

Mometasone furoate nasal spray plus oxymetazoline nasal spray: Short-term efficacy and safety in seasonal allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) and associated congestion adversely affect patients' lives. The intranasal corticosteroid mometasone furoate nasal spray (MFNS) is effective for AR symptoms including nasal congestion, and the intranasal decongestant oxymetazoline (OXY) is effective against nasal congestion, but the combination has not been fully studied. This study was designed to assess the efficacy of the combination of MFNS and OXY for the relief of seasonal allergic rhinitis (SAR) symptoms.

Methods: This phase 2 controlled clinical trial randomized adolescent and adult subjects (≥ 12 years; 2-year SAR) to MFNS q.d. (200 μ g) + 3 sprays/nostril of OXY 0.05% (MFNS + OXY3); MFNS q.d. + 1 spray/nostril of OXY (MFNS + OXY1); MFNS q.d.; OXY b.i.d.; or placebo for 15 days, with 1-week follow-up. Coprimary end points were change from baseline in morning/evening (A.M./P.M.) instantaneous (NOW) total nasal symptom score (TNSS) over days 1–15 and AUC ($AUC_{[0-4 \text{ hr}]}$) change from baseline in day 1 congestion.

Results: In 705 subjects, both combinations reduced A.M./P.M. NOW TNSS over days 1–15 significantly more than OXY b.i.d. or placebo ($p \leq 0.002$). Mean standardized AUC ($AUC_{[0-4 \text{ hr}]}$) day 1 congestion change from baseline was significantly greater in combination and OXY b.i.d. groups (MFNS + OXY3, -0.92 ; MFNS + OXY1, -0.80 ; OXY b.i.d., -1.06) versus placebo (-0.57) and MFNS q.d. (-0.63). Combinations and MFNS q.d. were significantly effective for A.M./P.M. NOW TNSS over each weekly period; OXY b.i.d. was superior to placebo in week 1. Adverse events (AEs) were few and similar across treatments; one MFNS q.d. and one placebo subject experienced a serious AE, with neither considered treatment related.

Conclusion: Combining MFNS with OXY relieves SAR symptoms, including congestion, with faster onset of action than MFNS q.d. and better sustained efficacy than OXY b.i.d.

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Allergic rhinitis (AR) is a prevalent disease with adverse effects on the daily lives of sufferers. In a U.S. survey of 2500 adults with AR, patients most often identified congestion as their most bothersome symptom.¹

Mometasone furoate nasal spray (MFNS) is an intranasal corticosteroid (INS) shown to be safe and efficacious for seasonal AR (SAR)

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and perennial AR (PAR).^{2–4} Recent clinical trials established the ability of MFNS to significantly relieve SAR nasal symptoms, including congestion, for a full 24-hour dosing interval and to sustain relief over a 2-week treatment period.^{2,5} Oxymetazoline (OXY) is an intranasal decongestant used to treat nasal congestion by activating α -adrenergic receptors, resulting in constriction of nasal blood vessels and, with rapid onset of action, improving airflow.⁶ INS monotherapy, though recommended as the most effective single pharmacologic treatment for AR,¹ is insufficient to provide adequate relief for all patients.⁷ Although OXY has strong decongestant effects, national and international guidelines recommend limiting its use to a few days at most because of concerns of tachyphylaxis and rebound congestion.^{8–11} Combining OXY with MFNS is attractive for clinicians and patients, because it holds the potential for both rapid onset from the decongestant and anti-inflammatory activity plus protection from receptor tachyphylaxis by the INS,¹² yielding better efficacy than either alone.

Recently, a small study ($n = 60$) evaluated INS fluticasone furoate (FF), OXY, or both agents combined in a 4-week treatment of PAR, with a 2-week follow-up period.¹³ The study found significantly improved congestion score versus placebo for combination but not for either monotherapy, and follow-up indicated no rebound congestion after treatment cessation.¹³ The concept remained to be proven by a large-scale trial.

METHODS

This phase 2, randomized, single-dummy, placebo-controlled, multicenter study included a 3- to 14-day screening period, a 2-week (15-day) treatment period, and a 1-week follow-up period. In this proof-of-concept study, no formulation was available that could be administered from a single device allowing for proper blinding. MFNS and matching placebo were identical; OXY was supplied as a commercially available product with no matching placebo. Unblinded members of the center staff were required to obtain randomization numbers and dispense medication. Center personnel responsible for seeing subjects and assessing symptoms,

Table 1 Treatment regimens

Treatment Group	A.M.	P.M.
MFNS + OXY3 (MFNS + OXY3)*	MFNS, 2 sprays/nostril OXY, 3 sprays/nostril	Placebo, 2 sprays/nostril
MFNS + OXY1 (MFNS + OXY1)*	MFNS, 2 sprays/nostril OXY, 1 spray/nostril	Placebo, 2 sprays/nostril
MFNS q.d.	MFNS, 2 sprays/nostril Placebo, 1 spray/nostril	Placebo, 2 sprays/nostril
OXY b.i.d.	Placebo, 2 sprays/nostril OXY, 2 sprays/nostril	OXY, 2 sprays/nostril
Placebo	Placebo, 2 sprays/nostril Placebo, 3 sprays/nostril	Placebo, 2 sprays/nostril

MFNS was given once daily (50 µg/spray, with the recommended dose of 2 sprays/nostril for a total daily dose of 200 µg). OXY formulation was 0.05%, 100 µL/spray for a total daily dose of 600 µL in the MFNS + OXY3 group, 200 µL in the MFNS + OXY1 group, and 800 µL in the OXY b.i.d. group.

*Treatment sequence was stratified such that 50% of this group was administered MFNS first followed by OXY; the remaining 50% was administered OXY first followed by MFNS.

A.M. = morning; P.M. = evening; MFNS = mometasone furoate nasal spray; OXY = oxymetazoline nasal spray; OXY1 = 1 spray of oxymetazoline; OXY3 = 3 sprays of oxymetazoline.

however, were blinded to treatment. Written informed consent was obtained from each subject or a legal representative; study protocol and consent forms were approved by Sterling Institutional Review Board before initiation. Subjects were ≥ 12 years of age, with a minimum 2-year SAR history documented by skin-prick test to an appropriate seasonal allergen. Subjects had to be clinically symptomatic at screening, based on instantaneous (NOW) nasal symptom scores: rhinorrhea (nasal discharge/runny nose or postnasal drip), ≥ 2 ; nasal congestion/stuffiness, ≥ 2 ; and total nasal symptom score (TNSS; combined congestion, rhinorrhea, sneezing, and nasal itching), ≥ 6 . Symptoms were scored as follows: 0 = none (no sign/symptom evident), 1 = mild (sign/symptom was clearly present but awareness of it was minimal), 2 = moderate (definite awareness of sign/symptom, which was bothersome but tolerable), and 3 = severe (sign/symptom was hard to tolerate and caused interference with activities of daily living and/or sleeping). For 3 days preceding the baseline visit, the seven twice-daily NOW diary scores (b.i.d. + morning [A.M.] of the baseline visit day) for rhinorrhea and nasal congestion were required to be >14 ; TNSS scores were required to be >42 .

Subjects were randomly assigned to one of five treatment groups (Table 1). MFNS was given q.d. (the approved dosing for AR). OXY was given q.d. in combination groups to determine if its effects would be sustained >12 hours if given with an INS; 3 sprays of OXY (OXY3) was chosen as near equivalent to the highest recommended dose, and 1 spray of OXY (OXY1) was chosen to evaluate effect at this low level. OXY monotherapy was given b.i.d. in accordance with standard SAR dosing. Postbaseline visits were scheduled for days 8 and 15, with a posttreatment follow-up visit scheduled for day 22. If subjects discontinued early, a final visit was required; "end-of-treatment" values include assessments from these visits.

The coprimary efficacy end points were A.M./evening (P.M.) NOW TNSS change from baseline (the average of the seven twice-daily TNSS evaluations before first dose) averaged over days 1–15 and the standardized area under the curve ($AUC_{[0-4 \text{ hr}]}$) of the day 1 nasal congestion score change from baseline (the average of A.M. NOW nasal congestion scores assessed every 15 minutes for 1 hour before dosing). AUC was calculated using the trapezoidal rule, and then standardized by dividing the calculation by 4 hours. A.M. and P.M. assessments were made before dosing.

To show the contribution of MFNS to combination therapies (expected to be indicated by efficacy against nasal symptoms over the treatment period), the primary comparison was MF + OXY versus OXY in improvement of A.M./P.M. NOW TNSS over days 1–15. To show the contribution of OXY (expected to be indicated by rapid

onset of action against congestion), the measurement of interest was the effect on day 1 $AUC_{(0-4 \text{ hr})}$ on the comparison of MF + OXY versus MFNS.

Other end points were secondary; Table 2 shows those measured in all subjects. Subjects ≥ 18 years of age self-administered the Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).¹⁴ RQLQ total scores were evaluated for change from baseline at day 15 and last treatment visit. To assess possible tachyphylaxis and associated reduced end-of-interval efficacy, changes from baseline in A.M. NOW nasal congestion were compared between combination regimens and MFNS q.d. (for tachyphylaxis due to the combination) and OXY b.i.d. versus placebo (for tachyphylaxis due to OXY b.i.d.). Safety was evaluated by adverse events (AEs); vital signs taken at each visit; nasal examinations performed at screening, baseline, end of treatment, and day 22 (follow-up visit); and 12-lead electrocardiograms taken at screening and end of treatment.

Between-group differences in change from baseline were evaluated using an analysis of covariance model with treatment, center, and dosing sequence (stratification variable) as classification variables and baseline score as a covariate.

The target sample size of 875 subjects (175 per treatment arm) was determined necessary to detect a ≥ 0.8 -point treatment difference in A.M./P.M. NOW TNSS change from baseline, with a two-sided α of 0.05 and 90% power. Because a 0.2-point difference between treatments in each individual symptom is considered clinically relevant, 0.8 points was determined as the clinically relevant difference in TNSS; this is in excess of the 0.55-point minimal clinically important difference in TNSS that has been calculated from distribution-based and anchor-based methods.¹⁵ Power assumptions were based on the treatment effect in A.M./P.M. TNSS of 1.3 points that was seen in past studies.

RESULTS

Fall enrollment was slower than expected and was extended to mountain cedar season (December through February). At the end of season, 707 patients were randomized; after calculating the resultant power with that population, it was decided to complete enrollment and assess treatment. The intent-to-treat population comprised 705 subjects, representing 80% power to detect the expected treatment difference. Treatment groups were similar regarding sex, age, and race. Baseline demographics are summarized in Table 3. Baseline scores for A.M./P.M. NOW TNSS ranged from 9.61 to 9.89 and nasal congestion AUC scores ranged from 2.59 to 2.64 among groups, indicating moderate-to-severe disease. Twenty-eight subjects discon-

Table 2 Secondary end points measured in entire study population

Assessment	Timing of End Point Measurement
Change from baseline in A.M. and P.M. NOW and prior (reflective) TNSS, individual nasal symptom scores (congestion, rhinorrhea, sneezing, and nasal itching), TOSS, individual ocular symptom scores; change from baseline in A.M., P.M., and A.M./PM PNIF	Days 1, 2, 3, 4, 1–8, 9–15, 16–22, and 1–15*
Change from baseline in A.M./PM NOW TNSS	Days 1, 2, 3, 4, 1–8, 9–15, and 16–22*
Change from baseline in standardized AUC _(0–4 hr) of PNIF	Days 1 and 15 or end-of-treatment visit#
Change from baseline in standardized AUC _(0–4 hr) of nasal congestion score	Day 15 or end-of-treatment visit#
Change from baseline in overall condition of SAR, evaluated separately by investigator and subject (0 = none [no symptoms evident] to 3 = severe [symptoms hard to tolerate, may interfere with activities of daily living and/or sleeping])	Interim, day 15 or end-of-treatment visit and posttreatment follow-up visit
Response to study drug evaluated separately by subject and investigator on a scale of 1 (virtually no symptoms present) to 5 (no relief)	Interim and day 15 or end-of-treatment visits†

*Assessments were made at home immediately before dosing.

#If subjects discontinued early, an end-of-treatment visit was scheduled.

AUC = area under the curve; PNIF = peak nasal inspiratory flow; SAR = seasonal allergic rhinitis; TNSS = total nasal symptom score; TOSS = total ocular symptom score (combined redness of eyes, itching/burning eyes, eye tearing scores); A.M. = morning; P.M. = evening; NOW = instantaneous.

Table 3 Baseline demographics

	No. (%) of Subjects				
	MFNS + OXY3	MFNS + OXY1	MFNS q.d.	OXY b.i.d.	Placebo
Subjects randomized	139	146*	139	141*	142
ITT population	139	145	139	140	142
Subjects completed study	134 (96.4)	142 (97.3)	137 (98.6)	133 (94.3)	133 (93.7)
Subjects discontinued from study	5 (3.6)	4 (2.7)	2 (1.4)	8 (5.7)	9 (6.3)
Serious or life-threatening AE	0	0	1 (0.7)	0	0
Failure to comply with study requirements	1 (0.7)	1 (0.7)	1 (0.7)	0	1 (0.7)
Intolerable symptoms	0	1 (0.7)	0	1 (0.7)	4 (2.8)
Withdrawal of consent	2 (1.4)	0	0	3 (2.1)	2 (1.4)
Lost to follow-up	0	0	0	1 (0.7)	1 (0.7)
Other	2 (1.4)	2 (1.4)	0	3 (2.1)	1 (0.7)
Age, yr					
Mean (SD)	40.1 (14.44)	38.7 (12.48)	39.7 (12.56)	40.2 (12.44)	38.0 (13.51)
Range	12–76	13–71	12–73	15–73	12–70
Sex, n (%)					
Male	46 (33.1)	52 (35.9)	38 (27.3)	45 (32.1)	53 (37.3)
Female	93 (66.9)	93 (64.1)	101 (72.7)	95 (67.9)	89 (62.7)
Race, n (%)					
White	107 (77.0)	115 (79.3)	104 (74.8)	110 (78.6)	117 (82.4)
Black/African American	27 (19.4)	26 (17.9)	26 (18.7)	19 (13.6)	19 (13.4)
Native Hawaiian/other Pacific Islander	0 (0.0)	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)
Asian	1 (0.7)	1 (0.7)	3 (2.2)	3 (2.1)	3 (2.1)
American Indian/Alaska Native	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)
Other	3 (2.2)	2 (1.4)	4 (2.9)	7 (5.0)	2 (1.4)
Weight, kg					
Mean (SD)	79.7 (22.02)	81.6 (19.63)	80.5 (22.23)	82.0 (20.76)	80.8 (20.18)

*One subject in the MFNS + OXY1 and one subject in the OXY b.i.d. group were randomized but excluded from the ITT population because they did not have any dosing records.

AE = adverse event; ITT = intent to treat; MFNS = mometasone furoate nasal spray; OXY = oxymetazoline nasal spray; OXY1 = 1 spray of oxymetazoline; OXY3 = 3 sprays of oxymetazoline.

tinued, because of failure to comply with study requirements ($n = 4$), intolerable symptoms ($n = 6$), withdrawal of consent ($n = 7$), lost to follow-up ($n = 2$), serious or life-threatening AEs ($n = 1$), and other ($n = 8$) reasons. Although the protocol specified that daily symptom scores were to be collected from diaries over the follow-up period to assess potential rebound, the clinical research organization responsible for management of the study only collected data throughout treatment or until the last day a subject took the study drug. Thus, daily scores throughout the follow-up period could not be compared.

All active groups showed significant superiority to placebo in the coprimary end point of reduction from baseline in A.M./P.M. NOW TNSS over days 1–15 (Fig. 1). The primary comparison of combination therapy to OXY b.i.d. achieved significance (-3.36 , -3.29 , and -2.44 for MFNS + OXY3, MFNS + OXY1, and OXY b.i.d., respectively; $p \leq 0.002$), indicating the contribution of MFNS to the combination. Reductions from baseline in A.M./P.M. NOW TNSS over days 1–8 and 9–15 are shown in Fig. 2. Combination treatments and MFNS q.d. were effective over each weekly treat-

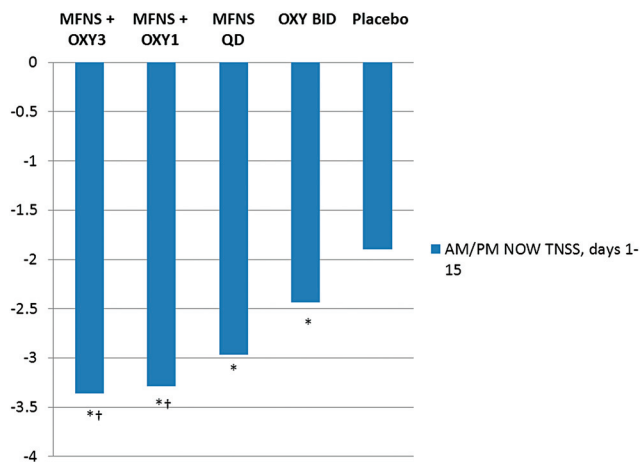


Figure 1. Reduction from baseline in A.M./P.M. NOW TNSS, days 1–15. * $p \leq 0.05$ versus placebo; † $p \leq 0.05$ versus OXY b.i.d. A.M., morning; P.M., evening; NOW, instantaneous; MFNS, mometasone furoate nasal spray; OXY, oxymetazoline; TNSS, total nasal symptom score.

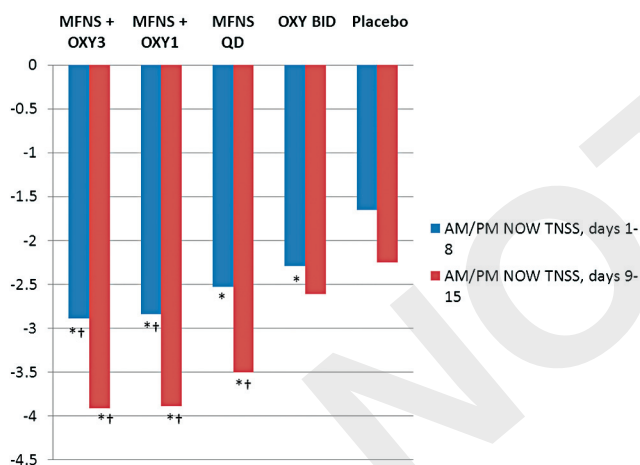


Figure 2. Reduction from baseline in A.M./P.M. NOW TNSS, days 1–8 and 9–15. * $p \leq 0.05$ vs placebo; † $p \leq 0.05$ versus OXY b.i.d. A.M., morning; P.M., evening; NOW, instantaneous; MFNS, mometasone furoate nasal spray; OXY, oxymetazoline; TNSS, total nasal symptom score.

ment period, but OXY b.i.d. was superior to placebo only over days 1–8. There were no significant differences between combinations or between either combination and MFNS q.d. over days 1–8, 9–15, or 1–15; both combinations were superior to OXY b.i.d. over days 1–8, 9–15, and 1–15 ($p \leq 0.030$), and MFNS q.d. was superior to OXY b.i.d. over days 9–15 ($p = 0.005$).

Onset of nasal congestion relief was rapid in the MFNS + OXY combination regimens and in OXY b.i.d.; mean standardized $AUC_{[0-4h]}$ was significantly greater in each of these groups (–0.92, –0.80, and –1.06 for MFNS + OXY3, MFNS + OXY1, and OXY b.i.d., respectively) versus MFNS q.d. (–0.63) and placebo (–0.57; Fig. 3). Each combination was significantly superior to MFNS q.d., indicating the contribution of OXY to the combination.

All active treatments were significantly superior to placebo in A.M. NOW TNSS change from baseline over days 2–15, indicating that MFNS q.d. and the combinations had 24-hour duration of action. All active treatments were significantly superior to placebo in A.M. prior (over the previous 12 hours) TNSS change from baseline over days 2–15; both combinations were significantly superior to OXY b.i.d. ($p =$

0.004 and $p = 0.013$ for MFNS + OXY3 and MFNS + OXY1, respectively) but not to MFNS q.d..

Changes from baseline in A.M./P.M. NOW nasal congestion are shown in Table 4. All active treatments were significantly superior to placebo over the 15-day treatment period except OXY b.i.d. ($p = 0.087$).

In A.M. NOW nasal congestion change from baseline over days 2–15, both combinations and MFNS q.d. showed statistically significant superiority to placebo (least squares [LS] mean differences –0.77, –0.78, –0.66, and –0.44 for MFNS + OXY3, MFNS + OXY1, MFNS q.d., and placebo, respectively; $p \leq 0.002$). OXY b.i.d. change from baseline showed numerical but no significant difference versus placebo over days 2–15 (–0.55 and –0.44 for OXY b.i.d. and placebo; $p = 0.126$). Neither combination was significantly superior to MFNS q.d.; both were significantly superior to OXY b.i.d. ($p \leq 0.001$). OXY b.i.d. showed efficacy at day 2 (LS mean change vs placebo, –0.26; $p < 0.001$); treatment effect over days 2–8 was –0.13 ($p = 0.053$) versus –0.06 over days 9–15 ($p = 0.479$).

Changes from baseline in A.M./P.M. prior average individual nasal and nonnasal symptom scores over days 1–15 are shown in Table 5. Both combinations statistically significantly improved rhinorrhea, nasal itching, and sneezing versus placebo; MFNS q.d. showed significant improvement versus placebo in the three nasal symptoms and itchy ears/palate.

Baseline total ocular symptom score was similar among groups. Both combinations were statistically superior to placebo in change from baseline total ocular symptom score and all three individual ocular symptom scores over the treatment period, while neither monotherapy achieved significance.

In A.M. peak nasal inspiration flow (PNIF) score change from baseline, MFNS + OXY3 showed a nonsignificant change of 16.07 versus 13.88 for placebo over days 2–15 ($p = 0.525$). Only MFNS + OXY1 was significantly superior to placebo ($p = 0.034$) over days 2–15. Significance was driven by the change over days 2–8 (LS mean difference versus placebo 6.77; $p = 0.041$); the PNIF of MFNS + OXY1 was not significant versus placebo over days 9–15 ($p = 0.057$). In $AUC_{(0-4 \text{ hr})}$ of PNIF, at all time points, both combination therapies and OXY b.i.d., but not MFNS q.d., were superior to placebo (Table 5).

In subject-evaluated overall condition, all treatments showed statistically significant improvement versus placebo at end of treatment, and both combinations were significantly superior to placebo at end of follow-up. Additionally, MFNS + OXY3 was significantly superior to OXY b.i.d. at all time points and to MFNS q.d. at follow-up. In investigator-evaluated overall condition, all treatments except OXY b.i.d. showed significant superiority to placebo at end of treatment, and both combinations were significantly superior to placebo at end of follow-up. Therapeutic response evaluated by subjects and investigators was significantly superior for both combinations versus placebo at all time points ($p \leq 0.001$).

Overall, RQLQ scores at baseline ranged from 4.06 to 4.41 across treatment groups, indicating high impairment levels. Change from baseline in overall RQLQ is shown in Fig. 4. The effect size seen with MFNS + OXY combinations exceeded a minimal important difference of 0.5 point score, the marker for clinical significance.¹⁶ Both MFNS + OXY combinations significantly improved all RQLQ scores for individual domains versus placebo at end of treatment (MF + OXY3, $p < 0.001$; MFNS + OXY1, $p \leq 0.024$).

A nonprotocol-specified analysis of changes from days 15–22 in nasal examinations conducted as a safety assessment evaluated whether there was evidence of rebound congestion as per observed nasal obstruction. Across treatment groups, the majority of subjects either maintained or reduced nasal obstruction level (none, mild, moderate, or complete) over follow-up.

The percentage of subjects reporting treatment-related AEs was low (most common, headache) and similar across treatment groups (Table 6). The incidence of sinus headache across treatment groups was too low to make meaningful comparisons about congestion-related headache.

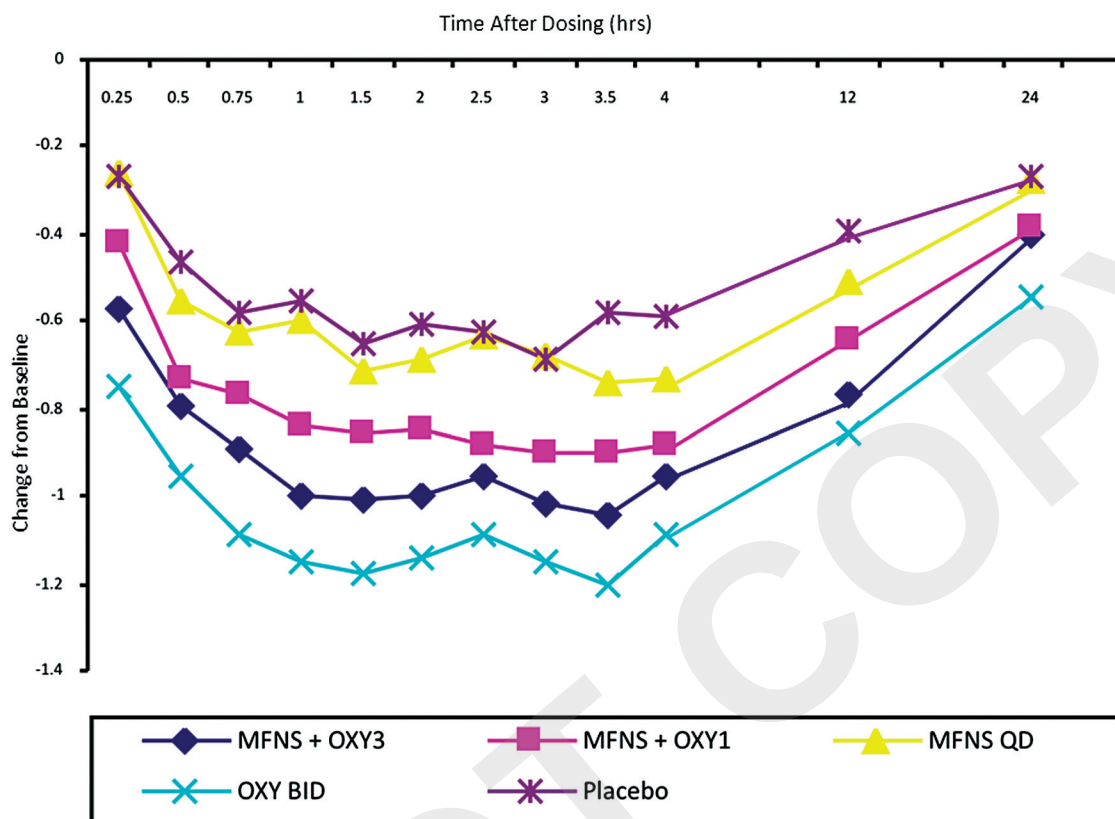


Figure 3. Nasal congestion scores, day 1. MFNS + OXY3, $p < 0.05$ versus placebo from 0.25 to 4 hours and 12 hours; MFNS + OXY1, $p < 0.05$ versus placebo from 0.25 to 4 hours and 12 hours; MFNS q.d., $p > 0.05$ versus placebo at all times; OXY b.i.d.: $p < 0.05$ versus placebo at all times. MFNS, mometasone furoate nasal spray; OXY, oxymetazoline nasal spray; OXY1, 1 spray of oxymetazoline; OXY3, 3 sprays of oxymetazoline.

Table 4 Change from baseline in A.M./P.M. NOW nasal congestion

	MFNS + OXY3 (n = 138)	MFNS + OXY1 (n = 145)	MFNS q.d. (n = 139)	OXY b.i.d. (n = 140)	Placebo (n = 140)
Day 1 (P.M. only)	-0.81 (-28.8%)*	-0.68 (-24.3%)*§	-0.54 (-19.0%)	-0.89 (-32.1%)*§	-0.44 (-14.8%)
Day 2	-0.58 (-21.7%)*§	-0.50 (-19.1%)*	-0.43 (-15.8%)	-0.53 (-20.0%)*	-0.29 (-10.7%)
Day 3	-0.68 (-23.2%)*#	-0.67 (-22.9%)*	-0.57 (-19.5%)*	-0.53 (-17.6%)	-0.40 (-13.0%)
Day 4	-0.73 (-25.7%)*#	-0.69 (-24.5%)*#	-0.61 (-21.5%)*#	-0.46 (-15.5%)*	-0.41 (-13.7%)
Days 1-8	-0.75 (-27.0%)*#§	-0.71 (-25.9%)*#	-0.60 (-21.7%)*	-0.55 (-19.5%)*	-0.40 (-13.9%)
Days 9-15	-0.95 (-33.9%)*#	-0.93 (-34.2%)*#	-0.82 (-29.6%)*#	-0.58 (-20.4%)	-0.52 (-18.1%)
Days 1-15	-0.84 (-30.3%)*	-0.81 (-29.5%)*	-0.70 (-25.3%)*	-0.57 (-20.0%)	-0.45 (-15.6%)

* $p < 0.05$ vs placebo; # $p < 0.05$ vs OXY b.i.d.; § $p < 0.05$ vs MFNS q.d.

MFNS = mometasone furoate nasal spray; OXY = oxymetazoline nasal spray; A.M. = morning; P.M. = evening; OXY1 = 1 spray of oxymetazoline; OXY3 = 3 sprays of oxymetazoline.

The low rate of epistaxis is noteworthy, particularly given the number of topical administrations in the MFNS + OXY3 group. No life-threatening AEs or clinically meaningful changes in laboratory parameters or vital signs were seen; electrocardiogram findings were unremarkable except for one prolonged QT time in the MFNS q.d. group. Two serious AEs were seen; esophageal bleeding in one subject in the MFNS q.d. group and chest pain secondary to gastroesoph-

ageal reflux in one subject in the placebo group. Neither was considered likely related to treatment.

DISCUSSION

In this study, MFNS + OXY established efficacy advantages over monotherapy with either agent. Both once-daily dosage combinations

Table 5 Change from baseline, standardized AUC of PNIF at day 1, day 15, and end point

	MFNS + OXY3 (n = 138)	MFNS + OXY1 (n = 145)	MFNS q.d. (n = 139)	OXY b.i.d. (n = 140)	Placebo (n = 140)
Baseline	78.06*	80.11*	88.30	80.96*	93.23
Day 1 change from baseline (%)	27.49 (40.7%)*§	25.45 (36.1%)*§	13.27 (22.0%)	28.82 (57.4%)*§	10.80 (13.0%)
Day 15 change from baseline (%)	44.16 (66.1%)*#§	41.17 (57.1%)*§	26.95 (41.1%)	34.63 (88.4%)*	20.29 (23.1%)
End point change from baseline (%)	44.12 (65.8%)*#§	41.05 (57.7%)*§	27.35 (40.9%)	33.81 (84.4%)*	20.61 (23.2%)

* $p < 0.05$ vs placebo; # $p < 0.05$ vs OXY b.i.d.; § $p < 0.05$ vs MFNS q.d.

AUC = area under the curve; MFNS = mometasone furoate nasal spray; OXY = oxymetazoline nasal spray; PNIF = peak nasal inspiratory flow; OXY1 = 1 spray of oxymetazoline; OXY3 = 3 sprays of oxymetazoline.

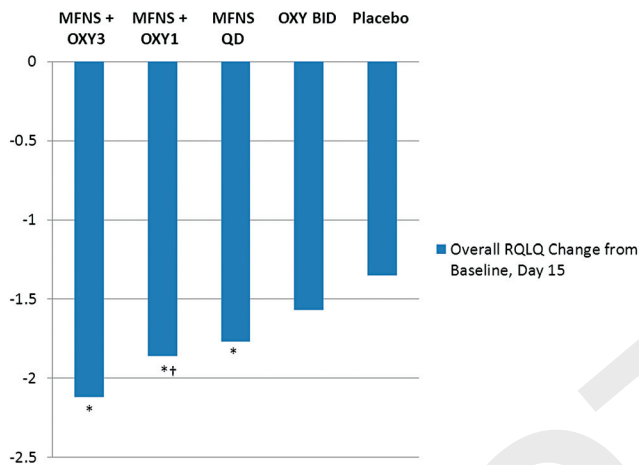


Figure 4. Change from baseline in overall RQLQ score, days 1–15. * $p \leq 0.05$ versus placebo; ** $p \leq 0.05$ versus OXY b.i.d. MFNS, mometasone furoate nasal spray; OXY, oxymetazoline; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

were significantly superior to OXY b.i.d. and placebo in TNSS reductions over the treatment period and to MFNS q.d. and placebo in AUC_(0–4 hr) onset of congestion relief. Primary comparisons indicated that each agent contributed to the combination.

The significant effect of OXY b.i.d. on A.M. NOW congestion at day 2 but not over days 2–15 suggests some reduced efficacy, *i.e.*, tachyphylaxis, of OXY b.i.d. monotherapy after prolonged treatment. Additionally, on day 1 MFNS q.d. did not achieve the AUC_(0–4 hr) superiority versus placebo seen in the combination groups, which were both significantly superior to MFNS q.d. in this day 1 measurement. Combination treatments were superior to placebo in AUC_(0–4 hr) onset and superior to placebo in A.M. NOW congestion at the beginning of treatment and throughout the study, suggesting that both the quick onset of OXY b.i.d. and the sustained efficacy of MFNS q.d. contributed to the effects of combined therapy.

These findings have some limitations. Follow-up data for overall SAR condition and nasal obstruction changes assessed by examination showed no worsening of condition after treatment cessation. However, daily symptom data were not collected during follow-up, making it difficult to evaluate the possible occurrence of rebound congestion after end of therapy. Differing OXY dosing regimens also make it difficult to precisely characterize each drug's contribution to the efficacy of combination treatment (combinations included OXY1 or OXY3, with no corresponding OXY monotherapy group receiving 1 or 3 sprays). Onset of action was measured over 4 hours, a shorter time than the 11-hour labeled onset of action of MFNS.¹⁷ Further study is needed to evaluate combination effects over longer periods in patients with SAR as well as in patients with PAR; it is possible that a longer treatment period may reveal a rebound effect of OXY b.i.d..

Updated guidelines from the Allergic Rhinitis and Its Impact on Asthma World Health Organization workshop recommend using intranasal decongestants for no longer than 5 days, partially because of concerns about tachyphylaxis.^{10,11} However, evidence is inconsistent regarding the potential risk of tachyphylaxis with long-term topical decongestant use. One study of nightly OXY in 10 healthy volunteers found that 8 subjects developed nighttime congestion after 1–4 weeks of OXY therapy, whereas a placebo-controlled study by Yoo *et al.* of 30 healthy volunteers found no tachyphylaxis after 4 weeks of OXY dosed 3 times/day.^{18,19} Vaidyanathan *et al.* detected tachyphylaxis in healthy volunteers after 14 days of OXY 3 times/day, as reflected by reduced nasal patency and increased mucosal blood flow; moreover, by using the selective α_1 -antagonist prazosin and intranasal fluticasone propionate the authors were able to show that tachyphylaxis occurred primarily at the α_1 -receptor type and could be reversed by addition of an INS.¹² The present study's size and allergic population lend relevance to its findings of some tachyphylaxis during prolonged OXY b.i.d. monotherapy, as suggested by the lack of efficacy at the end of the dosing interval—findings not seen when OXY was combined with MFNS. Guidelines also warn of possible rebound congestion after prolonged use of decongestants, because abrupt cessation can result in marked increases in turbinate swelling.^{11,20,21} However, the Yoo study found a lack of rebound congestion 2 weeks after cessation of 4 weeks of OXY 3 times/day.¹⁹ Although the present study found no sign of rebound congestion in nasal examination changes, the lack of daily diary entries during follow-up makes it impossible to draw firm conclusions.

Allergic Rhinitis and Its Impact on Asthma guidelines continue to recommend INS for AR treatment, citing efficacy against congestion.^{10,11} Compelling evidence indicates the efficacy of MFNS in relieving congestion in AR.² Combined results from two trials including 684 total patients aged ≥ 12 years with SAR randomly assigned to MFNS at 200 μ g q.d. or placebo for 2 weeks found MFNS to be associated with reduced A.M./P.M. prior congestion (0–3 scale) of 0.68 point versus 0.45 points for placebo ($p < 0.001$), a 0.24-point difference in A.M. NOW congestion ($p < 0.001$) indicated 24-hour duration of action of MFNS.² The efficacy of MFNS against congestion associated with drug-induced rhinitis, however, has until now been limited to an animal study.²² In the present study, OXY b.i.d. did not show efficacy versus placebo in A.M. NOW congestion over the study period or in A.M./P.M. congestion over days 9–15. Because MFNS q.d. and combination treatments were effective in these assessments, these results suggest possible contributions of MFNS q.d. against tachyphylaxis from repeated dosing of OXY. It is difficult to make direct inferences about the potency of MFNS against tachyphylaxis, however, given the different OXY doses.

A recent, small trial evaluated simultaneous use of another INS with a decongestant¹³; 60 patients with PAR were randomly assigned to FF at 110 μ g/day, OXY 0.05%, 2 puffs/nostril per day, both agents, or placebo. Combination therapy relieved congestion significantly more over the 4-week treatment period versus placebo ($p = 0.003$) or OXY ($p = 0.025$); treatment with FF approached significance versus placebo ($p = 0.06$). The combination significantly reduced TNSS versus placebo ($p = 0.007$).

Table 6 Treatment-related AEs reported in >1% of any treatment group (ITT population)

	MFNS + OXY3 (n = 139)	MFNS + OXY1 (n = 145)	MFNS q.d. (n = 139)	OXY b.i.d. (n = 140)	Placebo (n = 142)
Any AE, n (%)	11 (7.9)	13 (9.0)	5 (3.6)	9 (6.4)	8 (5.6)
Headache	3 (2.2)	3 (2.1)	3 (2.2)	2 (1.4)	1 (0.7)
Nasal discomfort	0	3 (2.1)	0	2 (1.4)	0
Sinus headache	0	2 (1.4)	0	0	0
Epistaxis	2 (1.4)	1 (0.7)	1 (0.7)	2 (1.4)	0
Feeling jittery	1 (0.7)	0	0	2 (1.4)	0
Throat irritation	1 (0.7)	1 (0.7)	1 (0.7)	0	2 (1.4)

AE = adverse event; ITT = intent to treat; MFNS = mometasone furoate nasal spray; OXY = oxymetazoline nasal spray; OXY1 = 1 spray of oxymetazoline; OXY3 = 3 sprays of oxymetazoline.

or OXY ($p = 0.036$) and numerically reduced TNSS versus FF ($p = 0.074$) and showed significant improvement versus placebo ($p = 0.014$) or OXY ($p = 0.025$) using acoustic rhinometry (an objective measurement of nasal volume) at 4 weeks; FF was numerically but not significantly better than placebo. Rhinometry performed 2 weeks after treatment cessation showed further increases in nasal volume for FF and combination groups, whereas no difference was seen in placebo or OXY groups, indicating lack of rebound congestion.¹³ Because monotherapy with OXY was not associated with worse congestion versus placebo after treatment, and combination treatment was not associated with decreasing efficacy versus FF toward the later period of treatment, no evidence was found to indicate the development of rhinitis medicamentosa with OXY. Despite obvious differences in study design, the present, larger study involving 705 subjects confirms the efficacy of combined once-daily INS + intranasal decongestant in patients with AR. In addition, it adds to the research indicating little or no rebound congestion with OXY, though with unusual dosing schedules and a limited duration of treatment.

In this study, the combination of q.d. MFNS + OXY (3 sprays and 1 spray) was well tolerated and effective in relieving TNSS and individual symptoms, including congestion, in subjects with SAR. Combining MFNS with OXY offers a promising treatment option for relief of symptoms of SAR, including congestion.

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REFERENCES

1. Blaiss MS, Meltzer EO, Derebery MJ, et al. Patient and healthcare-provider perspectives on the burden of allergic rhinitis. *Allergy Asthma Proc* 28(suppl 1):S4-S10, 2007.
2. Meltzer EO, Shekar T, and Teper AA. Mometasone furoate nasal spray for moderate-to-severe nasal congestion in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc* 32:159-167, 2011.
3. Clement P, and Gates D. Symptom suppression in subjects with perennial allergic rhinitis treated with mometasone furoate nasal spray. *Int Arch Allergy Immunol* 157:387-390, 2012.
4. Yamada T, Yamamoto H, Kubo S, et al. Efficacy of mometasone furoate nasal spray for nasal symptoms, quality of life, rhinitis-disturbed sleep, and nasal nitric oxide in patients with perennial allergic rhinitis. *Allergy Asthma Proc* 33:e9-e16, 2012.
5. Salapatek AM, Patel P, Gopalan G, and Varghese ST. Mometasone furoate nasal spray provides early, continuing relief of nasal congestion and improves nasal patency in allergic patients. *Am J Rhinol Allergy* 24:433-438, 2010.
6. Eskizmir G, Hirçin Z, Ozyurt B, and Unlü H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. *Eur J Clin Pharmacol* 67:19-23, 2011.
7. Naclerio RM, Hadley JA, Stoloff S, et al. Patient and physician perspectives on the attributes of nasal allergy medications. *Allergy Asthma Proc* 28(suppl 1):S11-S17, 2007.
8. Passali D, Salerni L, Passali GC, et al. Nasal decongestants in the treatment of chronic nasal obstruction: efficacy and safety of use. *Expert Opin Drug Saf* 5:783-790, 2006.
9. Wallace DV, Dykewicz MS, Bernstein DI, et al.; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: An updated practice parameter. *J Allergy Clin Immunol* 122(suppl 2):S1-S84, 2008.
10. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 126:466-476, 2010.
11. Bousquet J, Khaltaev N, Cruz AA, et al.; World Health Organization; GA²LEN; AllerGen. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and AllerGen). *Allergy* 63(suppl 86):8-160, 2008.
12. Vaidyanathan S, Williamson P, Clearie K, et al. Fluticasone reverses oxymetazoline-induced tachyphylaxis of response and rebound congestion. *Am J Respir Crit Care Med* 182:19-24, 2010.
13. Baroody FM, Brown D, Gavanescu L, et al. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol* 127:927-934, 2011.
14. Juniper EF, Thompson AK, Ferrie PJ, and Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol* 104:364-369, 1999.
15. Barnes ML, Vaidyanathan S, Williamson PA, and Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy* 40:242-250, 2010.
16. Juniper EF, Guyatt GH, Griffith LE, and Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 98:843-845, 1996.
17. Merck & Co., Inc. Nasonex package insert. Whitehouse Station, NJ; April 2012.
18. Watanabe H, Foo TH, Djazaeri B, et al. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. *Rhinology* 41:167-174, 2003.
19. Yoo JK, Seikaly H, and Calhoun KH. Extended use of topical nasal decongestants. *Laryngoscope* 107:40-43, 1997.
20. Ramey JT, Bailen E, and Lockey RF. Rhinitis medicamentosa. *J Invest Allergol Clin Immunol* 16:148-155, 2006.
21. Graf P. Rhinitis medicamentosa: Aspects of pathophysiology and treatment. *Allergy* 52(suppl):28-34, 1997.
22. Tas A, Yagiz R, Yalcin O, et al. Use of mometasone furoate aqueous nasal spray in the treatment of rhinitis medicamentosa: An experimental study. *Otolaryngol Head Neck Surg* 132:608-612, 2005. □

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