

Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment

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ABSTRACT

Vasomotor rhinitis (VMR) is a common but poorly understood disorder of which there are two major subgroups: VMR^{w/t}, triggered by weather/temperature and VMR^{ir}, triggered by airborne irritants. No specific biological pathways or specific treatments for VMR^{w/t} or VMR^{ir} have been identified. However, intranasal corticosteroids (INSs) are effective in treating many forms of nonallergic rhinitis that include these conditions. A recently introduced INS with established efficacy in allergic rhinitis and enhanced affinity, fluticasone furoate, may possess the potency and safety profile required to treat chronic VMR^{w/t}. Two replicate studies (FFR30006 and FFR30007) were conducted in six countries to evaluate the efficacy and safety of fluticasone furoate nasal spray in subjects with VMR^{w/t}. After a 7- to 14-day screening period, subjects (n = 699) with symptomatic VMR^{w/t} received fluticasone furoate, 110 µg q.d. or placebo for 4 weeks in these two randomized, double-blind, parallel-group studies. Subjects rated their nasal symptoms (congestion, rhinorrhea, and postnasal drip) twice daily on a 4-point categorical scale and evaluated their overall response to treatment at study end. Fluticasone furoate did not significantly improve daily reflective total nasal symptom scores, the primary end point, versus placebo (p = 0.259) and there was no improvement in any other measure of efficacy. The active treatment was well tolerated. Fluticasone furoate was not effective in treating subjects with a newly defined condition, weather-sensitive VMR. These unexpected results suggest that VMR^{w/t} is a distinct subgroup of VMR that is refractory to treatment with INSs. Additional study of other treatments for VMR^{w/t} (including INSs) is warranted.

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The chronic provocateurs associated with vasomotor rhinitis (VMR) fit into two categories: (a) those associated with weather or change in weather (VMR^{w/t}), such as temperature, humidity, barometric pressure, and air movements; and (b) those associated with airborne irritants (VMR^{ir}), such as chemicals, glues, solvents, perfumes, offensive odors, pollution, and smoke. The pathophysiology of VMR is not well understood, and the biological pathways resulting in VMR^{w/t} and VMR^{ir} may be quite different. Hence, the two major VMR subtypes may benefit from completely different treatments. The Food and Drug Administration has recently asserted that weather/temperature triggers best define VMR rather than airborne irri-

itants.¹ Clearly, treatments shown to be specifically effective for VMR^{w/t} are needed.

The only medications that are currently approved to treat VMR are the intranasal antihistamine, azelastine, and the intranasal corticosteroid (INS), beclomethasone dipropionate. However, the two pivotal azelastine VMR studies enrolled subjects whose most commonly reported triggers were a mixture of weather/temperature and irritant factors, and the results did not differentiate between efficacy in VMR^{w/t} and that in VMR^{ir}.² INSs have been studied and used to treat more general nonallergic rhinitis conditions. Several clinical studies of INS treatment have indicated that budesonide,³ beclomethasone dipropionate,^{4,5} and fluticasone propionate^{5–7} are efficacious in treating perennial nonallergic rhinitis (PNAR), but these studies have included patients with a variety of perennial rhinitis types and a variety of INS doses and regimens, making it difficult to compare the results of these studies. Although these azelastine and INS studies have included patients with VMR^{w/t} and VMR^{ir}, we are unaware of any that have established efficacy specifically and separately for those two conditions.

A new enhanced-affinity INS treatment may meet the unmet need of specifically treating VMR^{w/t} and VMR^{ir}. Fluticasone furoate is a corticosteroid with en-

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hanced selectivity, retention, and affinity for the glucocorticoid receptor. The receptor affinity of fluticasone furoate is ~3.5 times that of budesonide, 1.7 times that of fluticasone propionate, and 1.3 times that of mometasone furoate; and fluticasone furoate displays pronounced retention and stability in human lung tissue.⁸ Rosenblut *et al.* reported an acceptable safety profile over 52 weeks of treatment with fluticasone furoate for perennial allergic rhinitis,⁹ perhaps because of its low systemic bioavailability (~0.50%).¹⁰ With its superior potency and proven efficacy in other rhinitis conditions,^{11–13} fluticasone furoate seemed a good choice for treating VMR^{w/t}, because VMR is a condition known to be more resistant to steroid treatment than eosinophilic conditions.^{14,15} The 1-year safety data also suggest that the drug could be administered long term for a chronic condition such as VMR^{w/t} with the expectation of acceptable tolerability.⁹

To evaluate the efficacy and safety of fluticasone furoate nasal spray in subjects with VMR^{w/t}, two global, multicenter, randomized, double-blind, placebo-controlled studies were conducted. Subjects with rhinitis principally caused by airborne irritant triggers (VMR^{ir}), allergic rhinitis, infectious disease, or nonallergic rhinitis with eosinophilic syndrome were excluded; and subjects were required to meet minimum symptom criteria and show persistence of their symptoms. To our knowledge, this is the first reported clinical trial of an intervention to treat this unique population of rhinitis sufferers. To simplify the presentation of data for the purposes of this report, the results of the two replicate studies were pooled. The pooled data did not differ in statistical outcomes or conclusions from the individual study results.

METHODS

Study Design

Two randomized, double-blind, placebo-controlled, parallel-group studies with an identical study design (FFR30006 and FFR30007) were conducted at a total of 106 investigative centers in six countries (United States, Canada, Czech Republic, Germany, Norway, and Romania) from July 2005 to January 2006. The protocols, amendments, and informed consents were approved by national, regional, or individual center ethics committees or institutional review boards. The studies were conducted in accordance with good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from each subject or the parent/guardian if the subject was <18 years old.

The studies included a 4-week treatment period with weekly clinic visits preceded by a 7- to 14-day non-treatment screening period. A follow-up telephone call was made 3–5 days after the subject's final visit.

Study Procedures

At visit 1 (screening visit), subjects completed a Vasomotor Rhinitis Questionnaire, which indicated the predominant trigger group (weather/temperature changes or inhaled/strong odors) that worsened their year-round rhinitis symptoms of nasal congestion, rhinorrhea, and/or postnasal drip. Subjects who identified weather/temperature changes as the predominant trigger also completed a Vasomotor Rhinitis Trigger Questionnaire that identified the individual weather and temperature change triggers that worsened their rhinitis. Subjects were excluded if their rhinitis symptoms were primarily triggered by airborne irritants such as tobacco smoke, chemicals, perfumes, or environmental pollution. Skin-prick testing for perennial and seasonal allergens and histamine, nasal cytology (Rhinoprobe, Arlington Scientific, Springfield, UT, or Cytobrush Plus, Medscand, Malmö, Sweden), and sinus radiography were also performed at visit 1. All slides with nasal cytology smears were sent to a central laboratory (Quest Diagnostics, Van Nuys, CA, or Heston, United Kingdom) for staining and interpretation.

During the screening and treatment period, subjects rated their nasal symptoms (congestion, rhinorrhea, and postnasal drip) twice daily on diary cards using a 4-point categorical scale ranging from 0 (symptom not present) to 3 (symptom hard to tolerate; interferes with daily activities or sleeping). Subjects recorded both *reflective* symptom ratings (severity over the last 12 hours) and *instantaneous* symptom ratings (severity at the moment of the assessment). At the final study visit (visit 6 or early withdrawal), subjects evaluated their overall response to therapy over the entire treatment period using a 7-point categorical scale.

Safety was assessed by monitoring vital signs and performing physical examinations, clinical laboratory tests, and 12-lead electrocardiograms (ECGs) at screening and the final study visit. Nasal examinations were performed at each visit. Adverse events (AEs) were monitored at each visit by spontaneous reporting, standard queries, and review of events recorded on the daily diary cards. A follow-up telephone call was made 3–5 days after the subject's last visit to assess post-treatment AEs.

Subjects

Male or female outpatients ≥12 years of age (United States and Romania) or ≥18 years of age (Canada, Czech Republic, Germany, and Norway) with a history of VMR were recruited. VMR eligibility requirements included a confirmed 2-year clinical history of perennial VMR, negative skin-prick tests, and no history of responses to seasonal or perennial allergens, a positive response to histamine skin testing, a normal sinus radiograph (to rule out infectious sinusitis), and negative

nasal cytology for eosinophils, defined as the absence of eosinophils in nasal smears. In addition, a diagnosis of the VMR^{w/t} subtype was required, which required confirmation of disease fluctuation with weather conditions by selection of weather/temperature change as the predominant trigger for worsened rhinitis on the Vasomotor Rhinitis Questionnaire.

Subjects were excluded if they had evidence of significant concurrent disease, a clinically significant abnormal ECG, severe physical obstruction or septal perforation of the nose, moderate-to-severe asthma, rhinitis medicamentosa, upper respiratory tract infection, ocular disease (glaucoma, cataracts, or herpes simplex), nasal or oropharyngeal candidiasis, history of adrenal insufficiency or shingles, or a risk of developing chickenpox or measles during the study. Subjects could not use tobacco products. Pregnant women or those planning to become pregnant were excluded.

To be randomized to treatment at visit 2, subjects were required to be symptomatic (defined as ≥ 4.5 points out of 9 maximum points) on the average of the last 8 recordings of reflective total nasal symptom scores (rTNSS; comprised of the sum of congestion, rhinorrhea, and postnasal drip scores), including the morning assessment on the morning of visit 2. In addition, the average reflective congestion symptom score over the same period was required to be ≥ 2 points out of 3 maximum points.

Treatment

At visit 2, eligible subjects were randomized (1:1) to treatment with fluticasone furoate nasal spray, 110 μg q.d., or placebo nasal spray. Subjects administered treatment on arising in the morning after their predose symptom assessment and recorded treatment administration on their daily diary cards.

Use of other medications that could affect VMR symptoms was prohibited during screening and the treatment period and for the following periods before screening: INs (4 weeks); inhaled or systemic corticosteroids or immunosuppressive medications (8 weeks); oral astemizole (12 weeks); other long-acting antihistamines (10 days); intranasal astemizole, intranasal, or ocular cromolyn (2 weeks); short-acting antihistamines, oral or intranasal decongestants, anticholinergics, or oral antileukotrienes (3 days); and subcutaneous omalizumab (5 months). Other medications that could affect VMR symptoms were also prohibited during the screening and treatment periods, including ocular antihistamines; eyedrops; eyewashes or nasal irrigation solutions; lubricants; throat treatments; immunotherapy; and chronic use of tricyclic antidepressants, long-acting β -agonists, and intranasal medications. Use of topical hydrocortisone ($\leq 1\%$) and short-acting β -agonists as needed was permitted.

Statistical Analysis

A sample size of 350 subjects in each study (175 in each treatment group) was calculated assuming an SD for a mean change from baseline over the entire treatment period in daily rTNSS of 1.7 based on previous VMR and PNAR clinical studies of INs and antihistamines.^{2,7} The sample size provided 90% power to detect a difference of 0.6 between active and placebo treatments using a two-sample *t*-test with a two-sided significance level of 0.05.

The primary efficacy end point was the mean change from baseline over the entire treatment period in daily rTNSS. Two key secondary end points were assessed: mean change from baseline over the entire treatment period in morning predose instantaneous TNSSs (iTNSSs) and the overall response to therapy on a 7-point categorical scale. Subjects were stratified at randomization by country to account for possible country-specific medical practice differences and effects on study outcome. All efficacy and safety analyses were performed using the intent-to-treat population, defined as all randomized subjects who received at least one dose of study drug. Demographic, efficacy, and safety data from the studies were pooled for the purposes of this report. Symptom scores of active and placebo treatment groups were compared using analysis of covariance with adjustments for baseline rTNSS, age, sex, study, and country. Overall response to therapy was analyzed with logistic regression, adjusting for age, sex, country, and study. Safety data were summarized by treatment group.

RESULTS

Study Population

A total of 1800 subjects were screened for entry into the studies, of which 61% were screening failures. The primary reasons for screening failure are described in Table 1; they included testing positive for nasal eosinophils and seasonal or perennial allergens. Thirty-three (2%) of the subjects were excluded because weather/temperature triggers were not predominant. Six hundred ninety-nine subjects were enrolled, with approximately equal numbers in each trial, and 94% of subjects completed the trials with similar numbers in the two treatment groups. Pooled patient demographics and baseline characteristics were similar between the active and placebo groups (Table 2). Most subjects were between 18 and 65 years of age, women, with between 3 and 5 weather/temperature triggers that worsened their VMR symptoms. The most commonly experienced triggers were temperature changes, cold days, humidity changes, and damp days. The baseline mean rTNSS scores were similar between treatments (6.4 for placebo and 6.5 for fluticasone furoate). Seventy-two percent of active-treated subjects and 65% of

Table 1 Subject disposition (*n* [%*])

	Study 1 FFR30006	Study 2 FFR30007	Total
Screened	901	899	1800
Screen failures	549 (61)	552 (61)	1101 (61)
Nasal eosinophil positive	214 (24)	155 (17)	369 (20)
Skin-test positive	102 (11)	167 (19)	269 (15)
Inadequate congestion score	69 (8)	71 (8)	140 (8)
Inadequate rTNSS score	68 (8)	65 (7)	133 (7)
Abnormal sinus radiograph	60 (7)	35 (4)	95 (5)
Enrolled	352	347	699
Fluticasone furoate nasal spray	179	174	353
Placebo nasal spray	173	173	346
Completed			
Fluticasone furoate nasal spray	167 (93)	165 (95)	332 (94)
Placebo nasal spray	160 (92)	168 (97)	328 (95)

*Percent of total screened.

rTNSS = reflective total nasal symptom score.

placebo-treated subjects were $\geq 90\%$ compliant with study medication use during the 4 weeks of treatment.

Efficacy

The primary end point, mean change from baseline in rTNSS over the entire treatment period, was not significantly different between active and placebo treatment groups (Table 3). Fluticasone furoate treatment improved rTNSS by 30% compared with 28% improvement with placebo. For the pooled results, the least square mean difference between active and placebo treatments was -0.140 ($p = 0.259$). For the individual studies, the least square mean difference was -0.335 ($p = 0.0504$) and 0.094 ($p = 0.604$), respectively. Figure 1 displays the change in rTNSS by study day and treatment. The key secondary end points, mean change from baseline in morning predose iTNSS over 4 weeks (Table 3), and overall evaluations of response to therapy assessed by subjects at the end of treatment (Table 4) did not show statistically significant differences between groups.

Safety

AE results are summarized in Table 5. The incidence of subjects who experienced any AE and the incidence of the most common AEs were similar between treatment groups. Drug-related AEs were rare, occurring in $\geq 1\%$ of either treatment group only for headache and epistaxis. No fatalities and only one serious AE (a non-drug-related occurrence of nephrotic syndrome in a subject receiving fluticasone furoate) occurred during either study. The incidence of subject withdrawal due to AEs was low (1% in each group).

The incidence of laboratory abnormalities was low and similar between treatment groups. Findings of the

nasal examinations were generally similar for the two treatment groups throughout the studies. All changes in vital signs were minor and similar between treatment groups. The proportion of subjects in each group with minor ECG findings at baseline or end point was low and similar between groups. One subject in the fluticasone furoate group had an abnormal clinically significant ECG finding of moderate intensity at week 4. It was reported as an AE but not drug related.

DISCUSSION

In these two randomized controlled studies, fluticasone furoate nasal spray was not effective in reducing the nasal symptoms of VMR^{w/t}, an unexpected result. None of the end points showed statistically significant efficacy in either study, including the primary end point of rTNSSs. Likewise, iTNSSs and individual symptom scores did not improve with fluticasone furoate treatment, and there was no difference between the active and placebo groups in subjects' overall evaluation of response to treatment.

These two trials enrolled subjects with a new and narrowly defined nonallergic rhinitis condition, VMR triggered primarily by weather and temperature conditions. They were carefully screened for VMR^{w/t}, with 41% excluded because they were skin-test positive to seasonal or perennial allergens, had nasal eosinophilia, or had an abnormal sinus radiograph, all of which suggested their rhinitis was caused by conditions other than VMR. Subjects whose rhinitis was primarily triggered by airborne irritants such as tobacco smoke, chemicals, perfumes, or environmental pollution were also excluded. Subjects enrolled in the trial had moderate-to-severe rhinitis symptoms and a long history of

Table 2 Subject demographics and baseline characteristics

	Fluticasone Furoate, 110 µg (n = 353)	Placebo (n = 346)	Total (n = 699)
Age (yr)			
Mean (SD)	45.2 (16.2)	44.5 (14.7)	44.9 (15.4)
Minimum-maximum	12–83	12–81	12–83
Age groups, n (%)			
12 to <18 yr	17 (5)	16 (5)	33 (5)
18 to <65 yr	290 (82)	299 (86)	589 (84)
65 to <75 yr	32 (9)	27 (8)	59 (8)
≥75 yr	14 (4)	4 (1)	18 (3)
Sex, n (%)			
Female	249 (71)	230 (66)	479 (69)
Male	104 (29)	116 (34)	220 (31)
Weather/temperature triggers, n (%)			
Temperature changes	272 (77)	266 (77)	538 (77)
Cold days	244 (69)	218 (63)	462 (66)
Humidity changes	227 (64)	226 (66)	453 (65)
Damp days	219 (62)	211 (61)	430 (62)
Windy days	193 (55)	174 (50)	367 (53)
Weather fronts	147 (42)	173 (50)	320 (46)
Change in barometric pressure	148 (42)	146 (42)	294 (42)
Hot summer days	147 (42)	115 (33)	262 (38)
Number of triggers, n (%)			
1–2	42 (12)	39 (11)	81 (12)
3–5	211 (60)	214 (62)	425 (61)
6–8	100 (28)	92 (27)	192 (28)
Duration of VMR, n (%)			
2 to <5 yr	78 (22)	95 (28)	173 (25)
5 to <10 yr	79 (22)	76 (22)	155 (22)
≥10 yr	196 (56)	174 (50)	370 (53)
Baseline symptom scores, mean (SD)			
Daily reflective total (rTNSS)	6.5 (1.2)	6.4 (1.2)	6.5 (1.2)
Morning instantaneous total (iTNSS)	6.5 (1.4)	6.5 (1.5)	6.5 (1.4)
Daily reflective congestion	2.4 (0.4)	2.4 (0.4)	2.4 (0.4)
Daily reflective rhinorrhea	2.0 (0.7)	1.9 (0.7)	2.0 (0.7)
Daily reflective postnasal drip	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)

rTNSS = reflective total nasal symptom score; iTNSS = instantaneous total nasal symptom score; VMR = vasomotor rhinitis.

Table 3 Mean change in nasal symptom scores over treatment period (weeks 1–4)

	Fluticasone Furoate, 110 µg (n = 353)	Placebo (n = 346)	p-Value
Change in symptom scores, mean (SD)			
Daily reflective total (rTNSS)	−2.00 (0.12)	−1.86 (0.12)	0.259
Morning instantaneous total (iTNSS)	−1.69 (0.12)	−1.50 (0.12)	0.138
Daily reflective congestion	−0.77 (0.04)	−0.71 (0.04)	0.208
Daily reflective rhinorrhea	−0.64 (0.04)	−0.58 (0.04)	0.258
Daily reflective postnasal drip	−0.59 (0.04)	−0.56 (0.04)	0.555

rTNSS = reflective total nasal symptom score; iTNSS = instantaneous total nasal symptom score.

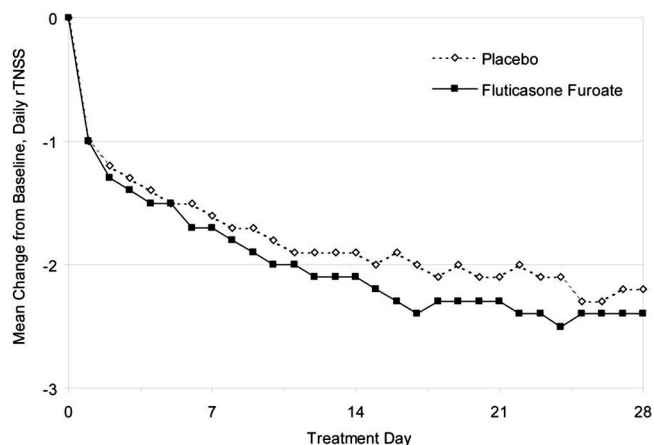


Figure 1. Mean change from baseline in daily reflective total nasal symptom scores over 28 days of treatment with fluticasone furoate nasal spray or placebo nasal spray.

the disorder. The results of these studies lead us to hypothesize that VMR^{w/t} is a condition not responsive to INS treatment, because fluticasone furoate is the most potent INS currently available and has been shown to be effective in allergic rhinitis. Our results do not rule out the possibility that VMR^{w/t} could be effectively treated by other non-INS therapies or combinations of therapies, because treatment combinations are frequently used for VMR in clinical practice.¹⁴ Our results do not rule out the possibility that fluticasone furoate can be efficacious in treating VMR^{ir}.

These results can not be compared easily with those reported previously for INS treatment because of the differences in patient populations. Webb *et al.* reported integrated data from 983 subjects in three randomized controlled trials showing that fluticasone propionate provided significant relief of nasal symptoms in PNAR subjects both with and without nasal eosinophilia and at both doses studied (fluticasone propionate, 200 and 400 μ g daily)⁷; however, the subjects in the fluticasone propionate studies had almost equivalent responsiveness to weather/temperature and airborne irritant triggers (GlaxoSmithKline, unpublished data). Earlier studies of INS treatments for PNAR, including beclomethasone dipropionate,^{4,5} budesonide,³ and fluticasone propionate,^{6,16} showed efficacy, but the study populations contained other patient types in addition to those suffering from VMR^{w/t}. The efficacy of INS observed in these studies is probably because of the efficacy on patients with the VMR^{ir} subtype or other PNAR categories. On the other hand, mometasone, 200 μ g q.d., was not significantly more effective than placebo in improving PNAR subjects' overall evaluation of rhinitis symptoms.¹⁷

Our results do concur with those of Blom *et al.* who reported that PNAR patients responded to fluticasone propionate with reduced local nasal eosinophilia but

not improved symptoms.¹⁸ The results of Blom *et al.* support the hypothesis that local inflammation and nasal IgE production may be responsible for the symptoms in some patients with VMR.¹⁹ Other theories explaining the VMR response include neurogenic explanations that postulate excessive parasympathetic and/or reduced sympathetic activity,^{20,21} nitric oxide production,^{22,23} polymorphisms in odorant receptor genes,²⁴ glandular or vascular hyperreactivity,²⁵ and increased responsiveness or hyperreactivity to stimuli, including histamine, methacholine, and other agents.²⁶ VMR caused by irritant triggers has been more widely studied than that caused by weather/temperature conditions. Occupational and nonoccupational environmental irritants that trigger chronic rhinitis include ambient air pollutants, building materials such as aldehydes, cleaning products such as ammonia, and environmental tobacco smoke, as has been shown in several controlled laboratory experiments with rhinitis and other volunteers.²⁷ Studies of VMR^{w/t}, on the other hand, are fairly limited. One experiment using a hyperbaric chamber showed that peak inspiratory flow increases with decreasing barometric pressure.²⁸ Braat *et al.* showed that nasal symptoms in nonallergic rhinitis patients correlated with daily measurements of temperature, humidity, and air pollutant levels in The Hague, Netherlands, from March to October 1994.²⁹

There is no indication that the ineffectiveness of fluticasone furoate in the current study was related to dose selection, frequency, or study duration. However, we can not rule out that possibility without further study. In clinical practice, it is not uncommon to increase the dose and frequency in nonresponsive patients. Fluticasone furoate has significantly higher potency than INS previously selected for nonallergic studies, and the dose used, 110 μ g q.d., was established in a dose-ranging study as the optimal dose for all symptom measures of seasonal allergic rhinitis.¹² Webb *et al.* reported almost equivalent efficacy with 200 or 400 μ g daily fluticasone propionate in treating nonallergic rhinitis,⁷ results consistent with the lack of a dose response and plateau effect with INS in rhinitis.³⁰ Because fluticasone furoate has shown clinical evidence of effectiveness within 8 hours in allergic rhinitis,³¹ it is doubtful that 4 weeks would be insufficient to show efficacy in VMR.

Our studies had several limitations. The inability to standardize and control environmental conditions across multiple U.S. and non-U.S. sites during the studies was an obvious limitation to characterizing the effects of fluticasone furoate in VMR^{w/t}. Patient selection and screening methods may also have been a limitation. Cold dry air challenge may have been a helpful screening tool to confirm self-reports of those subjects sensitive to weather/temperature triggers; however, it remains to be established that cold dry air response is a biomarker for VMR^{w/t}. Also, some of these subjects may have had

Table 4 Overall evaluation of response to therapy (n [%])

	Fluticasone Furoate, 110 µg (n = 353)	Placebo (n = 346)
Responses	348	341
Significantly improved	61 (18)	46 (13)
Moderately improved	81 (23)	76 (22)
Mildly improved	90 (26)	87 (26)
No change	101 (29)	116 (34)
Mildly worse	7 (2)	4 (1)
Moderately worse	4 (1)	6 (2)
Significantly worse	4 (1)	6 (2)
p-value for treatment difference	0.099	

Table 5 Most common AEs* (n [%])

	Fluticasone Furoate, 110 µg (n = 353)	Placebo (n = 346)
Any AE	127 (36)	129 (37)
Headache	26 (7)	39 (11)
Nasopharyngitis	19 (5)	18 (5)
Epistaxis	16 (5)	9 (3)
Pharyngolaryngeal pain	9 (3)	6 (2)
Diarrhea	9 (3)	0
Sinus headache	5 (1)	4 (1)
Nausea	5 (1)	2 (<1)
Back pain	4 (1)	6 (2)
Dysphonia	4 (1)	1 (<1)
Vomiting	4 (1)	1 (<1)

*Any AE occurring at an incidence of 1% or greater in the active treatment group.

AE = adverse event.

inferior turbinate hypertrophy unresponsive to medication; study inclusion based on reversibility to a vasoactive nasal decongestant, implying the need for surgical rather than medical intervention,^{32,33} would have eliminated such inappropriate subjects.

VMR is a widespread condition, although the lack of agreed positive diagnostic criteria results in misdiagnosis, inappropriate treatment, and poor clinical outcomes. Estimates suggest that over 20 million Americans suffer from PNAR, with another 26–40 million Americans suffering from mixed rhinitis (seasonal allergic rhinitis or perennial allergic rhinitis with exacerbations from nonallergic triggers).¹⁴ Nonallergic rhinitis is a condition with problematic symptoms and reduced quality of life.^{34,35} Misdiagnosis and inadequate treatment raise health care costs and reduce productivity,³⁶ and there is evidence that VMR, like AR, is a risk factor for the development of asthma.³⁷ Other health consequences of VMR include sleep disorders,³⁸ olfactory disorders,^{39,40} and vocal cord dysfunction.⁴¹ Further exploration of potential treatments for both VMR^{w/t} and VMR^{ir} is needed to maximize pos-

sible benefits to patients with the condition, as is clearer explication of the differences in diagnosis, pathophysiology, and, hence, treatment for VMR^{w/t} versus VMR^{ir}.

In summary, we conducted the first studies of INS treatment in a subtype of VMR that is responsive primarily to weather/temperature conditions and found that fluticasone furoate treatment was not effective in treating subjects with this condition. Although fluticasone furoate is effective in the treatment of allergic rhinitis, its failure to show efficacy in VMR^{w/t} may reflect a distinct subgroup of VMR that is refractory to INS treatment. Additional studies are warranted to identify whether other treatments or treatment combinations would improve VMR^{w/t} symptoms and to evaluate the effectiveness of INS, including fluticasone furoate, in patients with the other VMR subtype, VMR^{ir}.

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