Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis

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ABSTRACT

The combination of intranasal antihistamines and intranasal corticosteroids results in superior relief of seasonal allergic rhinitis (SAR) symptoms compared with monotherapy. This study was designed to evaluate the safety and efficacy of olopatadine hydrochloride nasal spray, 0.6% (OLO), administered in combination with fluticasone nasal spray, 50 micrograms (FNS), relative to azelastine nasal spray, 0.1% (AZE), administered in combination with FNS in the treatment of SAR. This was a multicenter, double-blind, randomized, parallel-group comparison of OLO + FNS versus AZE + FNS administered for 14 days to patients ≥12 years of age with histories of SAR. Efficacy assessments recorded by patients in a daily diary included nasal symptom scores. Safety was evaluated based on adverse events (AEs). Pretreatment values for reflective total nasal symptoms scores (rTNSS) were similar for both treatment groups. The mean (SD) 2-week average rTNSS was 4.28 (2.63) for OLO + FNS and 4.15 (2.63) for AZE + FNS; these scores were not statistically different between treatment groups. No significant differences ($p > 0.05$) between OLO + FNS and AZE + FNS were observed for the average 2-week percent changes from baseline in rTNSS or in the individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing). Compared with baseline, both groups had statistically significant improvement in rTNSS ($p < 0.05$). No serious AEs were reported in either group during the study period. Overall, 19 AEs were reported in the OLO + FNS group and 29 AEs were reported in the AZE + FNS group. OLO, when administered adjunctively with FNS, is effective, safe, and well-tolerated in patients with SAR.

(Allergy Asthma Proc 31:132–140, 2010; doi: 10.2500/aap.2010.31.3326)

Key words: Allergic rhinitis, antihistamine, azelastine, corticosteroid, efficacy, fluticasone, nasal spray, olopatadine, safety

Allergic rhinitis is a chronic, allergen-induced inflammatory reaction of the nasal mucous membranes. This condition afflicts 30–60 million individuals in the United States each year, with a global prevalence estimated to be between 9 and 42%.[1,2] Allergic rhinitis may occur both seasonally and perennially. Perennial allergic rhinitis symptoms are usually caused by exposure to indoor allergens such as house-dust mites, animal dander, and cockroach allergens. Perennial symptoms in the absence of allergy to indoor allergens may occur in geographic areas where winters are mild and pollination occurs throughout the year.[1] Seasonal allergic rhinitis (SAR), on the other hand, is an allergen-induced inflammatory reaction that occurs during periods of substantial pollen.[1,3] Regardless of whether the allergic reaction is seasonal or perennial, on exposure to a specific antigen, allergic patients experience a hypersensitivity response that may manifest itself over a period ranging from minutes to days.[4] The symptoms of allergic rhinitis vary from occasional sneezing to significant responses such as severe nasal congestion, constant sneezing and rhinorrhea, persistent ocular itching and watering, paranasal pressure, and fatigue.[4]

The primary goal of all allergic rhinitis treatments is to prevent or relieve allergic signs and symptoms. Thus, treatment generally begins with allergen avoidance. If that fails, medicinal approaches, including oral antihistamines, intranasal antihistamines, and/or intranasal corticosteroids are commonly used.[5] Among prescription therapies, systemic antihistamines often are not preferred by patients because they do not provide the targeted relief of symptoms that generally are reported for nasal sprays.[6] Thus, intranasal therapies

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Alcon Research, Ltd., funded the study, developed its design, selected the investigators, collected the data, and conducted the statistical analyses

W. Carr, B. Chipps, C. LaForce, and W. Storms are consultants and speakers for Alcon. W. Carr, E. Meltzer, and W. Storms have received grant/research support from Alcon. M. Edwards is an Alcon employee and stockholder

An Institutional Review Board reviewed and approved the protocol and associated informed consent/assent form used in the study presented here

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may offer greater potential for the treatment of allergic rhinitis.

Olopatadine is both a selective antihistamine, capable of antagonizing histamine at the end organ, and an inhibitor of the release of histamine and other proinflammatory mediators from human mast cells.[7,8] Although olopatadine has a high affinity and selectivity for the histamine H_1-receptor, it is receptor specific and has no effect on α-adrenergic receptors.[9–11] A formulation of olopatadine, in which the active ingredient is present at a concentration of 0.6%, has been developed for nasal administration in the treatment of allergic rhinitis. Results from clinical studies with olopatadine HCl nasal spray, 0.6% (OLO), (Patanase; Alcon Laboratories, Fort Worth, TX) showed the efficacy of OLO in the treatment of total nasal symptom scores (TNSSs) in patients with SAR.[12–14] OLO further has been shown to have a fast onset and is effective within 30 minutes of administration.[15,16]

Azelastine HCl nasal spray 0.1% (AZE; (Astelin; Meda Pharmaceuticals, Somerset, NJ) is also an intranasal antihistamine spray that has been reported to be effective in the treatment of both allergic and nonallergic rhinitis, provides relatively fast relief from nasal symptoms,[17] and has a favorable efficacy profile when compared with orally administered antihistamines.[18,19] A recently published study found reductions from baseline in TNSS to be similar after treatment with OLO and with AZE.[20]

Fluticasone propionate nasal spray, 50 μg (FNS; Par Pharmaceutical, Woodcliff Lake, NJ) is an intranasal corticosteroid with anti-inflammatory properties. FNS has been shown to be effective for the management of SAR, although treatment with FNS requires regular administration and, although benefit may be seen within 12 hours, maximal relief may not occur for several days.[21]

Combining an intranasal corticosteroid with an antihistamine is common in clinical practice, although the evidence supporting this approach is limited and appears to relate to the route of administration of the antihistamine. For example, the addition of an oral antihistamine to an intranasal corticosteroid does not appear to result in additional benefit.[22–24] In contrast, a recent clinical study found that a combination of AZE and FNS was more effective in the treatment of SAR than was either agent alone.[25] The objective of the current study was to evaluate the efficacy of coadministration of OLO and FNS relative to coadministration of AZE and FNS in a 2-week SAR trial.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Eligible for inclusion in this study were patients ≥12 years of age with a 2-year history of spring or summer allergic rhinitis. Patients must have been allergic to the prevalent seasonal allergen in their geographic area as confirmed by a positive case history and skin-prick or intradermal skin test. Patients also must have been symptomatic, with a TNSS of a threshold level (at least 6 with a maximum score of 10), and must not have had any significant anatomic abnormalities, infections, bleeding, or mucosal ulcerations of the nose. Patients must not have had any concurrent diseases that might have interfered with the evaluation of the study medication, required the use of prohibited medications, or had a history of chronic sinusitis or asthma more severe than mild–intermittent. Patients who were known nonresponders to antihistamines for SAR symptoms were excluded, as were those patients who used systemic, inhaled, or ocular corticosteroids within the 30 days before entry. Finally, patients were excluded if they chronically used antihistamines or chronically or intermittently used inhaled, oral, intramuscular, i.v., dermal potent, or superpotent topical corticosteroids.

Test Articles

The study medications were supplied in commercial packaging with foil overwraps that were designed to cover each bottle, including the pumps and nasal adapters; only the applicator tips were exposed. The overwraps were labeled with investigator and patient numbers along with storage instructions and the dosing regimen. The study medications were provided to the patients within sealed envelopes. In this manner, the investigators, their study staff, the monitors, and all others involved with the conduct of the study were kept blinded in regard to each individual patient's treatment assignment. Additionally, subjects were instructed not to discuss the appearance or any other aspects of their assigned treatments with the investigator and the study staff.

All randomized patients administered 2 sprays of randomized study medication (OLO or AZE) into each nostril twice daily (morning and evening) for the duration of the study. All patients also administered 2 sprays of FNS into each nostril once daily (15–30 minutes after the morning dose of the randomized study medication).

Study Design

This study was a multicenter, double-blind, randomized, parallel-group clinical trial designed to evaluate OLO coadministered with FNS relative to AZE coadministered with FNS in patients with SAR. Approximately 150 patients were planned for enrollment across 11 sites in the United States. This study consisted of four in-office study visits.

At the screening visit (visit 1), patients provided informed consent; were evaluated against the inclu-

sion/exclusion criteria; described their allergic rhinitis symptoms and medical histories; disclosed information regarding their concomitant medication usages; underwent a diagnostic allergy test (skin-prick/intradermal test) for the currently prevalent seasonal allergen of the geographic area (≥3-mm wheal greater than diluent after skin-prick testing or ≥7-mm wheal greater than the diluent after intradermal testing), if not previously preformed within the last 5 years; and had a brief physical and nasal examination. Female patients of childbearing potential also underwent a urine pregnancy test. At the conclusion of the visit, all eligible patients began a washout period for prohibited medications. If no washout was needed, visit 2 may have been conducted on the same day.

At visit 2, the patients were rescreened against the inclusion/exclusion criteria, and their medical histories and concomitant medication usages were updated if necessary; female subjects of childbearing potential also underwent a repeat urine pregnancy test. All patients then underwent a nasal examination to confirm the absence of significant anatomic anomalies. After the examination, patients evaluated their nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) using a scale that ranged in whole units from 0 (none) to 3 (severe); based on these individual symptom scores, the investigators calculated the TNSS. Eligible patients were randomized (1:1) sequentially to study medication (OLO or AZE) in accordance with an electronically generated schedule that was blocked within sites to ensure a balance of treatment assignments. Finally, at this visit, patients were dispensed diaries in which they were instructed to record the severity of their nasal symptoms (itchy nose, runny nose, stuffy nose, and sneezing) twice daily before dosing (on awakening and before bedtime). Symptoms were reported both instantaneously (*i.e.*, as experienced at that moment) and reflectively (*i.e.*, as experienced since the last dose of study medication).

Visits 3 and 4 were each conducted 7 days after the previous visit. During each of these visits, patients were queried regarding changes to their concomitant medication usages and the occurrence of adverse events (AEs). Additionally, diary pages were collected and reviewed for completeness. Before exiting the study at visit 4, a brief physical and nasal examination was conducted, and, for female subjects of childbearing potential, a urine pregnancy test was performed.

The study was conducted in accordance with Good Clinical Practices and the ethical principles described within the Declaration of Helsinki. All participating patients gave written informed consent. A parent or legal guardian signed the consent document for children <18 years of age; the individual patient separately signed or otherwise marked an assent form as approved by the Institutional Review Board. As stated previously, target enrollment for the study was ~150 patients to ensure that 75 evaluable patients were included in each treatment arm. This number provided a 90% power to detect treatment differences assuming that the mean percent changes from baseline between groups in TNSS would not exceed 10%.

Efficacy Analyses

All statistical analyses were conducted using the per protocol population, which included all patients who completed the 2-week treatment period, had outcome assessments, and maintained study eligibility throughout the study period. Statistical analyses were conducted using SAS (SAS Institute, Cary, NC), with inferences drawn at the 0.05 α-level.

In this study, efficacy was based on the TNSS, which was calculated as the sum of the individual nasal symptom scores reported at each time point (*i.e.*, every morning and evening); the scores were averaged across days. Between-group comparisons were conducted using Student's *t*-tests.

The primary efficacy variable was the percent change from baseline in the overall, reflective TNSS (rTNSS). The rTNSS was an indication of how the patient felt since the last symptom assessment. Additionally, the percent changes from baseline in instantaneous TNSS (iTNSS) and in the reflective and instantaneous individual nasal symptom scores were evaluated. For these evaluations, the average of the morning and evening scores from each patient was used and the percent change from baseline for each patient was computed and averaged for each study day. In each evaluation, two-sample *t*-tests were used to assess differences between OLO used in combination with FNS (OLO + FNS) and AZE used in combination with FNS (AZE + FNS).

Safety Analyses

All patients who received study medication were included in the safety analysis. This evaluation included AEs (including blinded investigator assessments of relationships to the study drugs), vital sign measurements, nasal examination outcomes (significant anatomic abnormalities), and physical examination findings.

RESULTS

Patient Disposition

In this study, a total of 150 patients were enrolled across 11 study sites in the United States between March and April 2009. Of the enrolled patients, 75 were randomized to the OLO + FNS group and 75 were randomized to the AZE + FNS group. A total of 135 patients (90%) were included in the per protocol pop-

Table 1 **Demographics (per protocol population)**

Variable	OLO + FNS (n = 67)	AZE + FNS (n = 68)	Total (n = 135)	p Value*
Age (yr)				
Mean (SD)	34.25 (11.59)	36.09 (11.72)	35.18 (11.65)	0.3617
Range	12–60	15–58	12–60	
Gender [n (%)]				
Male	37 (55.22)	26 (38.24)	63 (46.67)	0.0479
Female	30 (44.78)	42 (61.76)	72 (53.33)	
Race [n (%)]				
White	48 (71.64)	47 (69.12)	95 (70.37)	0.0946
Black	7 (10.45)	12 (17.65)	19 (14.07)	
Hispanic/Latino	7 (10.45)	3 (4.41)	10 (7.41)	
Asian	2 (2.99)	6 (8.82)	8 (5.93)	
Other#	3 (4.48)	0 (0.00)	3 (2.22)	

**The p values of between-group comparisons using Student's t-test for numerical variables and Pearson χ^2-test for categorical variables.*
#"Other" races included Hawaiian/Irish, Catalan, and Mulatto.
AZE = azelastine nasal spray, 0.1%; FNS = fluticasone nasal spray, 50 μg; OLO = olopatadine hydrochloride nasal spray, 0.6%.

Table 2 **Baseline characteristics—nasal symptom scores (per protocol population)**

Variable	OLO + FNS n = 67 Mean (SD)	AZE + FNS n = 68 Mean (SD)	p Value* Mean (SD)
Runny nose	2.00 (0.78)	1.93 (0.95)	0.6242
Itchy nose	1.85 (0.78)	1.84 (0.89)	0.9311
Stuffy nose	2.03 (0.76)	2.18 (0.79)	0.2736
Sneezing	1.58 (0.87)	1.46 (0.89)	0.4066
TNSS	7.46 (1.60)	7.40 (1.95)	0.8310

**The p values of between-group comparisons using Student's t-test.*
AZE = azelastine nasal spray, 0.1%; FNS = fluticasone nasal spray, 50 μg; OLO = olopatadine hydrochloride nasal spray, 0.6%; TNSS = total nasal symptom score.

ulation (67 patients in the OLO + FNS group and 68 patients in the AZE + FNS group).

Patient Demographic and Baseline Characteristics

Across both treatment groups, 53.33% of the enrolled patients were women and the mean (SD) patient age was 35.18 years (11.65 years). The majority of the patients were white (70.37%), but a substantial proportion of patients also were black (14.07%; Table 1). Patients reported mean scores between 1 and 3 for each individual nasal symptom, indicating that patients experienced mild to severe disease intensity at baseline. Within the OLO + FNS and AZE + FNS groups, the mean (SD) TNSS was 7.46 (1.60) and 7.40 (1.95) U, respectively. Within the OLO + FNS group, the mean (SD) baseline scores for runny nose, itchy nose, stuffy nose, and sneezing were 2.00 (0.78), 1.85 (0.78), 2.03 (0.76), and 1.58 (0.87) U, respectively. Similarly, within the AZE + FNS group, the mean (SD) baseline scores for runny nose, itchy nose, stuffy nose, and sneezing were 1.93 (0.95), 1.84 (0.89), 2.18 (0.79), and 1.46 (0.89) U, respectively (Table 2).

With the exception of gender, there were no statistically significant differences in demographic or baseline characteristics between treatment groups. In regard to gender, however, the proportion of male subjects in the OLO + FNS group was significantly greater than in the AZE + FNS group (55.22% versus 38.24%, respectively; p = 0.0479).

Primary Efficacy: Change from Baseline in Reflective TNSS

In the OLO + FNS and the AZE + FNS groups, the rTNSS decreased from baseline in each subsequent assessment. Specifically, in the OLO + FNS group, the mean (SD) rTNSS was 6.23 (2.71) U at day 1, which

Table 3 **Mean changes from baseline in reflective and instantaneous individual and TNSSs averaged over the treatment period (per protocol population)**

	OLO + FNS $n = 67$ Mean (SD)	AZE + FNS $n = 68$ Mean (SD)	p Value*
Reflective			
Runny nose	1.08 (0.72)	1.12 (0.83)	0.7552
Itchy nose	1.07 (0.72)	0.98 (0.78)	0.5477
Stuffy nose	1.30 (0.72)	1.33 (0.76)	0.7892
Sneezing	0.84 (0.69)	0.72 (0.68)	0.3567
TNSS	4.28 (2.63)	4.15 (2.63)	0.8039
Instantaneous			
Runny nose	1.06 (0.74)	1.08 (0.79)	0.8529
Itchy nose	1.06 (0.77)	0.97 (0.74)	0.5505
Stuffy nose	1.36 (0.75)	1.39 (0.72)	0.8007
Sneezing	0.74 (0.70)	0.60 (0.66)	0.2669
TNSS	4.22 (2.69)	4.04 (2.45)	0.7339

**The p values of between-group comparisons using Student's t-test.*
AZE = azelastine nasal spray, 0.1%; FNS = fluticasone nasal spray, 50 μg; OLO = olopatadine hydrochloride nasal spray, 0.6%; TNSS = total nasal symptom score.

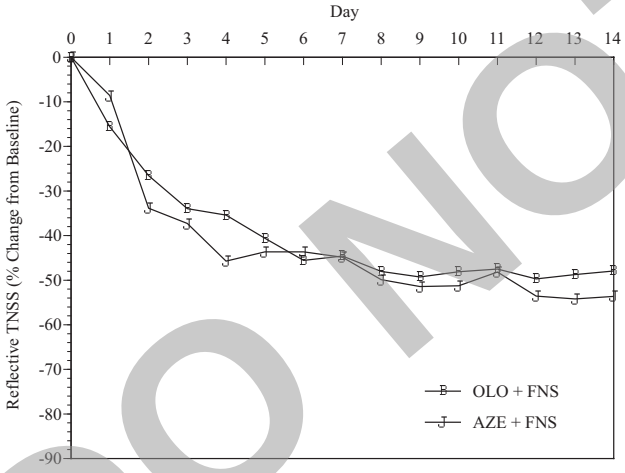

Figure 1. *Percent changes in reflective total nasal symptom scores by day (per protocol population).*

decreased to 3.79 (2.97) U at day 14; in the AZE + FNS group, the mean (SD) rTNSS was 6.13 (2.71) U at day 1, which decreased to 3.50 (2.51) U at day 14. Overall, there were no significant differences between the OLO + FNS group and the AZE + FNS group in the mean change from baseline in rTNSS when averaged over the 2-week treatment period (4.28 and 4.15 U, respectively; $p = 0.8039$; Table 3).

At the day 1 visit, the mean percent reductions from baseline in rTNSS were 15.60% in the OLO+FNS group and 8.59% in the AZE+FNS group (Fig. 1). Although the percent reduction in rTNSS in the OLO+FNS group was numerically greater than the corresponding reduction in the AZE+FNS group, this difference was not significant ($p = 0.4603$).

On day 14, the mean percent reduction from baseline in rTNSS was 47.95% in the OLO + FNS group and 53.65% in the AZE + FNS group; again, the difference between groups was not significant ($p = 0.3668$; Fig. 1). Furthermore, there were no significant differences between treatment groups for the mean percent reductions from baseline in rTNSS at any assessment time point. Overall, when averaged over the 2-week treatment period, no significant differences were observed between the OLO + FNS and AZE + FNS groups for the mean percent reductions from baseline in rTNSS (41.61 and 44.28%, respectively; $p = 0.7044$; Table 4). Both groups, OLO + FNS and AZE + FNS, had statistically significant improvements over baseline in rTNSS ($p < 0.05$).

Other Efficacy End Points

Changes from Baseline in Instantaneous TNSS. In the OLO + FNS and AZE + FNS groups, the iTNSS decreased over the 2-week treatment period. Specifically, in the OLO + FNS group, the mean (SD) iTNSS was 6.02 (2.56) U at day 1, which decreased to 3.46 (3.09) U at day 14; in the AZE + FNS group, the mean (SD) iTNSS was 5.93 (2.63) U at day 1, which decreased to 3.21 (2.40) U at day 14. There were no significant differences between the OLO + FNS and AZE + FNS groups in the mean (SD) change from baseline in iTNSS when averaged over the 2-week treatment period (4.22 and 4.04 U, respectively; $p = 0.7339$; Table 3).

Table 4 **Mean percent changes from baseline in reflective and instantaneous individual and TNSSs averaged over the treatment period (per protocol population)**

	OLO + FNS n= 67 Mean (SD)	AZE + FNS n= 68 Mean (SD)	p Value*
Reflective			
Runny nose	−45.23 (35.69)	−36.49 (39.23)	0.1507
Itchy nose	−35.44 (47.74)	−42.33 (44.21)	0.4152
Stuffy nose	−29.71 (49.58)	−32.72 (45.08)	0.7293
Sneezing	−34.13 (60.94)	−38.24 (56.88)	0.7083
TNSS	−41.61 (40.31)	−44.28 (30.96)	0.7044
Instantaneous			
Runny nose	−45.69 (36.65)	−36.58 (42.48)	0.1463
Itchy nose	−35.99 (48.50)	−42.50 (43.67)	0.4553
Stuffy nose	−26.07 (51.17)	−29.56 (43.47)	0.6785
Sneezing	−40.20 (60.48)	−46.50 (53.22)	0.5620
TNSS	−42.40 (39.81)	−45.57 (29.11)	0.6522

**The p values of between-group comparisons using Student's t-test.*
AZE = azelastine nasal spray, 0.1%; FNS = fluticasone nasal spray, 50 μg; OLO = olopatadine hydrochloride nasal spray, 0.6%; TNSS = total nasal symptom score.

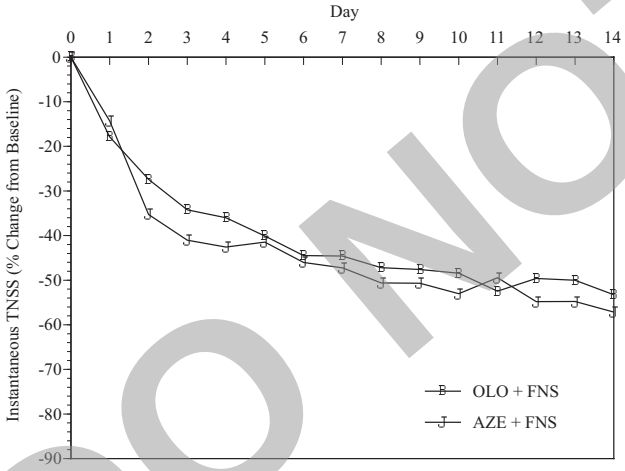

Figure 2. *Percent changes in instantaneous total nasal symptom scores by day (per protocol population).*

After 1 day of treatment, the mean percent reductions from baseline in iTNSS in the OLO + FNS and AZE + FNS groups were 17.87 and 14.29%, respectively; this difference was not significant (p = 0.6564; Fig. 2). On day 14, the mean percent reduction from baseline in iTNSS was 53.25% in the OLO + FNS group and 57.15% in the AZE + FNS group; again, the difference between groups was not significant (p = 0.4933).

Overall, there were no significant differences between treatment groups in the mean percent reductions from baseline in iTNSS at any assessment time point. Additionally, when averaged over the 2-week treatment period, no significant differences were observed between the OLO + FNS and AZE + FNS groups for the mean percent reductions from baseline in iTNSS (42.40 and 45.57%, respectively; p = 0.6522; Table 4).

Changes from Baseline in Individual Nasal Symptom Scores. In regard to the mean reflective and instantaneous individual nasal symptom scores (*i.e.*, reflective and/or instantaneous scores for itchy nose, runny nose, stuffy nose, and sneezing), there were no statistically significant differences between treatment groups at any assessment time point. Furthermore, when averaged over the 2-week treatment period, no significant differences were observed between the OLO + FNS and AZE + FNS groups in the mean reflective or instantaneous scores for any individual nasal symptom (*i.e.*, $p > 0.05$ for each comparison between treatment groups; Table 3).

Statistically significant differences between treatment groups for the mean percent reductions from baseline in individual nasal symptom scores were observed on days 6 and 11 for the symptom of runny nose; no other statistically significant differences in individual scores were observed between treatment groups at any assessment time point. Specifically, on day 6, the mean percent reductions from baseline in the reflective and instantaneous scores for runny nose were significantly greater in the OLO + FNS group relative to the AZE + FNS group (reflective, 51.24 and 33.58%, respectively [p = 0.0288]; instantaneous, 50.75 and 30.27%, respectively [p = 0.0168]). On day 11, the mean percent reduction from baseline in the reflective

score for runny nose also was significantly greater in the OLO + FNS group relative to the AZE + FNS group (58.46 and 39.46%, respectively [$p = 0.0323$]). When averaged over the 2-week treatment period, however, there were no significant differences between treatment groups for the mean percent reductions from baseline in any of the individual nasal symptom scores (Table 4).

Safety

In this study, 31 (23.0%) patients reported one or more AE (regardless of severity, seriousness, or relationship to the study drug). In the OLO + FNS group, 15 (22.4%) patients reported 19 AEs and in the AZE + FNS group, 16 (23.5%) patients reported 29 AEs. The reported AEs were generally mild to moderate in severity, resolved either with or without the need for concomitant therapy, and did not interrupt patient continuation in the study. None of the patients experienced serious AEs. However, one event in the OLO + FNS group (sinus headache, unrelated) and four events in the AZE + FNS group (bad taste, related; headache, unrelated; burning in nostrils after dosing, related; and migraine worse than usual, unrelated) were considered severe.

Overall, 23 treatment-related events were reported (7 in the OLO + FNS group and 16 in the AZE + FNS group). With 3 exceptions (drowsiness reported by 2/67 patients in the OLO + FNS group, bad taste reported by 2/68 patients in the AZE + FNS group, and nasal burning reported by 4/68 patients in the AZE + FNS group) no single treatment-related AE was reported by more than 1 patient in either treatment group. Finally, one patient in the OLO + FNS group discontinued because of a treatment-related AE (exacerbation of gastroesophageal reflux disease); no other patients discontinued due to treatment-related AEs. A summary of the number of patients who experienced AEs that were considered related to treatment is presented in Table 5.

There were no clinically relevant changes from baseline observed across treatment groups in physical examination parameters (head, eyes, ears, nose, throat, neck, cardiovascular, pulmonary, abdomen, skin and extremities, neurological, and lymph nodes). Additionally, few occurrences of nasal abnormalities were observed after examination. A treatment-related ulcer in the right septum was observed in one patient in the AZE + FNS group. This nasal ulceration was mild in severity. Overall, based on an analysis of AEs, vital signs, and nasal and physical examination outcomes, no safety signals or trends were identified.

Table 5 **Treatment-related adverse events by treatment group (per protocol population)**

Event*	No. of Patients
OLO + FNS ($n = 67$)	7
Drowsiness	2
Irritation of nasal passages	1
Exacerbation of GERD	1
Bad taste	1
Epistaxis	1
Fatigue	1
AZE + FNS ($n = 68$)	16
Ulceration right septum	1
Hyperosmia	1
Bad taste	2
Physically jittery	1
Nasal burning	4
Loss of taste	1
Mild bleeding on right outer turbinate	1
Bad scent	1
Dryness inside of nose	1
Feeling "out of sorts" after dosing	1
Fatigue	1
Nose bleed	1

**Verbatim descriptions of AEs are presented within the table. Events were not coded and therefore identical and similar events may be listed separately instead of under a single term.*

AZE = azelastine nasal spray, 0.1%; FNS = fluticasone nasal spray, 50 μg; GERD = gastroesophageal reflux disease; OLO = olopatadine hydrochloride nasal spray, 0.6%.

DISCUSSION

Given the fact that intranasal antihistamines and intranasal corticosteroids have different mechanisms of action and consequently distinct times to onset of action, it was proposed that combination therapy with both classes of drugs would act in a complementary manner, providing enhanced efficacy over either monotherapy in the treatment of SAR.[25] Combination therapy with an intranasal corticosteroid and an intranasal antihistamine has therefore been suggested to be beneficial in patients who do not respond sufficiently to intranasal corticosteroids or in patients who do not achieve adequate relief of their nasal symptoms from a single nasal spray.[1,24,26] In this study, the outcome of the primary efficacy analysis showed that OLO, when coadministered with FNS, is an effective treatment that provides comparable relief for the nasal symptoms of SAR relative to a combination of AZE and FNS. In addition, over a 2-week period, each of the combination treatments (OLO + FNS and AZE + FNS) decreased the individual nasal symptom scores progressively at each visit relative to baseline. This outcome is comparable with a previous report that evaluated a combination of AZE and FNS in the treatment of SAR[25]

and supports the use of OLO in combination with FNS in the treatment of SAR. Despite the comparability of the AZE + FNS results reported in this study with those reported in the literature, it should be noted that this study was not designed to address whether concurrent therapy with an intranasal corticosteroid and an intranasal antihistamine is more effective than monotherapy alone. Furthermore, generalizing the results of this study might be complicated by the fact that neither a placebo nor a monotherapy control was included.

Intranasal allergy products in general (antihistamines and corticosteroids) have been associated with AEs such as cough, headache, and epistaxis.[20] In the current study, no instances of treatment-related coughs or headaches were reported by patients in either treatment group. In addition, the occurrences of epistaxis or nasal bleeding in this study were few in number (one report in the OLO + FNS group and three reports in the AZE + FNS group), nonserious, generally mild in severity, usually resolved without the need for any new therapy, and did not interrupt patient participation. Although epistaxis is a common AE reported in association with the use of intranasal corticosteroids and antihistamines, it is generally considered minor and self-limiting.[27,28]

It has been reported in the literature that patient perceptions of sensory attributes such as taste, odor, nasal irritation, and nasal/throat dryness can influence adherence to intranasal spray regimens.[29] Overall, negative reports related to sensory attributes (including bad taste, bad scent, nasal burning, and nasal dryness) were more frequent among patients who received AZE + FNS relative to those who received OLO + FNS.

No safety concerns for changes in nasal or physical examination parameters were observed during the study in either treatment group. In general, the AEs reported by patients in both treatment groups were similar to one another.

CONCLUSIONS

OLO, when used in combination with FNS, is well tolerated and effective for the treatment of SAR in patients ≥12 years of age. No statistically significant differences between the combination of OLO + FNS and AZE + FNS in either rTNSS or iTNSS were observed across a 2-week treatment period. Thus, given its general safety and efficacy profile, the coadministration of OLO and FNS provides an additional approach to the management of SAR.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of other investigators that participated in this study: B. Lanier, M.D.; R. Tan, M.D.; S. Spector, M.D.; A. Darter, M.D.; and S. Shah, M.D. Cullen Vogelson, Ph.D., and Usha Sivaprasad, Ph.D., of Illuminated Research LLC provided medical writing support.

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