

A comparison of fluticasone propionate nasal spray and cetirizine in ragweed fall seasonal allergic rhinitis

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ABSTRACT

Background: Intranasal corticosteroids are generally considered the most effective medication class for controlling allergic rhinitis. Previous comparative studies with oral antihistamines have been only partially informative due to a variety of variables encountered during their execution.

Objective: To compare fluticasone propionate nasal spray (FPNS) with the second-generation antihistamine cetirizine (oral tablet) and with placebo in a head-to-head study in a 2-week treatment study during fall ragweed season.

Methods: A total of 978 subjects were screened for this study. Six hundred and eighty-two subjects were randomized into the study (170 subjects, FPNS 200 mcg once daily; 170, cetirizine 10 mg once daily; 171, FPNS placebo; 171, cetirizine placebo) and comprised the intent-to-treat population. A 1-week placebo run-in was followed by a 2-week active treatment period during which time a total nasal symptom score (TNSS), total ocular symptom score, and the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire were collected.

Results: The primary efficacy end point was the mean change from baseline over the entire treatment period in A.M. reflective TNSS. The TNSS was the sum of the four individual nasal congestion, nasal itching, rhinorrhea, and sneezing scores, in which each symptom was scored on a scale of 0 to 3. Both FPNS and cetirizine improved the primary end point when compared with placebo during the active treatment period. Although there was a trend that favored FPNS with regard to the primary and secondary end points, there was not a statistical difference between the two treatments.

Conclusion: FPNS and cetirizine were equally effective in treating fall seasonal allergic rhinitis during a 2-week head-to-head treatment investigation.

Clinical trial NCT01916226, www.clinicaltrials.gov

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Allergic rhinitis (AR) is a common chronic respiratory illness that affects quality of life and productivity. Seasonal AR (SAR), also known as hay fever, affects ~20% of people of all ages.¹ AR is an immunoglobulin E mediated disease that is thought to occur after exposure to airborne allergens, *e.g.*, pollen. Symptoms include rhinorrhea, nasal congestion, obstruction, and pruritus.² In 2001, Allergic Rhinitis and Its Impact

on Asthma guidelines were published in cooperation with the World Health Organization, which indicate that the treatment of AR makes use of a combination of patient education, allergen avoidance, pharmacotherapy, and immunotherapy.³ Pharmacologic options for the treatment of AR include intranasal corticosteroids, oral and topical antihistamines, decongestants, intranasal cromolyn (Nasalcrom; McNeil Consumer Healthcare, Fort Washington, PA), intranasal anticholinergics, and leukotriene receptor antagonists.

Second-generation oral antihistamines (OAHs) are now widely available over the counter (OTC) and have been recommended as first-line therapy for mild symptoms of AR⁴ because of their safety and ease of use. OAHs are predominantly effective on neurally mediated symptoms² of itching, sneezing, and rhinorrhea; however, these agents have a modest impact on nasal congestion.

Intranasal corticosteroids are considered the most-effective medications for treating AR^{5,6} and have been recommended as first-line therapy for moderate-to-severe symptoms.^{2,4} They act by decreasing the influx of inflammatory cells and inhibiting the release of cytokines, thereby reducing inflammation of the nasal mucosa.³ A meta-analysis of a large number of stud-

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ies demonstrated that intranasal corticosteroids are generally more effective than OAHs in the treatment of SAR symptoms, particularly nasal congestion.⁷ The effect on ocular symptoms has been reported to be of similar magnitude between these two pharmacotherapy classes.⁷

Intranasal steroids have recently been moved from prescription to OTC to widen treatment choices for patients. With OTC options, patients often self-medicate and self-diagnose.⁸ Given the importance of having robust, head-to-head comparisons among these medications, this phase IV investigational trial was conducted to evaluate the efficacy of a 2-week treatment of fluticasone propionate nasal spray (FPNS) versus oral cetirizine on AR nasal and ocular symptoms, and quality of life in adult patients with SAR.

METHODS

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 2-week study (NCT01916226) designed by using the U.S. Food and Drug Administration's Guidance for Industry on Allergic Rhinitis studies.⁹ Enrollment occurred during the 2013 fall allergy season at 32 investigative sites in the United States. Clinic visits were designed to occur according to the following schedule: visit 0, the prescreening visit, occurred up to 28 days before randomization; visit 1, the screening visit, occurred 4–7 days before randomization; visit 2 occurred on day 1, the day of randomization; and visit 3, the end-of-study visit, occurred 12–16 days after randomization.

Enrollment criteria were assessed at visit 1. Subjects were eligible to be enrolled if they were able to sign and understand the informed consent form, if they had been diagnosed previously with SAR or had a positive skin-prick test result to a prevalent seasonal allergen at visit 1, if their allergy was treatable on an outpatient basis, if they were at least 18 years of age as of visit 1, and if they were to be exposed to a local fall pollen during the study treatment period. Significant medical conditions, use of study protocol-prohibited concurrent medications, or hypersensitivity to any excipient of the study treatments precluded enrollment in the study. This study was approved by the Chesapeake Institutional Review Board on June 20, 2013.

After visit 1, each subject was provided vehicle placebo FPNS and placebo cetirizine to be taken once daily in the morning during the run-in period (between visit 1 and visit 2). The subjects were also provided with and instructed in the use of an electronic diary. The subjects used these electronic diaries from visit 1 through visit 3 to record their morning nasal and ocular symptom scores. Nasal (congestion, itching, rhinorrhea [runny nose], and sneezing) and ocular (tearing and/or watering, itching and/or burning, and red-

ness) symptoms were assessed in both a reflective (*i.e.*, over the previous 24 hours) and instantaneous (*i.e.*, at the moment of assessment) manner. All symptoms were assessed by using a 0- to 3-point scale (0, none; 1, mild; 2, moderate; 3, severe). The four nasal symptom scores were summed to create a total nasal symptom score (TNSS); the three ocular symptom scores were summed to create a total ocular symptom score (TOSS). Separate total scores were calculated to represent both reflective and instantaneous symptoms.

To be eligible for randomization, subjects had to have a reflective TNSS (rTNSS) of at least 7 (of a maximum score of 12) on at least 4 of the 7 days before randomization, including the day of randomization (visit 1). In addition, subjects were required to demonstrate at least 70% compliance with both placebo run-in study medications and completion of the electronic diary during the period starting on the day of visit 1 and ending on the day before visit 2. Subjects who met these criteria at visit 2 were randomized with equal allocation to one of four treatment groups: FPNS 200 mcg daily, overencapsulated cetirizine 10 mg orally daily, placebo nasal spray, or placebo capsule. In keeping with perceived real-world allergy treatment practices, no double-dummy treatments were incorporated into the design of this study. To establish adequate pollen exposure at the start and during the study, site personnel collected local fall pollen counts (grains/m³) at least 5 days per week for the duration of the study. Pollen count collection began at each site before the first subject screening.

End Points

The primary efficacy measurement defined for this study was the change in the rTNSS from baseline over the 2-week treatment period. Baseline was defined as the average rTNSS over the entire run-in period, including the assessment on the morning of randomization. Secondary efficacy measurements included changes from baseline over the 2-week treatment period in the following measurements: the four individual reflective nasal symptom scores, the instantaneous TNSS and TOSS, and the reflective TOSS (rTOSS). Because the severity of sneezing, blocked nose, and rhinorrhea tends to peak during the night and in the early morning, an additional secondary measurement was based on the overall change from baseline in the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ).¹⁰ The subjects answered this questionnaire at visit 2 and either at visit 3 or at the early withdrawal visit. An overall score was calculated from the responses to the 16 individual items on the NRQLQ, and a change from baseline (visit 2) to end point (either visit 3 or early withdrawal) was calculated. Safety assessments included adverse events, vital signs, and physical examinations.

Sample Size Considerations and Statistical Methods

Previous GlaxoSmithKline studies that compared an intranasal steroid (fluticasone furoate nasal spray [FFNS]) with a second-generation antihistamine (fexofenadine) were of a double-dummy design that included a placebo vehicle nasal spray and a placebo tablet matched to fexofenadine. To better estimate the “pure” effect of each class of drug, each average formulation-specific placebo effect noted in these studies was subtracted from its respective average active drug effect (*i.e.*, FFNS – placebo nasal spray, fexofenadine – placebo capsule). Subsequent calculations yielded expected treatment differences between FFNS and fexofenadine and between FFNS and placebo in rTNSS, which ranged from 1.0 to 1.2.

When assuming that FPNS and cetirizine would show similar effects as FFNS and fexofenadine, respectively, and when estimating the standard deviation of the change from baseline in rTNSS over 2 weeks to be ~2.6, then a two-sample *t*-test with $\alpha = 0.05$ indicated that a sample size of 144 subjects per arm would provide 90% power to show a difference of 1.0 between FPNS and cetirizine in the rTNSS. In anticipation of a 5–8% dropout rate, this study planned an enrollment of 156 subjects per treatment group to target 144 subjects per treatment group who would provide a full 2 weeks’ worth of data.

The primary measurement, the mean change from baseline in rTNSS compared between FPNS and cetirizine over the 2-week treatment period, was analyzed by using an analysis of covariance model that included baseline rTNSS as a covariate and include separate terms for treatment and investigator. The secondary measurements, the mean changes from baseline over the 2-week treatment period in the individual nasal symptom scores, the instantaneous TNSS and TOSS, the rTOSS, and the change from baseline NRQLQ score at the end point, were each summarized by treatment group and analyzed by using similar models. The Hochberg method¹¹ was used to adjust for statistical multiplicity across the three total symptom scores and the NRQLQ, and across the set of four individual reflective nasal symptom scores.

Disposition

A total of 978 subjects were screened for this study. Of these, 223 subjects had failed screening and/or run-in and 73 subjects had failed the prescreen. Six hundred and eighty-two subjects were randomized into the study (170 subjects, FPNS 200 mcg daily; 170, cetirizine 10 mg daily; 171, FPNS placebo; 171, cetirizine placebo) and comprised the ITT population. The ITT population was used for all efficacy, safety, and health outcomes analyses, except for the primary analysis of ocular symptoms, which was based on the

ocular subpopulation. The number of subjects enrolled at each of the 32 sites ranged from 1 (<1%) to 40 (6%).

Ninety-nine percent of the subjects completed the study. The early withdrawal rate was low for all treatment groups. Two subjects in the FPNS placebo group and one subject in the cetirizine placebo group withdrew due to a lack of efficacy: one subject in each of the FPNS, FPNS placebo, and cetirizine placebo groups withdrew due to an adverse event. Two patients were withdrawn as a result of protocol deviation (one cetirizine placebo, one cetirizine), and one patient (cetirizine placebo) was withdrawn at the investigator’s discretion.

Demographics

Demographics of the ITT population were generally comparable across the treatment groups. The mean age was similar among the four treatment groups, with 98% to >99% of the subjects 18 to 64 years old. There was a greater proportion of females in all treatment groups (56–66%) and the majority of subjects in all treatment groups (75–84%) were self-described as white. The majority of subjects in all groups (78–84%) reported having SAR for ≥ 10 years.

RESULTS

Primary End Point

The primary efficacy end point was the mean change from baseline over the entire treatment period in A.M. rTNSS. The TNSS was the sum of the four individual nasal congestion, nasal itching, rhinorrhea, and sneezing scores, in which each symptom was scored on a scale of 0 to 3. The maximum sum for TNSS was 12. For the statistical analysis, the baseline score was defined as the average of the A.M. rTNSS over the entire run-in period before randomization (4 to 7 days), including the assessment on the morning of randomization. At baseline, the mean A.M. rTNSS values were similar in all treatment groups (FPNS, 9.5; cetirizine, 9.4; FPNS placebo, 9.6; cetirizine placebo, 9.3), which demonstrated moderate-to-severe nasal symptoms at the start of the double-blind study treatment. The mean change from baseline rTNSS over the entire 2-week treatment period was numerically greater for FPNS (–2.2) than for cetirizine (–1.9) (Table 1). The least squares mean difference between the two active treatments (FPNS versus cetirizine) in the change from baseline A.M. rTNSS over the entire 2-week treatment period was –0.3. This treatment difference did not reach statistical significance ($p = 0.278$; 95% confidence interval, –0.7 to 0.2) (Table 1).

Secondary End Points

The secondary end points for this study included the following:

Table 1 Summary of the change from baseline over 2 weeks in A.M. rTNSS[†] (intent-to-treat population)

rTNSS	FPNS (n = 170)	Cetirizine (n = 170)	FPNS Placebo (n = 171)	Cetirizine Placebo (n = 171)
Baseline, no.	170	170	171	171
Mean ± SE	9.5 ± 0.12	9.4 ± 0.12	9.6 ± 0.11	9.3 ± 0.11
Weeks 1–2 (0n)	169	169	171	171
Mean ± SE	7.3 ± 0.22	7.5 ± 0.20	8.1 ± 0.19	8.3 ± 0.19
Change from baseline				
Weeks 1–2 (n)	169	169	171	171
Mean ± SE	–2.2 ± 0.19	–1.9 ± 0.18	–1.5 ± 0.18	–0.9 ± 0.16
FPNS-cetirizine LS mean difference ± SE	–0.3 ± 0.23		—	—
p value (95% CI)*	0.278 (–0.7 to 0.2)		—	—

SE = standard error, LS = least squares, CI = confidence interval.

*The p value and CI were adjusted for multiplicity by using the Hochberg method.

[†]TNSS maximum score = 12.

- Mean change from baseline in the individual A.M. reflective nasal symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing
- Mean change from baseline in the NRQLQ overall score
- Mean change from baseline in the A.M. instantaneous TNSS
- Mean change from baseline in the A.M. predose rTOSS
- Mean change from baseline in the A.M. predose instantaneous TOSS
- Mean change from baseline in the combined nasal and ocular A.M. reflective total symptom score (reflective total symptom score = rTNSS + rTOSS). This measurement was only assessed in the subpopulation with a baseline rTOSS of ≥ 4.

Because the primary end point did not achieve statistical or clinical significance, none of the secondary end points achieved statistical and clinical significance.

The NRQLQ was used in this study to measure rhinitis-related quality of life. The NRQLQ is a 16-item, validated, self-administered, disease (AR) specific, quality-of-life instrument that measures the functional problems most troublesome to patients with nocturnal allergy symptoms over a 1-week interval.¹⁰ At baseline, the subjects in all the treatment groups had similar overall NRQLQ scores (Table 2). The least squares mean difference in the change from baseline overall NRQLQ score between the two active treatments (FPNS versus cetirizine) resulted in a statistically significant difference of –0.4, with a Hochberg-adjusted p value of 0.011 (adjusted 95% confidence interval, –0.7 to –0.1), which favored FPNS (Table 2). However, this result also cannot be considered statistically significant because of multiplicity considerations and is not

deemed clinically relevant because it was less than the –0.5 cutoff for clinical relevance stipulated *a priori*.

Each active study treatment was compared with its corresponding placebo study treatment with respect to the primary efficacy measure (rTNSS) only. These two comparisons were not adjusted for multiple comparisons. As can be seen in Table 3, both active treatments demonstrated statistically significant improvement in rTNSS versus their respective placebos. Mean rTNSS remained within the moderate range (4–8) at the end of the 2-week treatment period. Ocular symptom score data (ocular subpopulation) are provided in the Supplemental Table. All treatments (FPNS, cetirizine, FPNS placebo, cetirizine placebo) were well tolerated, with comparable rates of adverse events and no serious adverse events.

DISCUSSION

AR is usually associated with inflammation, and characteristic symptoms include one or more of the following: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching. AR is also frequently accompanied by symptoms that involve the eyes, ears, and throat.² There is no generally accepted method of grading rhinoconjunctivitis severity. Although patients frequently characterize the severity of rhinitis based on one predominant symptom (*e.g.*, nasal stuffiness), patients with AR can, in fact, present with multiple symptoms.

The intranasal corticosteroids (INSSs) are considered the most-effective medication class available for AR, and they are often used as the first-line therapy for moderate cases of SAR and perennial AR (PAR).¹² Regular persistent use of INSSs is effective in reducing nasal congestion, rhinorrhea, sneezing, and nasal itching in both adults and children, and recent publications

Table 2 Summary of the change from baseline[†] in secondary end points (intent-to-treat population)

Secondary End Point	FPNS (n = 170)	Cetirizine (n = 170)	FPNS Placebo (n = 171)	Cetirizine Placebo (n = 171)
iTNSS [‡] , no.	169	169	171	171
Mean ± SE	−1.9 ± 0.18	−1.3 ± 0.17	−1.2 ± 0.18	−0.6 ± 0.15
FPNS-cetirizine LS mean difference ± SE	−0.5 ± 0.23		—	—
p value (95% CI)*	0.058 (−1.1 to <0.1)		—	—
NRQLQ [§] , no.	170	170	171	171
Mean ± SE	−1.0 ± 0.10	−0.6 ± 0.09	−0.8 ± 0.10	−0.5 ± 0.08
FPNS-cetirizine LS mean difference ± SE	−0.4 ± 0.12		—	—
p value (95% CI)*	0.011 (−0.7 to −0.1)		—	—

iTNSS = instantaneous Total Nasal Symptom Score, SE = standard error, LS = least squares, CI = confidence interval.

*The p values and CIs were adjusted for multiplicity by using Hochberg's method.

†Change from baseline iTNSS was over the 2-wk treatment period.

§Change from baseline NRQLQ is at end point.

‡TNSS maximum score = 12.

Table 3 Analysis of change from baseline over 2 weeks in rTNSS-placebo comparisons (intent-to-treat population)

rTNSS	FPNS vs. FPNS Placebo	Cetirizine vs. Cetirizine Placebo
LS mean difference	−0.7	−1.0
SE	±0.23	±0.23
95% CI	−1.1 to −0.2	−1.4 to −0.5
p Value	0.004	<0.001

LS = least squares, SE = standard error, CI = confidence interval.

reported that they may also be effective in relieving ocular symptoms.¹³ Unlike histamine receptor antagonists, INSs can suppress multiple mediators at several stages of the allergic inflammatory process; this may, in part, explain their potent effect on allergic symptoms.²

Although the mechanism of action and clinical trials with INS support a delayed onset of action (12–24 hours) and peak of effect (several days) and the need for continuous use to achieve optimal effect, there are reports with FPNS of onset of benefit within the first 2 hours and of effectiveness when used as needed.^{14,15} Nevertheless, for optimal control of nasal symptoms, induced by repeated or persistent exposure to an allergen, INSs must be used daily, and it may take several days for their maximal efficacy to develop.¹⁴

Second-generation OAHs are generally preferred over first-generation antihistamines for the treatment of AR because they have less tendency to cause seda-

tion, performance impairment, and/or anticholinergic adverse effects.¹⁶ The onset of action of second-generation OAHs is fast, within 1–3 hours, which makes them more suitable than INSs for as-needed use. They have been shown to be effective on ocular as well as nasal symptoms,² with the exception of nasal congestion,¹⁶ which explains why they are frequently paired with a decongestant such as pseudoephedrine or phenylephrine in a fixed combination.

Our study did not show a statistically or clinically significant difference between FPNS and cetirizine in the subjective primary end point of rTNSS in patients with SAR. When considering the statistical hierarchy, no statistical conclusions can be made concerning any of the secondary end points. Both active treatments demonstrated statistically significant improvement versus their respective matching placebo with respect to rTNSS. However, mean rTNSS remained within the moderate range (4–8) at the end of the 2-week treatment period, which indicates that monotherapy, whether with an INS or with an OAH may not be sufficiently effective for some patients.

In most previous studies, INSs were shown to be more effective than the combined use of an antihistamine and leukotriene receptor antagonist in the treatment of SAR.¹⁷ Furthermore, the addition of an OAH to an INS generally has not demonstrated greater clinical benefit than INS alone, although one study showed that the addition of loratadine to FPNS was superior to FPNS alone for some patient-rated symptoms,¹⁸ and that 50% of patients in another study needed to take both INSs and OAHs to control symptoms of SAR adequately.¹⁹

In this study, we observed a muted treatment effect in the change from baseline in rTNSS with FPNS

(−23%) below what has been reported with the INS class generally (−40.7%) and FPNS specifically (−40% to −50%) in similarly designed studies in SAR. Of interest, the research sites that participated in this study with the highest pollen counts revealed trends for slightly greater improvements in rTNSS with FPNS versus cetirizine but not large enough to make either a statistical or a clinical difference. It is possible that, because nasal mucosal inflammation may have already been present at the onset of the double-blinded treatment, an earlier initiation of pharmacotherapy or a longer treatment phase may have allowed more time for the anti-inflammatory effects of the INS to be effective and could have differentiated the two treatments. It is also unclear how concomitant PAR may have affected the response to pharmacotherapy in this study. A recent meta-analysis by Benninger *et al.*²⁰ reported that, although INS produced greater improvements in nasal symptoms in patients with SAR, OAHs may be just as effective for some patients with PAR. In addition, a recent randomized double-blind study showed that cetirizine produced significant improvements in symptom severity and quality of life compared with placebo in patients with PAR.²¹

Our study offers several key strengths, including a randomized, double-blind, placebo-control design, the evaluation of all common nasal and ocular symptoms, and the use of four parallel treatment arms to mitigate the potential of topical washout with a placebo double-dummy nasal spray and the systemic placebo effect of a double-dummy pill. In fact, analysis of the data from this study provided valuable insights into the differential impact of two placebo vehicles, one oral and one topical, in AR. The study also had inherent limitations, including the lack of a robust characterization of previous AR treatment and treatment responses that may have helped to better understand the muted effect to FPNS in this instance.

CONCLUSION

This study did not show a statistically or clinically significant difference between once-daily FPNS and once-daily oral cetirizine given for 2 weeks in the treatment of nasal and ocular symptoms in adults with SAR. Both treatments were well tolerated, with comparable rates of adverse events and no serious adverse events, and both demonstrated statistically significant improvement in rTNSS versus their respective placebos, which supported their efficacy in SAR. Further studies in PAR or different seasons may shed more light on the comparative effects of these two products as monotherapies as well compared with combination INSs plus OAHs and of INSs plus intranasal antihistamines. This study also highlighted again the previously reported variability in treatment response to AR

therapies, raising the need for further investigations to better understand the determinants of response to AR pharmacotherapy (exogenous environmental, endogenous genetic, *etc.*).

Patients' access to second-generation OAHs and INSs has been rendered simple and easy with the prescription-to-OTC switch of these safe and effective remedies. The choice of which one to use remains not a straightforward one, however, and depends on several factors, such as SAR versus PAR, the prominence of nasal congestion or ocular symptoms, persistent symptoms while on therapy, onset of action, and preference between a topical nasal application or an oral route of administration to name a few. Monotherapy with either an OAH or an INS agent may be sufficient to quell nasal and ocular discomfort in many cases, but there will be instances in which stepping up to combined pharmacotherapy by using different classes (INS, OAH, intranasal antihistamines, intraocular antihistamine, leukotriene modifier) may be necessary and helpful to achieve the desired relief. For more severe and intractable cases, allergen-specific immunotherapy under the direction of an allergy specialist may also be warranted.

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Erratum

In the article *Effect of TRPV1 gene mutation on bronchial asthma in children before and after treatment*, *Allergy Asthma Proc* 36, 29–36, 2015; doi: 10.2500/aap.2015.36.3828, there was an error in the author information. One of the affiliations for Chuan-Liang Chen was not included. Also, the degrees for the authors were incorrectly listed. The correct author line and affiliations are:

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