

Effect of mometasone furoate nasal spray on moderate-to-severe nasal congestion in seasonal allergic rhinitis: A responder analysis

Eduardo Urdaneta, M.D.,¹ Kaan Tunceli, M.A., Ph.D.,² and Davis Gates, Ph.D.³

ABSTRACT

Background: Nasal congestion is consistently identified as the most bothersome symptom of seasonal allergic rhinitis (SAR), and, in guidelines, intranasal corticosteroids are the preferred treatment for nasal congestion.

Objective: The aim of this post hoc cumulative responder analysis was to examine the nasal congestion response in detail by depicting the level of response obtained in two double-blind, placebo controlled studies of mometasone furoate nasal spray (MFNS) therapy for SAR, conducted from August to October 2008 at U.S. sites, in which nasal congestion was prespecified as the primary end point.

Methods: Patients ≥ 12 years of age with a ≥ 2 -year SAR history, positive skin test result, and moderate or severe nasal congestion were randomly assigned to once-daily treatment in the morning with MFNS or placebo for 15 days. The primary end point was the change from baseline in morning and evening reflective nasal congestion scores averaged over days 1–15. Treatment response, which ranged from $>0\%$ to $>90\%$ improvement, was evaluated at 10% intervals; $>30\%$ and $>50\%$ improvements were further evaluated by using the Mietinnen-Nurminen method weighted by study to test the differences of proportions. The Breslow-Day equal odds ratios test was used to justify pooling.

Results: Of the 344 and 340 patients in the MFNS and placebo groups, respectively, the proportions of patients who experienced a $>30\%$ response in nasal congestion, averaged over 15 days, were 37% versus 19% in the MFNS and placebo groups, respectively ($p < 0.001$). Those who experienced a $>50\%$ response were 13% and 7%, respectively ($p = 0.003$). Among the patients treated with MFNS, the mean response was greater during the second versus the first week of treatment. There was no difference between responses in the morning versus evening or for patients with moderate versus severe nasal congestion at baseline.

Conclusion: MFNS is effective in relieving moderate-to-severe nasal congestion in patients with SAR. The response to MFNS is maintained with once-daily administration and improves with continuous use over 2 weeks.

(Allergy Asthma Proc 40:173–179, 2019; doi: 10.2500/aap.2019.40.4214)

In the 2017 National Health Interview Survey,^{1,2} a diagnosis of hay fever during the previous 12 months was reported by 8% of adults and 8% of children ages <18 years in the United States. Hay fever (seasonal allergic rhinitis; SAR) is common both in the United States and globally, and causes a constellation of symptoms that have been associated with impaired

daily functioning, reduced quality of life, and negative effects on productivity at work and at school.^{3–5} Nasal congestion (stuffy or blocked nose) is a leading symptom in patients who seek medical care for SAR and is consistently identified in patient and physician surveys to be the most bothersome of the nasal symptoms that characterize SAR.^{4–8} Patients with nasal congestion report the discomfort of difficult nasal breathing and impaired sleep that results in daytime sleepiness.⁹

Intranasal corticosteroids (INS) are considered by clinical consensus to be the most effective medication class for treating SAR-related nasal congestion.^{9–11} However, studies focused on nasal congestion are uncommon¹² because most studies of therapies for SAR use a composite nasal symptom score, of which congestion is only one component, as the primary end point to evaluate response. In 2011, Meltzer *et al.*¹² reported the results of a study for which nasal congestion was the primary end point of therapy with mometasone furoate nasal spray (MFNS), an agent with previously established efficacy and safety for treating both SAR and perennial allergic rhinitis.^{12–14} They

From ¹Global Medical Affairs, ²Center for Observational and Real-World Evidence (CORE), and ³Biostatistics and Research Decision Sciences, Merck & Co., Inc., Kenilworth, New Jersey

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey

Writing and editorial support was provided by Elizabeth V. Hillyer, D.V.M., funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey

Poster presentation at The American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress, Orlando, Florida, March 2–5, 2018

E. Urdaneta, K. Tunceli, D. Gates are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and stockholders of Merck & Co., Inc., Kenilworth, New Jersey

Address correspondence to Eduardo Urdaneta, M.D., Global Medical Affairs, Merck & Co., Inc., 2000 Galloping Hill Rd., Kenilworth, NJ 07030

E-mail address: eduardo.urdaneta@merck.com

Copyright © 2019, OceanSide Publications, Inc., U.S.A.

found that both nasal congestion and total nasal symptom scores (TNSS) fell significantly more from baseline to day 15 with MFNS compared with placebo among adolescent and adult patients with SAR. This study, similar to others of INS therapy for SAR, summarized MFNS efficacy in terms of the change from baseline in symptom scores. Instead, studies that examined the level of response are uncommon.¹⁵

The aim of this *post hoc* cumulative responder analysis was to examine the nasal congestion response in greater detail by depicting the level of response obtained in the previously described study.¹² Our primary objective was to evaluate the average level of response, defined as the percentage change from baseline in nasal congestion, to 15 days of treatment with MFNS in adolescents and adults with SAR and moderate or severe nasal congestion at baseline. In addition, we compared the nasal congestion response in the first versus the second week, in the morning versus the evening, and among patients with moderate versus severe nasal congestion.

METHODS

Study Design and Patient Populations

This was a non-prespecified *post hoc* analysis of two randomized, double-blind, placebo controlled trials for which the study design and eligibility criteria were reported in detail in a previous publication.¹² The conduct of the trials adhered to the principles of Good Clinical Practice, and appropriate institutional review board approvals of the study protocols were obtained, as previously reported.¹²

The trials were conducted with an identical design at 24 sites in the United States from August to October 2008.¹² After the screening visit, followed by a no-treatment screening period of at least 3–14 days, eligible patients were randomly assigned at the baseline visit in a 1:1 ratio to once-daily treatment in the morning with MFNS 200 μ g or placebo for 15 days, with study visits scheduled on days 8 and 15. During the screening period and the 15-day study period, the patients recorded nasal congestion and other nasal symptoms on a diary card each day on awakening and again ~12 hours later in the two categories of “prior” (or reflective, *i.e.*, during the previous 12 hours) and “now” (current) symptoms.

Eligible patients were ≥ 12 years old, had a ≥ 2 -year history of SAR and a positive skin test result to appropriate seasonal antigens, and presented at both screening and baseline visits with moderate-to-severe nasal congestion, in conjunction with active SAR symptoms. Key exclusion criteria were an upper respiratory or sinus infection that required antibiotic therapy without a 14-day washout before the screening visit or an upper respiratory viral infection within 7 days before screen-

ing. Women who were breast-feeding, pregnant, or intending to become pregnant were also excluded.

Study Assessments

At the screening visit, the patients scored each of four nasal symptoms (nasal congestion/stuffiness, rhinorrhea, sneezing, and nasal itching) during the previous 12 hours on a four-point scale, from 0 (none) to 3 (severe), as follows: 0, none (no evidence of symptoms); 1, mild (symptom clearly present but easily tolerated); 2, moderate (definite awareness of symptom that was bothersome but tolerable); and 3, severe (symptom was hard to tolerate and caused interference with activities of daily living and/or sleeping). These four scores were summed for the TNSS, with a possible range of 0 to 12.

For study eligibility at screening, the patients had to have a nasal congestion score ≥ 2 , TNSS ≥ 6 , and a patient- and physician-assessed overall evaluation of SAR score ≥ 2 . At the baseline visit, the seven reflective scores were summed for the preceding 3 days and the morning of the visit, and patients with a total reflective nasal congestion score ≥ 14 and TNSS ≥ 42 were then randomly assigned to treatment with MFNS or placebo. Change from baseline in reflective nasal congestion scores was the primary end point in the previously reported trials, with combined results published as a single study.¹²

Responder Analysis

This responder analysis used the reflective SAR scores recorded morning and evening during the trials (*i.e.*, SAR symptoms over the 12 hours preceding each twice-daily diary recording). The primary *post hoc* end point was the percentage change from baseline (treatment response) in the nasal congestion score averaged over 15 days. The baseline score was calculated as the mean of the seven scores used at the baseline visit to determine eligibility, with a mean score of 2 to <2.5 defined as moderate nasal congestion, and a mean score of ≥ 2.5 defined as severe nasal congestion. We calculated the percentage treatment response at 10% intervals, ranging from $>0\%$ to $>90\%$ response (defined as improvement), in nasal congestion from baseline. For the purpose of the primary analysis of responders, the patients who showed $>30\%$ and $>50\%$ response in nasal congestion scores, averaged over 15 days, were examined. The secondary *post hoc* end points included the mean treatment response (1) in week 1 versus week 2, (2) in morning versus evening, and (3) for moderate versus severe nasal congestion at baseline.

Statistical Analysis

We evaluated the treatment differences in the commonly accepted criteria of $>30\%$ and $>50\%$ response

Table 1 Duration of SAR and severity of nasal congestion at baseline*

	MFNS 200 µg q.d. (n = 344)	Placebo (n = 340)	Total (N = 684)
Duration of SAR, median (IQR), y	18 (10–30)	20 (10–31)	19 (10–30)
Baseline nasal congestion score#			
<2 (less than moderate), no. (%)	4 (1)§	5 (1)	9 (1)
Mean ± SD score	1.95 ± 0.02	1.76 ± 0.28	1.84 ± 0.22
2 to <2.5 (moderate), no. (%)	115 (33)	110 (32)	225 (33)
Mean ± SD score	2.20 ± 0.17	2.21 ± 0.16	2.20 ± 0.16
>2.5 (severe), no. (%)	225 (65)	225 (66)	450 (66)
Mean ± SD score	2.86 ± 0.17	2.84 ± 0.17	2.85 ± 0.17

SAR = Seasonal allergic rhinitis; MFNS = mometasone furoate nasal spray; q.d. = once daily; IQR = interquartile range; SD = standard deviation.

* Percentages may not add up to 100% due to rounding.

Nasal congestion during the previous 12 hours was scored from 0 (none) to 3 (severe), and the baseline score represents the average of seven scores from the morning of the baseline visit and the morning and evening on 3 preceding days.

§ Four patients with baseline scores of <2 were not included in the analyses that compared the response to MFNS for patients with baseline moderate vs severe nasal congestion.

(improvements) in baseline nasal congestion scores by using the Mietinnen-Nurminen method with Cochrane-Mantel-Haenszel weights on protocol to determine descriptive *p* values.^{16,17} The Breslow-Day test of equal odds ratios was applied to each of these response criteria to justify pooling of the two trials, with the Breslow-Day test *p* < 0.20 considered to indicate a descriptive difference in odds ratios that would potentially invalidate the ability to pool the data.¹⁸

For the secondary end points, the McNemar test for paired responses was used to compare the nasal congestion response to MFNS between week 1 (days 1–8) and week 2 (days 9–15), and between the morning and evening scores. The Mietinnen-Nurminen method with Cochrane-Mantel-Haenszel weights was used to compare the response for patients with baseline moderate versus severe nasal congestion. The proportions of patients with a mean response from 0 to 100% were plotted to generate cumulative response curves to assess treatment differences for each end point. The *p* values generated were descriptive in nature. We did not conduct a formal power calculation because we considered that *post hoc* power calculations would be biased given the primary results of the two trials that have already been published.¹²

RESULTS

Patients and Change from Baseline in Nasal Congestion

The combined trials enrolled 684 patients, including 344 assigned to MFNS 200 µg and 340 assigned to placebo once daily in the morning, all of whom were included in these *post hoc* analyses. The median age of

the pooled populations was 39 years (range, 12–74 years), 435 (64%) were women, and 537 (79%) were white, as previously described.¹² The median SAR duration was 19 years, and two-thirds of the patients had severe nasal congestion at baseline (Table 1). As previously reported, the change from baseline in the reflective nasal congestion score averaged for the morning and evening over 15 days was significantly (*p* < 0.001) greater for the MFNS than for the placebo group, with least-squares mean decreases from baseline of 0.68 points (25%) and 0.45 points (16%), respectively. In addition, the morning current (“now”) nasal congestion score showed a significantly greater least-square mean change from baseline with MFNS than with placebo, which suggested that MFNS sustained efficacy over 24 hours.¹²

Cumulative Responder Analysis

Overall Response of Nasal Congestion. Response to treatment significantly favored MFNS over placebo at each 10% interval ranging from >0% to >90% improvement from baseline in nasal congestion averaged over 15 days of treatment (Fig. 1). The proportions of patients who experienced a >30% response in nasal congestion were 37% in the MFNS group compared with 19% in the placebo group (*p* < 0.001), and those who experienced a >50% response were 13% and 7%, respectively (*p* = 0.003) (Table 2). For the Breslow-Day test of equal odds ratios applied to each response criterion, the *p* value was ≥0.394, which supported the justification to pool the data.

Table 2 Results of responder analysis for nasal congestion: cumulative responses for MFNS vs placebo

Response,* mean over 15 days	Treatment groups		Difference (95% CI)	p#	BD Test Result
	MFNS (n = 344)	Placebo (n = 340)			
>0%, no. (%)	302 (87.8)	265 (77.9)	9.9 (4.3–15.5)	<0.001	0.23
>30%, no. (%)	126 (36.6)	66 (19.4)	17.2 (10.6–23.8)	<0.001	0.39
>50%, no. (%)	46 (13.4)	22 (6.5)	6.9 (2.5–11.5)	0.003	0.88

MFNS = Mometasone furoate nasal spray; CI = confidence interval; BD = Breslow-Day.

* Response was defined as the percentage change from baseline in nasal congestion score.

Calculated with the Miettinen-Nurminen method by using the Cochrane-Mantel-Haenszel weights on protocol.

Table 3 Results in the MFNS treatment group (n = 344): Mean in week 1 vs week 2

Response,* mean for each week	Week 1 (days 1–8)	Week 2 (days 9–15)	Difference	p#
>0%, no. (%)	285 (82.8)	293 (85.2)	–2.3	0.23
>30%, no. (%)	105 (30.5)	153 (44.5)	–14.0	<0.001
>50%, no. (%)	33 (9.6)	78 (22.7)	–13.1	<0.001

* Response was defined as the percentage change from baseline in nasal congestion score.

Calculated by using the McNemar test of paired responses.

Table 4 Results in the MFNS treatment group (n = 344): Mean in AM vs PM

Response,* mean in AM and PM	Time of Day		Difference	p#
	Morning (AM)	Evening (PM)		
>0%, no. (%)	288 (83.7)	282 (82.0)	1.7	0.40
>30%, no. (%)	120 (34.9)	140 (40.7)	–5.8	0.005
>50%, no. (%)	52 (15.1)	58 (16.9)	–1.7	0.27

* Response was defined as the percentage change from baseline in nasal congestion score.

Calculated by using the McNemar test of paired responses.

Table 5 Results in the MFNS treatment group (n = 344): Moderate vs severe nasal congestion*

Response#	Nasal Congestion		Difference (95% CI)	p§	BD Test Result
	Moderate (n = 115)	Severe (n = 225)			
>0%, no. (%)	97 (84.3)	201 (89.3)	–5.0 (–13.5 to 2.3)	0.19	0.57
>30%, no. (%)	45 (39.1)	79 (35.1)	4.1 (–6.6 to 15.1)	0.46	0.12
>50%, no. (%)	19 (16.5)	27 (12.0)	4.5 (–3.0 to 13.2)	0.25	0.68

MFNS = Mometasone furoate nasal spray; CI = confidence interval; BD = Breslow-Day.

* Four patients with less than moderate congestion were not included in the analyses.

Response was defined as the percentage change from baseline in nasal congestion score.

§ Calculated with the Miettinen-Nurminen method by using Cochrane-Mantel-Haenszel weights on protocol.

Response of Nasal Congestion to MFNS in Week 1 Versus Week 2. The magnitude of response was greater during the second week than the first week at each response interval for patients randomized to the MFNS group

(Fig. 2; Table 3). Significantly greater proportions of patients experienced a >30% response or a >50% response in week 2 than in week 1 ($p < 0.001$ for both comparisons, McNemar test). A >50% response was

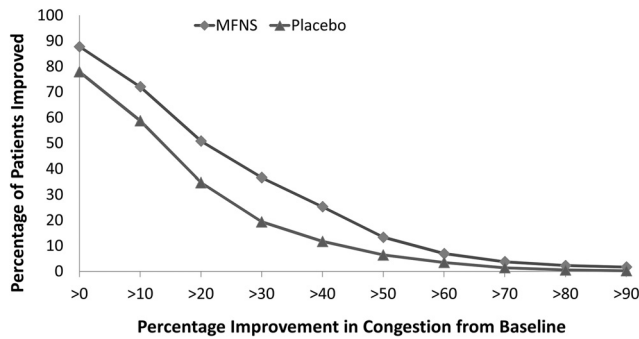


Figure 1. Cumulative response curves, showing the percentage improvement from baseline in nasal congestion scores averaged over 15 days of treatment with mometasone furoate nasal spray (MFNS) ($n = 344$) or placebo ($n = 340$).

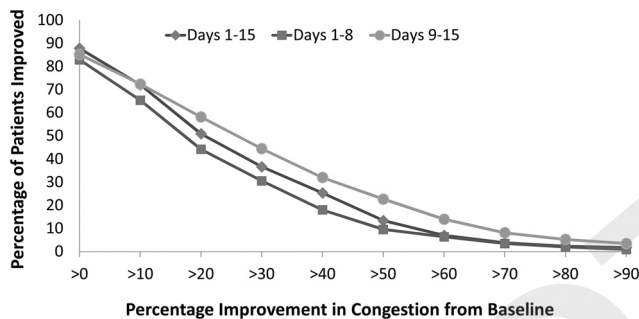


Figure 2. Cumulative response curves, showing the percentage improvement from baseline in nasal congestion scores averaged over week 1, week 2, and all 15 days of treatment with mometasone furoate nasal spray (MFNS) ($n = 344$).

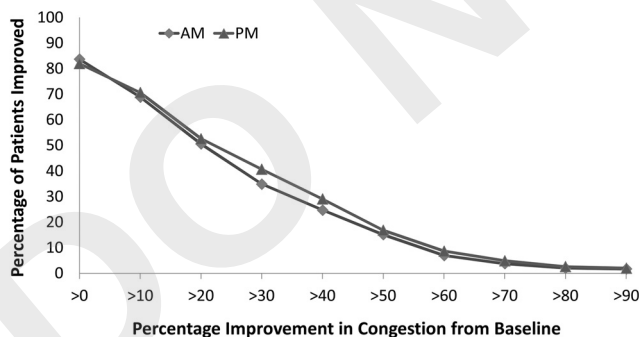


Figure 3. Cumulative response curves, showing the percentage improvement from baseline with mometasone furoate nasal spray (MFNS) in nasal congestion scores recorded in the morning (AM) and in the evening (PM).

calculated in week 1 for 10% and week 2 for 23% of patients in the MFNS group.

Response of Nasal Congestion to MFNS in the Morning Versus the Evening. The nasal congestion response in morning and evening was similar across most percentage intervals (Fig 3; Table 4). At the >30% response interval, there was a statistically significant difference of 6 percentage points (35% in the morning versus 41%

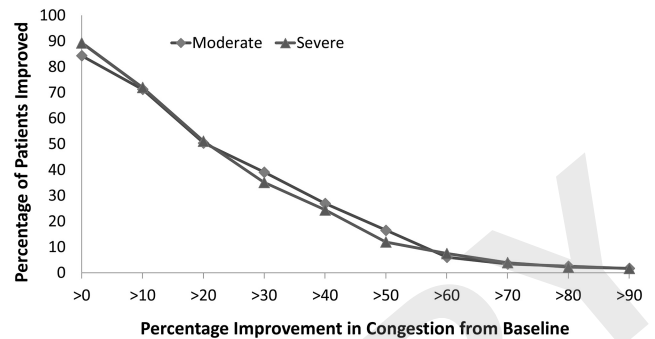


Figure 4. Cumulative response curves, showing the mean percentage improvement in nasal congestion from baseline with mometasone furoate nasal spray for patients with moderate or severe baseline nasal congestion.

in the evening; $p = 0.005$), whereas, at the >50% response interval, the nonsignificant treatment difference was ~2 percentage points (15% in the morning versus 17% in the evening; $p = 0.273$).

Response to MFNS of Moderate Versus Severe Baseline Nasal Congestion. The treatment response to MFNS was similar for patients with moderate or severe baseline nasal congestion (Fig 4; Table 5). (Four patients with less than moderate congestion were not included in the analyses.) Slightly higher proportions of patients with moderate nasal congestion showed a >30% response (39% versus 35% with severe congestion) and a >50% response (17% versus 12% with severe congestion), but these differences were not statistically significant ($p \geq 0.252$).

Handling of Missing Data. Missing data were considered as being a nonresponse in all analyses. Only 3 of 344 patients in the MFNS treatment group reported missing data (all were missing week 2 data), and 2 of 340 in the placebo group reported missing data (1 reported missing both weeks 1 and 2, and 1 reported missing week 2 data).

DISCUSSION

The nasal congestion response among patients prescribed MFNS was superior to that for placebo, as averaged over days 1–15 in this *post hoc* cumulative responder analysis of two combined clinical trials conducted from August to October 2008 at U.S. sites.¹² Significantly greater proportions of patients experienced any response (>0%), >30% response, and >50% response in the MFNS group compared with the placebo group. In the MFNS treatment group, significantly more patients showed responses to MFNS on days 9–15 compared with days 1–8, whereas morning and evening response proportions showed mostly comparable results, which suggested that once-daily

administration of MFNS was appropriate for patients with moderate-to-severe nasal congestion. In addition, the nasal congestion response was similar irrespective of congestion severity at baseline.

The results of this responder analysis provide clinically meaningful information with regard to expected improvements in nasal congestion, including the proportions of patients with various levels of improvement. This novel and uncommon analytic approach is different from and adds complementary information to the more usual clinical trial assessments of mean change from baseline nasal symptom scores relative to placebo. We were able to identify only one other responder analysis, also conducted *post hoc*, that evaluated therapy with an intranasal formulation of azelastine hydrochloride and fluticasone propionate for a similar patient population (≥ 12 years old, with moderate-to-severe SAR).¹⁵ However, comparisons with that analysis are not applicable because it differed in several regards from the present analysis by evaluating the response each day (rather than by week) of the TNSS (rather than solely nasal congestion). Moreover, the aim of the present study was to characterize the level of response over the 15-day treatment period, not to define a clinically relevant response *per se*.¹⁵

In the present study, nasal congestion responses occurred in both week 1 and week 2; however, significantly more patients showed mean responses of $>30\%$ or $>50\%$ on days 9–15 than on days 1–8, with a mean nasal congestion response during days 9–15 of $>30\%$ for almost half of patients (45%) and of $>50\%$ for almost one-fourth of the patients (23%). A clinical practice guideline for allergic rhinitis suggests that INS efficacy is reached within 1 week of therapy,¹¹ although 2 weeks of therapy may be required to attain maximum efficacy.¹⁰ Similarly, our findings suggest the benefit of continuous use of MFNS to achieve optimal anti-inflammatory effects and ongoing improvement in nasal congestion.

The required frequency of medication administration is an important factor in determining real-world adherence to therapy, with simpler regimens shown to maximize adherence.^{19–21} A review of studies that used electronic monitoring to determine medication adherence found that adherence was inversely proportional to the prescribed number of doses/day,²⁰ whereas a more-recent systematic review and meta-regression analysis of adherence in chronic disease found that patients are most adherent to once-daily regimens.²¹ For asthma, patients prescribed mometasone furoate *via* dry powder inhaler showed significantly better adherence with once-daily compared with twice-daily administration.²² In the present study, the response was sustained with once-daily administration. Although there was a statistical signal ($p = 0.005$)

that favored the evening (versus the morning response) in the $>30\%$ response bracket, we believe that the difference of <6 percentage points (34.9% in the morning versus 40.7% in the evening) is not clinically important.

Patients with moderate or severe nasal congestion responded similarly to treatment with MFNS. Baseline scores were higher, by definition, for the patients in the severe nasal congestion subgroup than those in the moderate subgroup, and the patients in the severe subgroup experienced larger absolute decreases from baseline because they had more room for improvement; however, the percentage improvements were similar in both subgroups after converting absolute scores to a percentage.

We drew on data from two well-designed, randomized, placebo controlled studies that enrolled 684 patients with SAR.¹² In addition to the large size and rigorous design, other strengths of this study include the well-characterized patient population, most of whom had long-standing SAR, and the fact that we used conservative assessments based on averaged symptom scores over 7–15 days, depending on outcome. A few data points were missing, and those we handled conservatively as constituting non-response. Moreover, we studied four different aspects of a SAR symptom long considered to be most bothersome, namely, nasal congestion. The data were drawn from clinical trials that designated nasal congestion as the primary end point.¹² Although we evaluated the same underlying data, we believe that use of a different metric, the responder analysis, provides additional relevant information that can be easily interpreted from a clinical perspective.

The main study limitation was the use of a *post hoc* analysis. In addition, the patient population was limited to patients with moderate or severe nasal congestion; we did not include patients with mild congestion, except for the nine patients in the MFNS versus placebo comparison. Moreover, the study design did not support an analysis of the speed of improvement of congestion, a topic for further study because quick relief is valued by patients with SAR.²³ Furthermore, work is needed to evaluate individual symptoms other than nasal congestion (outside of the composite symptom score).

CONCLUSION

In this study, we found that MFNS is effective in relieving moderate-to-severe nasal congestion in patients with SAR. The response to MFNS is maintained with once-daily administration and improves with continuous use over 2 weeks. Moreover, MFNS therapy produces similar levels of response in treating allergic rhinitis related nasal congestion regardless of the congestion severity at baseline.

ACKNOWLEDGMENTS

We thank Amanda Nafziger (Merck & Co., Inc., Kenilworth, NJ) for administrative support.

REFERENCES

1. Blackwell DL, Villarroel MA. Tables of summary health statistics for U.S. adults: 2017 National Health Interview Survey. 2018; https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-2.pdf. Accessed on March 18, 2019.
2. Black LI, Benson V. Tables of summary health statistics for U.S. children: 2017 National Health Interview Survey. 2018; https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_C-2.pdf. Accessed on March 18, 2019.
3. Blaiss MS, Hammerby E, Robinson S, Kennedy-Martin T, Buchs S. The burden of allergic rhinitis and allergic rhinoconjunctivitis on adolescents: a literature review. *Ann Allergy Asthma Immunol*. 2018; 121:43–52.e3.
4. Bielory L, Skoner DP, Blaiss MS, et al. Ocular and nasal allergy symptom burden in America: the Allergies, Immunotherapy, and Rhinoconjunctivitis (AIRS) surveys *Allergy Asthma Proc*. 2014; 35:211–218.
5. Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc*. 2012; 33(Suppl 1):S113–S141.
6. Popov TA, Kralimarkova TZ, Staevska MT, Dimitrov VD. Characteristics of a patient population seeking medical advice for nasal symptoms in Bulgaria. *Ann Allergy Asthma Immunol*. 2012; 108:232–236.
7. Scadding G, Price D, El-Shanawany T, et al. Multicentre, non-interventional study to assess the profile of patients with uncontrolled rhinitis prescribed a novel formulation of azelastine hydrochloride and fluticasone propionate in a single spray in routine clinical practice in the UK. *BMJ Open*. 2017; 7:e014777.
8. Marple BF. Targeting congestion in allergic rhinitis: the importance of intranasal corticosteroids. *Allergy Asthma Proc*. 2008; 29:232–240.
9. Thompson A, Sardana N, Craig TJ. Sleep impairment and daytime sleepiness in patients with allergic rhinitis: the role of congestion and inflammation. *Ann Allergy Asthma Immunol*. 2013; 111:446–451.
10. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization. GA(2)LEN and AllerGen). *Al-lergy*. 2008; 63(Suppl 86):8–160.
11. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015; 152(Suppl):S1–S43.
12. Meltzer EO, Shekar T, Teper AA. Mometasone furoate nasal spray for moderate-to-severe nasal congestion in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2011; 32:159–167.
13. Berkowitz RB, Roberson S, Zora J, et al. Mometasone furoate nasal spray is rapidly effective in the treatment of seasonal allergic rhinitis in an outdoor (park), acute exposure setting. *Allergy Asthma Proc*. 1999; 20:167–172.
14. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy*. 1996; 51: 569–576.
15. Meltzer E, Ratner P, Bachert C, et al. Clinically relevant effect of a new intranasal therapy (MP29–02) in allergic rhinitis assessed by responder analysis. *Int Arch Allergy Immunol*. 2013; 161: 369–377.
16. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med*. 1985; 4:213–226.
17. Lu K. Cochran–Mantel–Haenszel weighted Miettinen and Nurminen method for confidence intervals of the difference in binomial proportions from stratified 2 x 2 samples. In *JSM Proceedings*. Denver, CO: American Statistical Association, 2008; p. 3888–3893.
18. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. Lyon, France: IARC Scientific Publications; 1980.
19. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353:487–497.
20. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001; 23:1296–1310.
21. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm*. 2012; 18:527–539.
22. Price D, Robertson A, Bullen K, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med*. 2010; 10:1.
23. Meltzer EO, Farrar JR, Sennett C. Findings from an online survey assessing the burden and management of seasonal allergic rhinoconjunctivitis in US patients. *J Allergy Clin Immunol Pract* 2017; 5:779–78.e6. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.