over a screening period of ≥ 4 days were examined by rhinoscopy. The eligible subjects were additionally evaluated for severity of overall interference in activities of daily living (ADL) and then randomized in a 1:1 ratio to 2 weeks of treatment with either FFNS 110 μg o.p.d. or matched placebo nasal spray, provided by the study sponsor (GSK, Shanghai, China). Randomization to treatment was performed according to a computer-generated randomization code provided by the study sponsor, and the subjects were provided with the appropriate study medication in coded identical devices; without either the patient or the investigator knowing the identity of the medication to allow treatment in double-blind manner. New diary cards were also provided for the patients to record the severity of their symptoms twice daily in the morning and the evening, administration of study medication, any adverse effects experienced and concomitant medications taken. The subjects returned to the clinic after 1 and 2 weeks (visits 3 and 4) of treatment, during which they were examined for nasal/ocular symptoms and their diary cards were assessed for symptom scores, therapeutic compliance, and adverse events (AEs) experienced. At the end of treatment (visit 4/early withdrawal) all subjects were additionally examined by rhinoscopy and evaluated for severity of overall interference in ADL. All subjects were followed up by telephone 3–5 days after completion of study treatment/early withdrawal to assess for any post-treatment adverse effects.

The study was conducted during September 2009 and May 2010 in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice and was approved by the Ethics Committee of Beijing TongRen Hospital. All patients or parent/legal guardian of those aged <18 years provided written informed consent before study participation.

Assessment of Efficacy

Primary and Secondary End Points. The primary efficacy end point for the study was the mean change from baseline in daily rTNSS over the entire treatment period. The secondary efficacy end points included the mean change from baseline to the end of study (visit

4/early withdrawal) in rhinoscopy scores, mean change from baseline to the end of study (visit 4/early withdrawal) in severity of overall interference in ADL, and the mean change from baseline over the entire treatment period in daily reflective total ocular symptom score (rTOSS) in a subgroup of patients who showed mean rTOSS of ≥ 4 , over 2 consecutive days before randomization.

Evaluation of Symptom Severity Scores. Patients rated the severity of individual nasal and nonnasal symptoms in the morning and in the evening on a 4-point scale of 0–3, where 0 = none (symptom is not present), 1 = mild (sign/symptom is clearly present but minimal awareness; easily tolerated), 2 = moderate (definite awareness of sign/symptom that is bothersome but tolerable), 3 = severe (sign/symptom is hard to tolerate; causes interference with ADL and/or sleeping).

The TNSS was calculated as the sum of four individual symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing. Similarly, the TOSS was calculated as the sum of three individual symptom scores for eyes itching/burning, eyes tearing/watering, and eye redness. The rTNSS/rTOSS was a rating of the severity of symptoms over the previous 12 hours, calculated in the morning (A.M. rTNSS/rTOSS) and evening (P.M. rTNSS/rTOSS). The daily rTNSS/rTOSS was evaluated as the mean of A.M. rTNSS/rTOSS and P.M. rTNSS/rTOSS.

Evaluation of Rhinoscopy Score. The investigator rated the degree of swelling in the inferior turbinate, color of inferior turbinate mucosa, the volume of watery secretion, and description of rhinorrhea on a scale of 0–3 by rhinoscopy (Table 1). A rhinoscopy score was calculated as the sum of four individual item scores, at baseline (visit 2) and the end of study (visit 4/early withdrawal).

Assessment of Safety

Safety measures included AE reporting, routine laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECG), vital signs, physical examinations, and nasal examinations.

Table 2 Demographics and baseline characteristics

Demographic and Baseline Characteristics	FFNS (n = 181)	Placebo (n = 182)
Age (yr)		
Mean, SD	31.8, 10.72	33.0, 10.95
Range (minimum–maximum)	13–64	12–61
Gender		
Male	84 (46.4%)	83 (45.6%)
Female	97 (53.6%)	99 (54.4%)
Height (cm)		
Mean, SD	166.4, 7.84	166.4, 7.88
Range (minimum–maximum)	151–188	150–185
Weight (kg)		
Mean, SD	62.53, 11.856	61.99, 11.233
Range (minimum–maximum)	36.0–115.0	35.0–92.0
Classification of AR		
IAR	67 (37.0%)	70 (38.5%)
PER	114 (63.0%)	112 (61.5%)
Symptom scores, mean (SD)		
rTNSS	8.217 (1.6331)	8.432 (1.6549)
A.M. rTNSS	8.334 (1.7943)	8.544 (1.7395)
P.M. rTNSS	8.099 (1.8352)	8.308 (1.8379)
Rhinorrhea	2.070 (0.5396)	2.122 (0.5314)
Nasal congestion	2.309 (0.4017)	2.357 (0.4022)
Nasal itching	1.913 (0.6041)	1.959 (0.6035)
Sneezing	1.924 (0.6578)	1.993 (0.6889)
rTOSS	5.513 (1.1925)	5.672 (1.1986)
Nasal finding score, mean (SD)	9.1 (1.59)	9.0 (1.83)
ADL, Mean (SD)	2.3 (0.50)	2.3 (0.50)

FFNS = fluticasone furoate nasal spray; AR = allergic rhinitis; IAR = intermittent allergic rhinitis; PER = persistent allergic rhinitis; rTNSS: reflective total nasal symptom score; A.M. = morning; P.M. = evening; rTOSS: reflective total ocular symptom score; ADL = activities of daily living; FAS = full analysis set.

Statistical Analyses

All data were analyzed using the SAS 9.1.3 statistical software (SAS Institute Inc., Cary, NC). Three analysis populations were used for this study, including the full analysis set (FAS; randomized patients who received at least 1 dose of study drug and completed at least one diary assessment after treatment initiation), per protocol set (PPS; randomized patients in FAS with no major protocol deviations and with $\geq 80\%$ treatment compliance and diary compliance), and safety population (SP; randomized patients who had received at least 1 dose of study drug). FAS was used for the primary efficacy analysis, whereas the PPS was used to check the robustness of efficacy results and SP was used for all safety analyses. Demographic data and baseline characteristics were summarized for FAS. The primary and secondary efficacy end points were analyzed using analysis of covariance, adjusting for baseline, center, age, gender, and classification of AR, in addition to treatment effect. Frequency tabulations and descriptive statistics were produced for AEs, laboratory tests, ECG,

vital signs, physical examinations, and nasal examinations.

RESULTS

A total of 365 patients were screened, of whom 12 patients withdrew and 353 patients were randomized to the two treatment groups (177 in the FFNS 110 μg group and 176 in the placebo-treated group). The majority of subjects (96.7%) completed the study. The discontinuation rate was comparable for both treatment groups (FFNS 110 μg -treated group, 5 [2.7%]; placebo-treated group, 7 [3.8%]). None of the subjects in the FFNS 110 μg -treated group and 1 subject (0.5%) in the placebo-treated group discontinued due to AEs. Fifty-eight subjects (32 subjects [17.6%] in FFNS 110 μg -treated group and 26 subjects [14.2%]) in the placebo-treated group had major protocol deviations, of which the most common was failure to show the required nasal symptom score before randomization (FFNS 110 μg -treated group, 17 [9.3%]; placebo-treated group, 12 [6.6%]). Of the 365 randomized patients, two

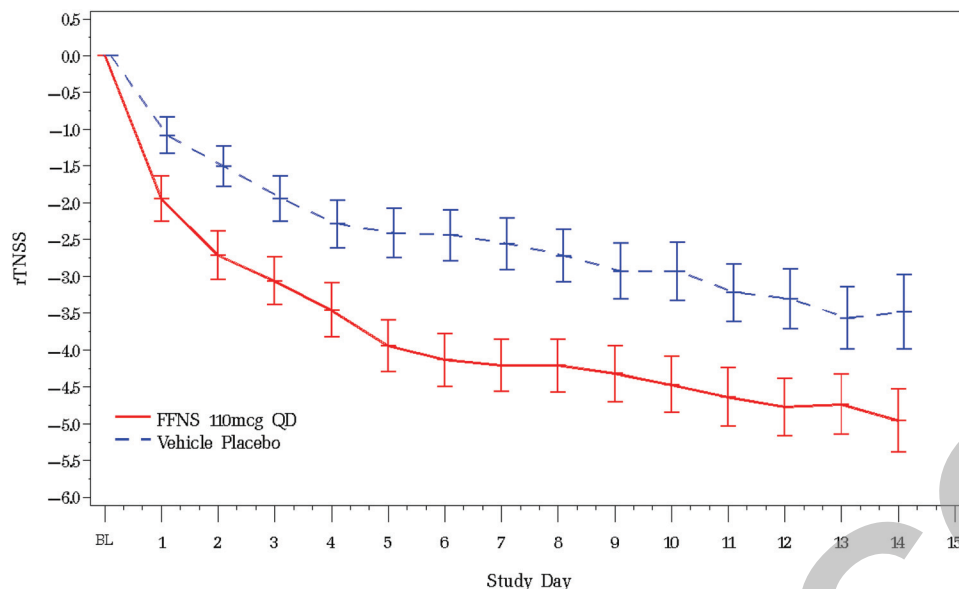


Figure 2. Mean change from baseline over the entire treatment period in daily reflective total nasal symptom score (rTNSS; full analysis set [FAS]).

FFNS: Fluticasone furoate nasal spray

rTNSS: Reflective total nasal symptom score

patients did not take any study medication and the FAS and SP therefore comprised 363 subjects. The PPS population comprised 307 patients after exclusion of the 58 patients with major protocol violations.

Demographic and clinical characteristics of the two study groups were comparable at baseline (Table 2), with patients' ages ranging from 12 to 64 years and there being few more women (54.0%); 62.3% of individuals had PAR and the remainder had IAR.

Efficacy Assessments

Primary Efficacy Measure. Figures 2 and 3 show the mean change from baseline in daily and A.M./P.M. rTNSS, respectively, over the entire treatment period. Assessment of the least square (LS) mean change in daily rTNSS from baseline over the entire study period showed this was greater for the FFNS 110 μ g-treated group (-4.226) than for the placebo-treated group (-2.728). The LS mean difference for rTNSS between the two treatment groups was statistically significant (-1.498 [95% CI, -1.897 , -1.099]; $p < 0.0001$; Table 3). Similarly, the LS mean treatment difference for A.M. rTNSS and P.M. rTNSS between the FFNS 110 μ g-treated and placebo-treated groups, for change from baseline over the entire treatment period, were also significant (A.M. rTNSS, LS mean difference = -1.607 and $p < 0.0001$; P.M. rTNSS, LS mean difference = -1.425 and $p < 0.0001$).

Assessment of mean change from baseline over the entire study period for daily reflective scores for individual nasal symptoms (rhinorrhea, nasal congestion,

nasal itching, and sneezing), further indicated that these were also significantly greater for all symptoms in FFNS 110 μ g-treated group compared with the placebo-treated group (Table 4). The onset of treatment effect was assessed by the mean change from baseline in daily rTNSS (days 1–14) and was supported by the mean change from baseline in A.M. rTNSS and P.M. rTNSS. The LS mean difference between the two treatments in daily rTNSS, A.M. rTNSS, and P.M. rTNSS for days 1–14 all achieved significance at day 1 and was sustained through day 14.

Subgroup analysis for IAR and PAR patients indicated that the mean change from baseline in daily rTNSS over the entire treatment period was also greater for FFNS 110 μ g-treated group than for placebo-treated group in both IAR patients (FFNS 110 μ g-treated group, -3.985 ; placebo-treated group, -2.898) and PAR patients (FFNS 110 μ g-treated group, -3.945 ; placebo-treated group, -2.389). An assessment of the consistency of treatment effect across centers, by including the treatment by center interaction in the analysis of covariance model, showed that the treatment by center interaction was also significant ($p = 0.0140$). Similarly, the treatment effect at each study center was found to be in favor of FFNS 110 μ g over the placebo-treated group.

Secondary Efficacy Measures. At baseline, the mean rhinoscopy score was similar for the two treatment groups. The LS mean change in rhinoscopy score from baseline to the end of study (visit 4/early withdrawal) was greater for the FFNS 110 μ g-treated group (-4.2)

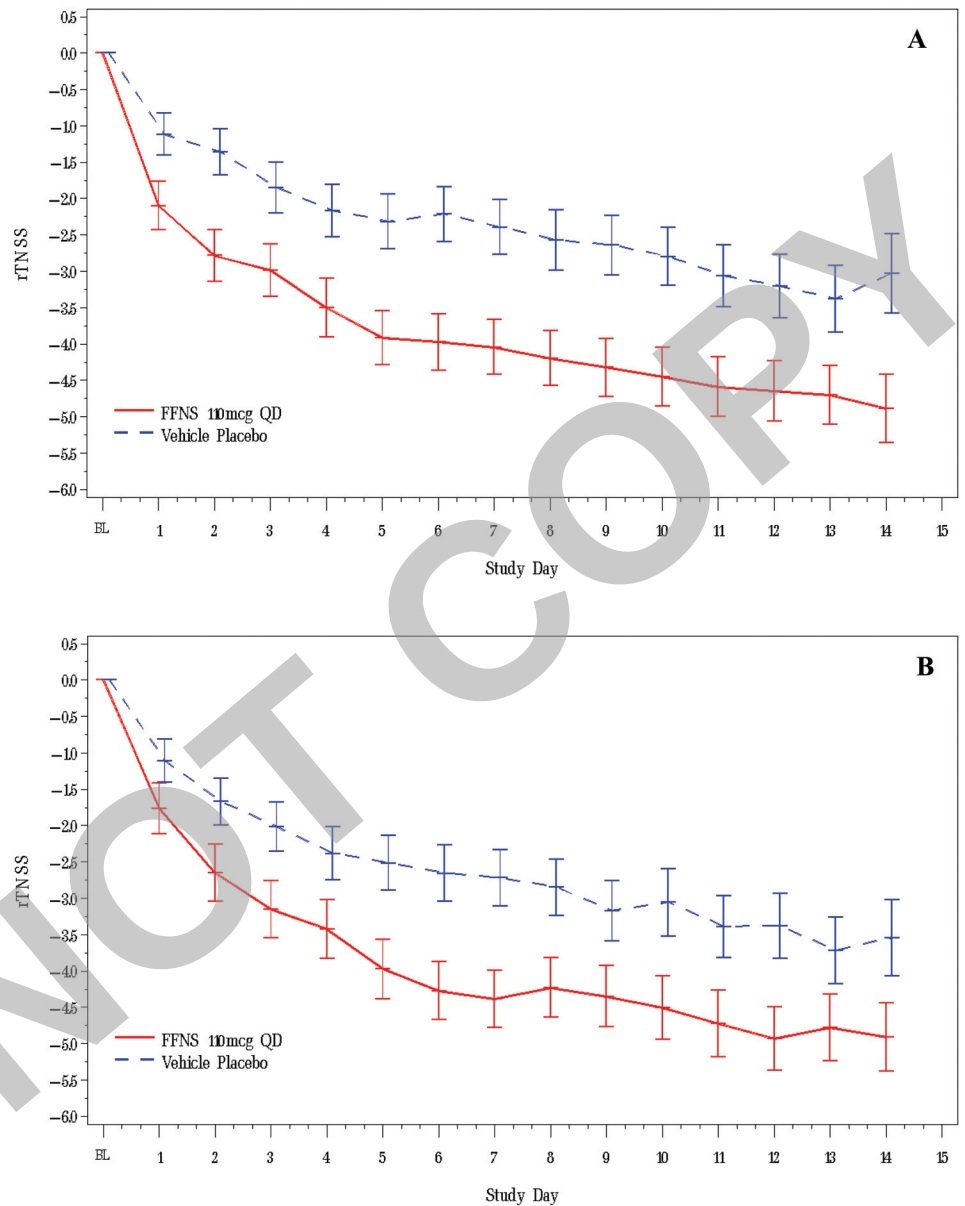


Figure 3. Mean change from baseline over the entire treatment period in daily morning reflective total nasal symptom score (A.M. rTNSS) and evening (P.M.) rTNSS (full analysis set [FAS]).

A: Mean change from baseline over the entire treatment period in daily AM rTNSS

B: Mean change from baseline over the entire treatment period in daily PM rTNSS

FFNS: Fluticasone furoate nasal spray

rTNSS: Reflective total nasal symptom score

compared with the placebo-treated group (-2.9), with the LS mean difference between the two treatment groups being significant (-1.3 [95% CI, -1.9 , -0.8]; $p < 0.0001$; Table 3).

The LS mean change from baseline to the end of study (visit 4/early withdrawal) in severity of overall interference in ADL was also greater for the FFNS 110 μg -treated group (-1.2) compared with the placebo-treated group (-0.8), with the LS mean difference be-

tween the two treatment groups being significant (-0.4 [95% CI, -0.5 , -0.2]; $p < 0.0001$; Table 3). The number of patients with an average rTOSS of ≥ 4 before randomization was relatively small (38 subjects for the FFNS 110 μg -treated group and 48 subjects for the placebo-treated group). The mean change from baseline over the entire treatment period in daily rTOSS in this subgroup of patients is shown in Fig. 4. The LS mean change from baseline over the entire treatment

Table 3 Mean change from baseline over the entire treatment period in daily rTNSS, nasal finding score, ADL, and daily rTOSS of patients treated with FFNS 110 µg od or placebo over the 2-wk treatment period (FAS)

	FFNS (n = 181)	Placebo (n = 182)
rTNSS		
LS mean change (SE)*	−4.226 (0.1646)	−2.728 (0.1656)
LS mean difference*		−1.498
p Value*		<0.0001
95% CI*		−1.897, −1.099
Nasal finding score		
LS mean change (SE)*	−4.2 (0.22)	−2.9 (0.22)
LS mean difference*		−1.3
p Value*		<0.0001
95% CI*		−1.9, −0.8
ADL		
LS mean change (SE)*	−1.2 (0.07)	−0.8 (0.07)
LS mean difference*		−0.4
p Value*		<0.0001
95% CI*		−0.5, −0.2
rTOSS (baseline rTOSS = 4, FFNS = 38 vs placebo = 48)		
LS mean change (SE)*	−3.097 (0.3850)	−2.450 (0.3379)
LS mean difference*		−0.646
p Value*		0.0853
95% CI*		−1.385, 0.092

*Based on analysis of covariance adjusting for baseline overall interference in ADL, center, classification of AR (IAR, OR, and PER), age, gender, and treatment.

SD = stand deviation; SE = standard error; LS = least square; CI = confidence interval; FFNS = fluticasone furoate nasal spray; IAR = intermittent allergic rhinitis; PER = persistent allergic rhinitis; rTNSS: reflective total nasal symptom score; rTOSS: reflective total ocular symptom score; ADL = activities of daily living; FAS = full analysis set; LS mean difference = least square mean change in FFNS − LS mean change in placebo.

period in daily rTOSS for the FFNS 110 µg-treated group was −3.097 and for the placebo-treated group was −2.450, with no significant difference between the two groups ($p = 0.0853$; Table 3).

Safety and Tolerability

The incidence of AEs was low in both treatment groups (FFNS 110 µg, 7.2%; placebo-treated group, 4.9%) and there were no reports of serious AEs, death, or other significant AEs during the treatment period. The most common AE was upper respiratory tract infection with incidence rates of 2.2% in the FFNS 110 µg-treated group and 1.1% in the placebo-treated group. Most of the AEs in the FFNS 110 µg-treated group were mild in nature, although one subject in reported dizziness as a severe AE. Six patients (3.3%) in the FFNS 110 µg-treated group and 3 subjects (1.6%) in the placebo-treated group experienced at least one AE deemed to be drug related by the investigator during the treatment period (Table 5). The most common drug-related AEs were rhinalgia and dizziness with incident rates of 1.1% in FFNS 110 µg-treated

group. Only one subject was discontinued from the study because of AEs (in placebo-treated group). The incidence of laboratory abnormalities was low and similar between the two treatment groups. Findings from the nasal examinations were generally similar for the two treatment groups. Changes in vital signs were minor and similar across the two treatment groups. Abnormal physical examinations were few and similar in the treatment groups. None of the subjects had unfavorable clinically significant changes in ECG assessment.

DISCUSSION

This study indicated that treatment with FFNS 110 µg o.p.d. was effective for alleviating the nasal symptoms of nasal congestion, itching, rhinorrhea, and sneezing in adult and adolescent Chinese subjects with AR. FFNS significantly improved both the mean change from baseline in daily rTNSS compared with placebo (treatment difference of −1.498; $p < 0.0001$) and the rhinoscopy score (treatment difference of −1.3; $p < 0.0001$). Moreover, efficacy was also shown in relief

Table 4 Treatment comparison for change from baseline to treatment average in daily reflective symptom scores (FAS)

	FFNS (<i>n</i> = 181)	Placebo (<i>n</i> = 182)
Rhinorrhea		
LS mean change (SE)*	−0.959 (0.6246)	−0.594 (0.5816)
LS mean difference*		−0.397
<i>p</i> Value*		<0.0001
95% CI*		−0.506, −0.288
Nasal congestion		
LS mean change (SE)*	−1.052 (0.0485)	−0.760 (0.0487)
LS mean difference*		−0.292
<i>p</i> Value*		<0.0001
95% CI*		−0.409, −0.175
Nasal itching		
LS mean change (SE)*	−1.024 (0.0445)	−0.647 (0.0450)
LS mean difference*		−0.377
<i>p</i> Value*		<0.0001
95% CI*		−0.486, −0.269
Sneezing		
LS mean change (SE)*	−1.118 (0.0469)	−0.669 (0.0474)
LS mean difference*		−0.449
<i>p</i> Value*		<0.0001
95% CI*		−0.563, −0.335

*Based on analysis of covariance adjusting for baseline overall interference in ADL, center, classification of AR (IAR, OR, and PER), age, gender, and treatment.

FFNS = fluticasone furoate nasal spray; SD = stand deviation; SE = standard error; LS = least square; CI = confidence interval; LS = least square; FAS = full analysis set.

of overall interference in ADL (treatment difference of −0.4; $p < 0.0001$). The subjects were not classified in the current study as PER or SAR patients as for previous clinical trials of FFNS,^{14–22} but were instead classified as IAR and PAR patients according to the ARIA classification,¹ which is more commonly used by ear, nose, and throat physicians in China.

Our findings for efficacy of FFNS are in accordance with the findings of similar studies conducted previously.^{14–20} Results of this study showed FFNS 110 µg o.p.d. produced significantly greater reductions from baseline in subjects' self-assessed total and individual nasal symptom scores compared with placebo. Moreover, the reductions in nasal symptoms were complemented by significant improvements in nasal anatomy, as indicated by rhinoscopy, and decreased severity of overall interference in ADL. Although recent studies have indicated FFNS to consistently improve also ocular symptoms of AR,^{21–23} our findings indicated that in a subgroup of patients who exhibited ocular symptoms and showed a baseline rTOSS of ≥ 4 , FFNS pro-

duced numerical, but not significant, improvement in daily rTOSS compared with placebo.

Data from narrative reviews advocate that not all INSs are equal regarding ocular symptoms of AR and the clinical trials of other INSs show that the effects on ocular symptoms are inconsistent.^{14,24} However, more recent literature supports the positive effects on ocular symptoms of INSs.^{25–29} Inconsistent efficacy across trials might be the result of variations in different factors: trial design, heterogeneity of patients enrolled (SAR or PAR patients), different baseline ocular symptom score, or different methods of assessing ocular symptoms (variable, categorical or visual scales, or patient or physician-rated scoring systems).²² We hypothesized that the lack of significance in the improvement of ocular symptoms noted in the present study was possibly caused by the relatively small number of patients evaluated in the subgroup analysis and/or the severity of ocular symptoms at baseline. To test this hypothesis, we performed a *post hoc* analysis of a much larger subgroup of subjects (126 in FFNS 110 µg-treated

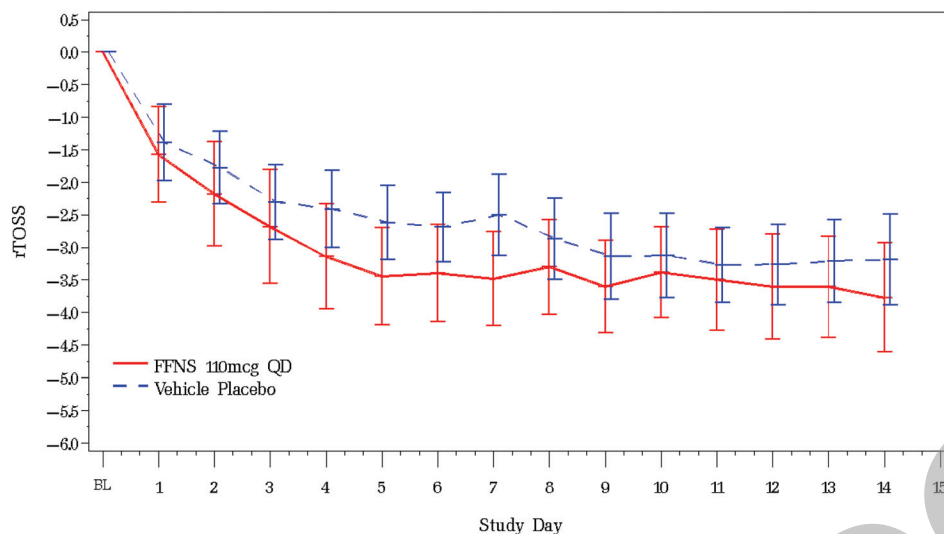


Figure 4. Mean change from baseline over the entire treatment period in daily reflective total nasal symptom score (rTNSS; full analysis set [FAS]; baseline rTOSS, ≥ 4).

FFNS: Fluticasone furoate nasal spray

rTOSS: Reflective total ocular symptom score

Table 5 A summary for the most common drug-related adverse events by system organ class during the treatment period

System Organ Class	FFNS (n = 181)	Placebo (n = 182)
Respiratory, thoracic, and mediastinal disorders	4 (2.2%)	1 (0.5%)
Rhinalgia	2 (1.1%)	0
Cough	1 (0.6%)	0
Epistaxis	1 (0.6%)	0
Increased upper airway secretion	0	1 (0.5%)
Throat irritation	0	1 (0.5%)
Nervous system disorders	2 (1.1%)	1 (0.5%)
Dizziness	2 (1.1%)	0
Headache	0	1 (0.5%)
Gastrointestinal disorders	0	2 (1.1%)
Abdominal pain	0	1 (0.5%)
Dry mouth	0	1 (0.5%)
Nausea	0	1 (0.5%)
Investigations	0	1 (0.5%)
Blood urine present	0	1 (0.5%)
Total	6 (3.3%)	3 (1.6%)

Total: Total number of subjects in the FFNS 110 μg group and in the vehicle placebo group, respectively, experienced at least one adverse event deemed to be drug-related by the investigator during the treatment period.

FFNS = fluticasone furoate nasal spray.

group and 135 in placebo-treated group) who had established a mean rTOSS of >1 , over two consecutive 3-day periods before randomization. This subgroup analysis showed that the LS mean change from baseline over the treatment period in daily rTOSS was -1.826 for the FFNS 110 μg -treated group and -1.379 for the placebo-treated group and the LS mean difference of -0.447 (95% CI, -0.751 , -0.142 ; $p < 0.005$; data not shown). However, these findings need to be confirmed in future trials specifically designed and powered to show the positive effects of FFNS on ocular symptoms in Chinese subjects.

With respect to the safety of FFNS, a few subjects (six in the FFNS 110 μg -treated group and three in placebo-treated groups) experienced at least one AE deemed to be drug related by the investigator during the treatment period. The most common drug-related AEs were rhinalgia and dizziness, both with incident rates of 1.1% in the FFNS 110 μg -treated group. No serious AEs, death, or other significant AEs were reported. No safety issues were identified with findings from AE reporting, vital signs, physical examinations, or ECG assessments. Laboratory values and nasal examinations were generally similar between the two treatment groups. The most common AEs established in short-term AR studies were headache, epistaxis, and nasopharyngitis. Indeed, a long-term safety study of FFNS in adults and adolescents with PER³⁰ indicated that the incidence of most AEs was similar to that observed with placebo, with the exception of epistaxis, which was more frequently reported on active treatment.

Taken together, the results of this randomized, double-blind, placebo-controlled, parallel-group, multicenter trial indicated that FFNS 110 μg o.p.d. is well tolerated and effective in the relief of nasal symptoms in adult and adolescent Chinese patients with IAR or PAR. The totality of data from this study confirms that FFNS 110 μg o.p.d. is a suitable treatment option for the management of AR also in Chinese patients.

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