

A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray

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Background: Topical nasal corticosteroids have become a mainstay of treatment for the symptoms of seasonal allergic rhinitis (SAR). It is likely that topical corticosteroids, by blocking an initial influx of inflammatory cells in the nasal mucosa induced by aeroallergens, may have a preventive effect on nasal allergy symptoms when administered before the pollen season.

Objective: This study was designed to assess the efficacy and safety of an 8-week course of mometasone furoate nasal spray (MFNS), 200 µg once daily, in the treatment of SAR compared with beclomethasone dipropionate aqueous nasal spray (BDP), 168 µg twice daily, and placebo vehicle, when treatment is initiated before the anticipated onset of the ragweed season.

Methods: Three hundred forty-nine patients with SAR to ragweed pollen from nine centers in the Northeast and Midwest of the United States were randomized to one of the three intranasal study medications (MFNS, 200 µg once daily, BDP, 168 µg twice daily, or placebo vehicle), starting 4 weeks before the estimated start of the ragweed season.

Results: The proportion of "minimal symptom" days (total nasal symptom score ≤ 2) was statistically significantly higher in both the MFNS and BDP groups when compared with the placebo vehicle group ($p < 0.01$). The two active treatment groups were not statistically significantly different from each other. MFNS and BDP displayed a similar safety profile that did not differ from placebo.

Conclusions: This suggests that MFNS, 200 µg (once daily), is a useful therapy in the prophylactic treatment of SAR. (*J Allergy Clin Immunol* 1996;98:724-31.)

Key words: Mometasone furoate, seasonal allergic rhinitis, ragweed, prophylaxis, intranasal corticosteroids

Seasonal allergic rhinitis (SAR), characterized by clear nasal discharge, nasal congestion, nasal itching, and sneezing is a common disease.¹ The pharmacotherapy of allergic rhinitis has advanced

in recent years² with the development of intranasal corticosteroids with high topical potency and minimal adverse effects.³⁻⁶

It has been proposed that low pollen counts

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Abbreviations used

BDP:	Beclomethasone dipropionate
MFNS:	Mometasone furoate nasal spray
SAR:	Seasonal allergic rhinitis

probably induce an initial accumulation of inflammatory cells in the nasal mucosa,^{7,8} and possibly their priming through the action of cytokines,⁹⁻¹³ without producing noticeably significant symptoms. Clinically significant symptoms will be noticed only during the ensuing pollen season, when an influx of inflammatory cells, including eosinophils and metachromatic cells, is observed in the nasal mucosa; this may be blocked by topical corticosteroids.¹⁴⁻¹⁶ A similar inhibitory effect of topical corticosteroids is also observed during nasal challenge with pollen allergens.^{6, 17-19} Therefore it is likely that topical nasal corticosteroids may have a preventive effect on nasal symptoms when administered before the start of the pollen season.

Mometasone furoate, a corticosteroid currently available in a topical dermatologic formulation (Elocon), is associated with a low incidence of systemic side effects.²⁰ An aqueous nasal spray formulation of mometasone has been developed for use in the treatment of allergic rhinitis. Previous studies have shown it to be effective, safe, and well-tolerated for relieving moderate to severe symptoms of allergic rhinitis when administered once daily in the morning.²¹

This placebo- and active-controlled study was designed to determine the efficacy and safety of mometasone furoate aqueous nasal spray (MFNS) versus beclomethasone dipropionate aqueous nasal spray (BDP) and placebo vehicle nasal spray in the treatment of patients with SAR when treatment is begun before the onset of the ragweed season.

METHODS

Nine U.S. centers participated in this double-blind, randomized, parallel-group comparison of the efficacy and safety of MFNS, 200 µg once daily, versus BDP, 168 µg twice daily, versus placebo vehicle in the prophylactic treatment of patients with SAR. Each patient (and parent or guardian if applicable) provided written informed consent, and the study and statements of informed consent were approved by a central institutional review board (Western Institutional Review Board, Seattle, Wash.) and local institutional review boards when required. The study was carried out in the fall allergy season of 1994.

Patients enrolled in this study were at least 12 years of

TABLE I. Four-point scale used to evaluate the severity of each nasal and nonnasal symptom of SAR*

Score	Description
0 None	No signs or symptoms evident
1 Mild	Sign or symptom clearly present but minimal awareness; easily tolerated
2 Moderate	Definite awareness of sign or symptom, which is bothersome but tolerable
3 Severe	Sign or symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping

*Nasal symptoms were rhinorrhea, stuffiness/congestion, nasal itching, sneezing. Nonnasal symptoms were itching/burning eyes, tearing/watering eyes, redness of eyes, itching of ears or palate.

age, of either gender and any race, and had at least a 2-year history of moderate to severe SAR and a positive skin (prick or intradermal) test response to ragweed. Women of nonchildbearing potential, as well as women of childbearing potential using a medically acceptable, adequate form of birth control (no premenarchal girls) were included.

Nasal and nonnasal symptoms were evaluated on a 4-point scale from 0 to 3 (Table I). Four nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) were scored. Total nasal symptom score was calculated as the sums of these, so that it could range from 0 to 12. Four nonnasal symptoms (eye itching/burning, eye tearing/watering, eye redness, itching of ears/or palate) were scored. Total symptom score was defined as the combined total score for the four nasal and four nonnasal symptoms. Patients were required to be clinically free of symptoms at the screening and baseline visits.

To qualify for randomization into the double-blind treatment period, patients were required to have, at most, a mild severity score (≤ 1) for any individual nasal or nonnasal symptom and a total nasal symptom score of 2 or lower at both screening and baseline visits.

Patients were excluded from the study if they were pregnant or breast feeding; receiving immunotherapy (unless receiving a stable dose for at least 2 years with at least moderate symptoms during the last ragweed season); had asthma requiring therapy with inhaled or systemic corticosteroids; were dependent on nasal, oral, or ocular decongestants or antiinflammatory agents; or had rhinitis medicamentosa. Other exclusion criteria were multiple drug allergies; a significant medical condition and/or long-term use of medication that might interfere with the study; clinically relevant abnormal laboratory values, vital signs, or electrocardiogram results; and use of any investigational drug within the previous 30 days.

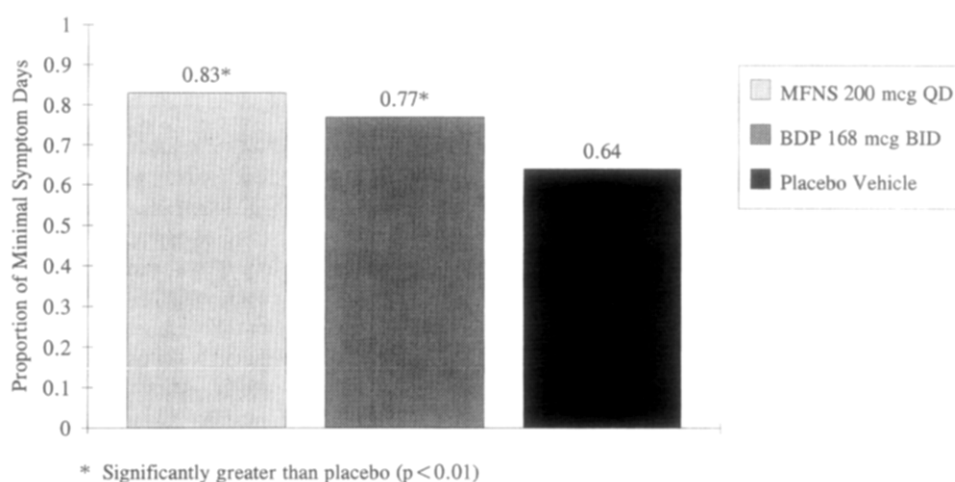


FIG. 1. Proportion of minimal symptom days from start of ragweed season. *QD*, Once daily; *BID*, twice daily.

TABLE II. Demographic data (efficacy population)

	Treatment group		
	MFNS (200 µg QD)	BDP (168 µg BID)	Placebo vehicle control
Number of patients	114	112	104
Age (yr)			
Mean	36	34	34
Range	12-69	12-60	13-62
Gender (<i>n</i>)			
Female	61	49	46
Male	53	63	58
Race (<i>n</i>)			
Caucasian	111	105	94
Black	2	3	6
Other	1	4	4
Body weight (lb)			
Mean	168	165	176
Range	85-350	98-272	109-296
Disease duration (yr)			
Mean	19	19	19
Range	2-62	2-51	2-50

QD, Once daily; *BID*, twice daily.

Before the start of the study, patients were required to have stopped using nasal, oral, or ocular decongestants for 24 hours; oral antihistamines for a variable time depending on the duration of action (short-acting, 12 hours; long-acting, 48 to 96 hours; astemizole, 3 months); systemic corticosteroids for 1 month (intramuscular or intraarticular for 3 months); and nasal or ocular corticosteroid medications or cromolyn for 2 weeks. Use of these drugs was not allowed during the study.

At the screening visit (up to 14 days before the baseline visit), medical history was assessed and a physical examination (including nasal examination) and laboratory tests (complete blood count, blood chemistries, and complete urinalysis) were performed. Patients were given daily symptom diaries and instructed to record their individual symptoms twice daily (each morning and evening) before dosing for the duration of the study by using the scoring scale shown in Table I. To minimize variation, all patients at each individual site were enrolled within 5 days, approximately 4 weeks before the estimated onset of the ragweed season for each particular site, and then allocated to one of three double-blind study treatments by a computer-generated random code: MFNS, 200 µg once daily, BDP 168 µg twice daily, or placebo vehicle for 8 weeks. All treatments were administered as two sprays per nostril in the morning and two sprays per nostril in the evening. The MFNS group therefore received placebo vehicle in the evening.

Efficacy and safety were assessed at screening and baseline visits (day 1) and on days 8, 22, 29, 36, 50, and 57 (final visit). Phone contacts with the patients to assess compliance with study medication use took place on days 15 and 43. Pollen counts were collected at each study center throughout the study, beginning at the time of the screening visit. The start of the season was represented by the appearance of "clinically relevant ragweed pollen counts," that is, on the basis of the observed ragweed pollen counts, supported by symptoms in comparable patients, within the investigators' and colleagues' practices.

At each visit each patient's diary was reviewed, compliance and adverse events were discussed, rhinitis signs and symptoms were assessed, and the physician evaluated the severity of each nasal and nonnasal symptom by using a 4-point scale (Table I).

The physician and the patient each filled out a global evaluation of response to treatment at each visit after

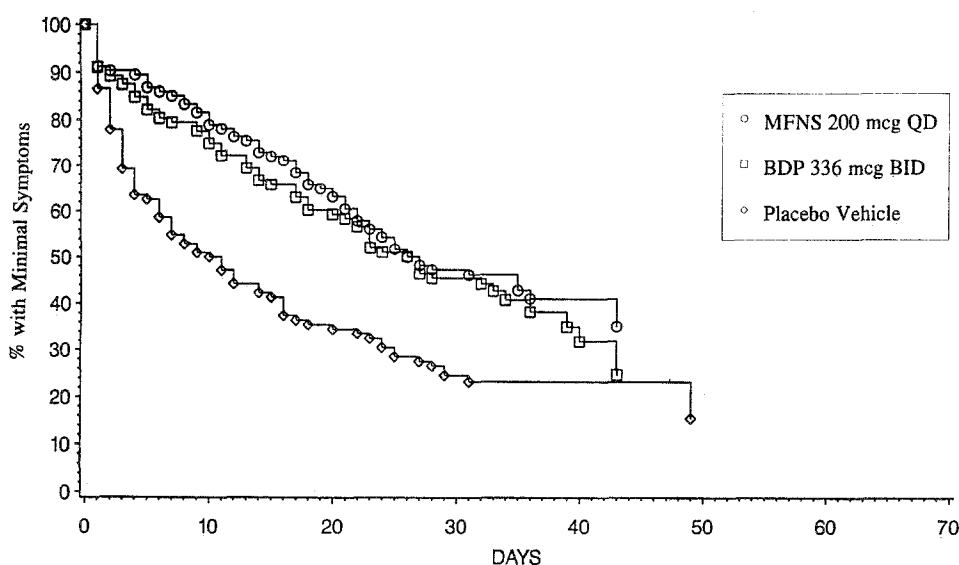


FIG. 2. Number of days from start of ragweed season to first occurrence of a nonminimal symptom day. QD, Once daily; BID, twice daily.

TABLE III. Mean total nasal symptom scores from patient diaries (efficacy population): Averaged morning and evening scores

	Treatment group					
	MFNS (200 µg QD)		BDP (168 µg BID)		Placebo vehicle control	
	n	Mean	n	Mean	n	Mean
Baseline	114	0.3	111	0.4	104	0.4
Preseason interval (baseline to start of season)	114	0.4*	111	0.6	104	0.7
Days 1 to 15 (after onset of season)	114	0.7†	111	1.0†	104	1.8
Days 16 to 30 (after onset of season)	114	1.1†	106	1.5†	101	2.4

QD, Once daily; BID, twice daily.

* $p = 0.05$ versus BDP; $p = 0.01$ versus placebo vehicle.

† $p < 0.01$ versus placebo vehicle.

baseline, using a 5-point scale (1 = complete relief, 2 = marked relief, 3 = moderate relief, 4 = slight relief, 5 = treatment failure).

Adverse events were recorded throughout the study. The severity of each adverse event was graded as mild, moderate, or severe; and a relationship to treatment was assigned. At all visits blood pressure, pulse, and body temperature were measured; and a nasal examination was performed. Spray bottles were examined to confirm use. Laboratory evaluations (hematology, blood chemistry, urinalysis), a 12-lead electrocardiogram, and a physical examination were carried out at the screening visit and repeated at the final visit.

Statistical analysis

The study was designed to have an alpha level of 5% and at least a 90% power to detect differences of approximately 15% or greater (considered clinically

significant) on proportion of "minimal symptom" days, assuming a pooled standard deviation of 35%. The observed difference was 19% and was statistically significant.

The primary efficacy variable was the proportion of minimal symptom days (days when the total nasal symptom score was 2 or lower) from the start of the ragweed season to study completion. Secondary parameters included: (1) the proportion of minimal symptom days from start of treatment to study completion, (2) the number of days from the start of the ragweed season to first occurrence of a day on which the total nasal symptom score was 3 or higher, (3) the number of days from the start of treatment to first occurrence of a day on which the total nasal symptom score was 3 or higher.

The primary comparison was between MFNS and placebo. Other pairwise comparisons were considered secondary.

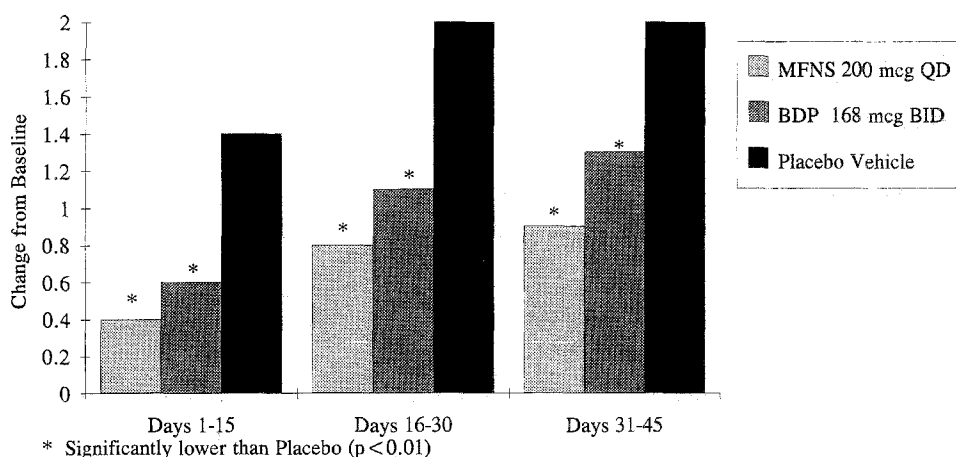


FIG. 3. Average change in patient diary morning and evening nasal symptom scores from start of ragweed season. QD, Once daily; BID, twice daily.

RESULTS

Patient population

Three hundred forty-nine patients from nine centers across the United States were randomized to treatment with one of the three study medications: MFNS, 200 μ g once daily; BDP, 168 μ g twice daily; or placebo. Patients entered the study an average of 23 ± 4 days (range, 12 to 30 days) before onset of the ragweed season. Two patients were excluded from all analyses because they dropped out immediately after randomization and had no follow-up data (efficacy or safety); therefore, the intent-to-treat (or safety) population consisted of 347 patients (116 patients each were treated with MFNS or BDP and 115 received placebo).

On the basis of patient eligibility and visit validity criteria, data from 17 patients were invalidated for a number of reasons (e.g., failure to meet entrance criteria, unacceptable baseline severity, noncompliance with dosing regimen, and/or lack of any valid follow-up visits), leaving a total of 330 patients (114 receiving MFNS, 112 receiving BDP, and 104 receiving placebo vehicle) in the efficacy population.

Overall, the treatment groups were comparable with respect to demographic characteristics (Table II) and baseline severity of signs and symptoms (Table III).

Efficacy analysis

The primary efficacy analysis was based on diary data from a total of 330 patients (efficacy population). For the primary efficacy variable (the average proportion of days with morning and evening

averaged total nasal symptom score ≤ 2), both MFNS and BDP groups demonstrated a significantly higher proportion of minimal symptom days compared with the placebo group ($p \leq 0.01$) during the ragweed season (Fig. 1). It appears that there is a trend in the data gathered, indicating that MFNS may be superior to BDP in increasing the proportion of minimal symptom days, but this trend did not reach statistical significance ($p = 0.08$). The intent-to-treat population on the same variable showed similar results. A secondary analysis performed on the proportion of minimal symptom days (total nasal symptom score ≤ 2) from the start of treatment to study completion also showed a significantly higher proportion of minimal symptom days for both MFNS and BDP groups compared with the placebo group ($p < 0.01$).

The survival analysis technique (log-rank test), which was used on secondary parameters, showed that during the ragweed season, a significant difference ($p < 0.01$) was observed among the three treatment groups in terms of the number of days to the first occurrence of a "nonminimal symptom" day. The MFNS and BDP groups demonstrated a distinct pattern of longer duration to the first occurrence of a nonminimal symptom day (diary morning and evening total nasal symptom score ≥ 3) than the placebo group (Fig. 2), with a median duration of 27 days to first nonminimal symptom day for patients in the MFNS and BDP groups compared with 10.5 days for patients in the placebo vehicle group. Similarly, the survival analysis on number of days to first occurrence of a nonminimal symptom day (diary morning and evening total nasal symptom score ≥ 3) from start of treat-

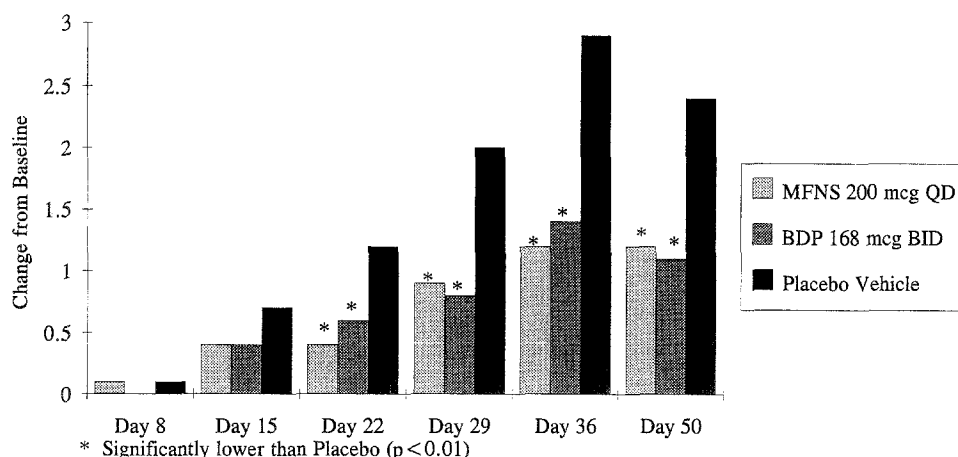


FIG. 4. Nasal symptom score change from baseline done by investigator at each visit. QD, Once daily; BID, twice daily.

TABLE IV. Number and percent of patients who discontinued treatment (enrolled population)

Reason for discontinuation	Treatment group		
	MFNS (200 μ g QD) (n = 117)	BDP (166 μ g BID) (n = 116)	Placebo vehicle control (n = 116)
Treatment failure	2 (1.7%)	1 (0.9%)	8 (7.0%)
Adverse event	1 (0.8%)	5 (4.3%)	4 (3.4%)
Patient did not wish to continue/lost to follow-up	1 (0.8%)	3 (2.6%)	4 (3.4%)
Noncompliance	—	4 (3.4%)	1 (0.9%)
Did not meet entry criteria	1 (0.8%)	—	2 (1.7%)
Total	5 (4.1%)	13 (11.2%)	19 (16.4%)

QD, Once daily; BID, twice daily.

ment showed a significantly longer duration for MFNS (51.5 days) and BDP (50 days) compared with placebo (34 days) ($p < 0.01$).

Total nasal symptom scores based on diary data were significantly lower in both active groups than in the placebo group (two-way analysis of variance, $p < 0.01$) (Fig. 3). Similar results were obtained for total nasal symptom scores on the basis of the physician's visit data (Fig. 4).

Safety evaluation

Safety data collected during the study indicated that mometasone was well tolerated. Ten patients discontinued the study because of adverse events: one patient in the MFNS group, five in the BDP group, and four in the placebo vehicle group (Table IV). Sixty-three percent of patients in the MFNS group, 51% of those in the BDP group, and 52% of those in the placebo group reported at least one adverse event (with-

out regard to relationship to treatment). The most common adverse event, headache, was reported by 36% of patients receiving MFNS, 22% of patients receiving BDP, and 23% of patients receiving placebo (Table V).

Most of the adverse events were mild to moderate and of short duration. Adverse events considered at least possibly related to treatment were reported by 16% of patients in the MFNS group, 14% in the BDP group, and 19% in the placebo vehicle group; in this category also headache was the most frequent adverse event (7% in MFNS group, 3% in BDP group, and 6% in placebo group).

The only group that showed severe related adverse events was the placebo vehicle group (3%, two patients with headache and one with epistaxis). There were no clinically relevant changes in vital signs, electrocardiograms, or laboratory test results in any of the treatment groups.

TABLE V. Adverse events regardless of relationship to treatment reported during the study by 5% or more patients in any treatment group (safety population)

	Treatment group		
	MFNS (200 µg QD) (n = 116)	BDP (168 µg BID) (n = 116)	Placebo vehicle control (n = 115)
Any adverse event	73 (63%)	59 (51%)	60 (52%)
Headache	42 (36%)	25 (22%)	27 (23%)
Pharyngitis	7 (6%)	12 (10%)	6 (5%)
Upper respiratory tract infection	7 (6%)	3 (3%)	1 (<1%)
Dysmenorrhea*	4 (6%)	—	4 (8%)

QD, Once daily; BID, twice daily.

*Percents calculated based on total female population.

DISCUSSION

This study evaluated a new nasal corticosteroid, MFNS, with respect to its prophylactic effect in fall SAR. The study demonstrated that MFNS, administered once daily in the morning about 4 weeks before the onset of the ragweed season, is effective in the prophylactic treatment of SAR. Patients started treatment an average of 23 ± 4 days before onset of the ragweed (range, 12 to 30 days).

Studies comparing BDP once daily versus twice daily dosing showed both regimens to be well tolerated and of equivalent efficacy.²²⁻²⁴ However, in this study BDP was used as labeled, in a twice daily regimen.

Two small studies in patients with asthma receiving inhaled BDP, measuring daily compliance accurately by using a new computerized technology, showed a better compliance for the early morning dose relative to the other doses.^{25, 26} MFNS offers the benefit of once daily dosing in the morning, which may enhance patient compliance through simplification of dosage regimen.

Results from the primary efficacy analysis showed that the proportion of minimal symptom days during the ragweed season was statistically significantly higher in both active groups (MFNS and BDP) when compared with the placebo group ($p < 0.01$). It appears that there is a trend in the data gathered, indicating that MFNS may be superior to BDP in increasing the proportion of minimal symptom days, but this trend did not reach statistical significance ($p = 0.08$). All secondary

analyses confirmed these results. The median time to the first appearance of symptomatic days (i.e., total nasal symptoms score ≥ 3) for the MFNS and BDP groups was statistically significantly longer than that for the placebo group. The averaged diary scores for the treatment period before the season onset were significantly lower for the patients in the MFNS group as compared with those in the BDP group ($p = 0.05$) and the placebo vehicle group ($p = 0.01$). The physicians' ratings showed comparable results.

MFNS in doses of 200 µg once daily was well tolerated in this study. The incidence and type of adverse events reported was similar to that observed in patients who received BDP or placebo vehicle. Most observed adverse events were transient, and their severity was mild to moderate. Less than 3% of patients discontinued treatment because of adverse events (MFNS, 0.8%; BDP, 4.3%; placebo vehicle, 3.4%). Local adverse events, such as nasal burning and epistaxis, often associated with the administration of nasal sprays, were not predominant in any treatment group in this study.

Whether the benefit provided by preseasonal treatment justifies the extra cost must be determined on an individual basis.

We conclude that MFNS, 200 µg once daily, should be a useful and well-tolerated prophylactic therapy for SAR.

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