Safety of a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in children: A randomized clinical trial

William Berger, M.D.,¹ Ellen Sher, M.D.,² Sandra Gawchik, D.O.,³ and Stanley Fineman, M.D.⁴

ABSTRACT

Background: The safety of a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) has been established in adults and adolescents with allergic rhinitis but not in children <12 years old.

Objective: To evaluate the safety and tolerability of an intranasal formulation of AZE and FP in children ages 4–11 years with allergic rhinitis.

Methods: The study was a randomized, 3-month, parallel-group, open-label design. Qualified patients were randomized in a 3:1 ratio to AZE/FP (n = 304) or fluticasone propionate (FP) (n = 101), one spray per nostril twice daily, and to one of three age groups: ≥4 to <6 years, ≥6 to <9 years, and ≥9 to <12 years. Safety was assessed by child- or caregiver-reported adverse events, nasal examinations, vital signs, and laboratory assessments.

Results: The incidence of treatment-related adverse events (TRAEs) was low in both the AZE/FP (16%) and FP-only (12%) groups after 90 days' continuous use. Epistaxis was the most frequently reported TRAE in both groups (AZE/FP, 9%; FP, 9%), followed by headache (AZE/FP, 3%; FP, 1%). All other TRAEs in the AZE/FP group were reported by ≤1% of the children. The majority of TRAEs were of mild intensity and resolved spontaneously. Results of nasal examinations showed an improvement over time in both groups, with no cases of mucosal ulceration or nasal septal perforation. There were no unusual or unexpected changes in laboratory parameters or vital signs.

Conclusion: The intranasal formulation of AZE and FP was safe and well tolerated after 3 months' continuous use in children with allergic rhinitis.

The study was registered on ClinicalTrials.gov (NCT01794741).

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Allergic rhinitis (AR) is one of the most prevalent chronic diseases in the general population and affects as many as 500 million people worldwide.^{1–3} Its prevalence in the United States is estimated at 60–90 million individuals, including as many as 40% of children.^{4,5} Although often considered no more than a nuisance, the overall U.S. health care cost of AR is high, with annual direct costs of ~\$7 billion² and indirect costs as high as \$12 billion.^{2,6}

The burden of nasal allergy symptoms has profound adverse effects on children's overall physical and emotional health, sleep quality, and daily lives, which results

in lower quality of life (QoL).⁵ In addition to nasal and ocular symptoms, many children with AR experience headache, fatigue, cognitive impairment, and problems with sleep,⁷ which affect learning and social activities.⁵ In the United States, as many as 2 million school days are lost to AR annually.^{8,9} Children with untreated AR often experience psychological difficulties, including low self-esteem, anxiety, and depression.¹⁰ Also, many children with AR have comorbid uncontrolled asthma.¹¹

There is a need for a new AR treatment option suitable for children that provides rapid and more complete symptom relief than past treatments (*i.e.*, intranasal corticosteroids [INS] and antihistamines), without safety repercussions. Among recent advances is Meda Pharma's AzeFlu (MP-AzeFlu) (Dymista; Mylan, Inc., Canonsburg, PA), a novel intranasal formulation that contains azelastine hydrochloride (AZE), fluticasone propionate (FP), and excipients delivered in a single spray.¹² In adults and adolescents, MP-AzeFlu provides twice the nasal and ocular symptom relief as INS or intranasal antihistamine monotherapy, and better long-term nasal symptom relief than FP in adults with perennial AR (PAR) or non-AR.^{13,14} Its short- and long-term safety in these populations is well established.^{13,15,16}

From the ¹Allergy and Asthma Associates of Southern California, Mission Viejo, California, ²Atlantic Allergy, Asthma and Immunology Associates of New Jersey, Ocean, New Jersey, ³Asthma Allergy Associates, Glen Mills, Pennsylvania, and ⁴Atlanta Allergy and Asthma Clinic, Marietta, Georgia

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Address correspondence to William E. Berger, M.D., Allergy and Asthma Associates of Southern California, Mission Viejo, CA 92691

E-mail address: weberger@uci.edu

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The short- and long-term efficacy of MP-AzeFlu in pediatric AR has also been assessed.^{17,18} Children ages 4–11 years with seasonal AR (SAR) treated with MP-AzeFlu for 2 weeks experienced statistically superior and clinically relevant improvement in their QoL compared with children treated with placebo. Superiority of MP-AzeFlu was also observed for both overall nasal and ocular symptom relief.¹⁷ A second study also found that MP-AzeFlu provided significantly greater AR symptom relief than FP alone.¹⁸ MP-AzeFlu has been granted approval for use in this age group by the U.S. Food and Drug Administration (FDA). The objective of this clinical trial was to evaluate the safety and tolerability of MP-AzeFlu in children ages 4–11 years with AR.

METHODS

Study Design

This was a prospective, randomized, multicenter, active controlled, open-label, parallel-group, outpatient safety study (NCT01794741) conducted in children 4–11 years of age with AR at 42 sites in the United States between March and October 2013. Ethics approval was obtained (Chesapeake Research Review Inc., Columbia, MD), and the study was conducted in accordance with Good Clinical Practice in compliance with the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.^{19,20} The study design was based on guidance from the FDA's Division of Pulmonary, Allergy, and Rheumatology Products. Caregiver written informed consent and pediatric assent (for children ≥ 7 years old) was obtained. The study consisted of a washout period for prohibited concomitant medications, a lead-in period (2–30 days), and a 3-month active-treatment period. After baseline screening (day 1), clinic visits were scheduled on study days 15, 30, 60, and 90.

Patients

Male and female children 4–11 years old with a history of AR (SAR or PAR) who, in the opinion of the study center investigators, could benefit from treatment with MP-AzeFlu were eligible for inclusion. Children were required to be in generally good health, without concomitant disease or medical treatment that could interfere with interpretation of study results. Generally, the use of concomitant medication was discouraged; however, medications considered necessary and that did not interfere with the evaluation of study medications were allowed at investigator discretion. (See the Online Supplement Text for a list of prohibited medications.) Children who were receiving immunotherapy on a stable regimen were eligible. Exclusion criteria are given in the Online Supplement Text.

Treatment Groups and Randomization

The children were randomized to either MP-AzeFlu (137 μg AZE and 50 μg FP per spray) or FP nasal spray (50 μg per spray). A centralized, age-group stratified, block randomization scheme using Proc Plan (SAS, Cary, NC) was used to assign subjects to treatment (3:1 ratio). An interactive Web response system ensured proper stratification. Treatments were administered as one spray per nostril twice daily, morning and evening, which provided total daily doses of 548 μg for MP-AzeFlu and 200 μg for FP. Assessment of treatment compliance and exposure is described in the Online Supplement Text.

Safety Variables

Safety variables included child- or caregiver-reported adverse events (AE), nasal examinations, vital signs, and laboratory assessments. AEs were recorded at baseline and each study visit, categorized by incidence, type, and severity (see Online Supplement Text), and were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 16.0) (see Online Supplement Text). Conditions already present that did not worsen were not considered AEs. The relationship of an AE to the study medication was assessed by study center investigators as unlikely, possibly, or probably related (see Online Supplement Text). The children underwent a direct visual nasal examination at baseline and each visit that included nasal mucosal grading (grade 0–4) (see Online Supplement Text). Epistaxis, mucosal edema, nasal discharge, mucosal erythema, mucosal bleeding, and mucosal crusting were also assessed and graded as none, mild, moderate, or severe. Vital signs were recorded at each visit. Laboratory assessments were recorded at baseline and day 90.

Statistical Analysis

The sample size for this study was based on clinical considerations and discussions with the FDA. The children were stratified into three age groups: ≥ 4 to < 6 years, ≥ 6 to < 9 years, and ≥ 9 to < 12 years. Safety analyses (SAS, version 9.2) were performed on the safety population, defined as all randomized children who received one or more doses of study medication. Data were summarized for each treatment group and age stratum, and were pooled across strata. Continuous data were summarized as mean $\pm$ standard deviation. Categorical data were presented as number and percentage.

RESULTS

Patient Disposition

A total of 405 children were randomized to treatment, and 404 were included in the safety population (Fig. 1). Completion rates were similar in both treat-

Figure 1. Subject disposition.

ment groups (MP-AzeFlu, 94%; FP, 91%) and across age strata (see Online Supplemental Table 1). The rate of discontinuation due to AEs was 2% with MP-AzeFlu and 4% with FP.

Demographic and Baseline Characteristics

Of the randomized patients, 51 (12.6%) were ≥ 4 to < 6 years old, 173 (42.7%) were ≥ 6 to < 9 years old, and 181 (44.7%) were ≥ 9 to < 12 years old. The treatment groups were comparable in demographic and baseline clinical characteristics overall and for each age stratum (Table 1). Fifteen children (all ages 6–11 years) were on stable immunotherapy during the study (13 MP-AzeFlu, 2 FP).

Exposure and Treatment Compliance

The mean duration of exposure to the study drug and of the total and average numbers of sprays taken were similar in both groups, in the overall population, and by age stratum (Table 2). The rate of treatment compliance was high ($> 96\%$) and comparable in both groups across the age strata.

AEs

The percentage of subjects with one or more treatment-emergent AEs (TEAE) and one or more treatment-related AEs (TRAEs) over 3 months was similar in the MP-AzeFlu and FP groups (Table 3). TEAEs and TRAEs were usually mild in severity. There were no deaths. One child in the MP-AzeFlu group reported two serious AEs (gastroenteritis and elevated liver function tests), consistent with flu-like symptoms, which resolved within days and were considered unlikely to be related to MP-AzeFlu treatment.

Epistaxis was the most common TEAE in both groups, followed by headache with MP-AzeFlu and diarrhea with FP (Table 4). Fewer than 1% of the subjects experienced somnolence or dysgeusia. Epistaxis was also the most common TRAE in both groups, followed by headache with MP-AzeFlu (Table 5). All other TRAEs in the MP-AzeFlu group occurred in $\leq 1\%$ of the children, for all age strata. In the FP group, the next most common TRAE was mucosal erosion (2%), with all other events reported by $\leq 1\%$ of the children.

Nasal Examinations

Children in both treatment groups had similar nasal examination findings. The severity of nasal symptoms generally reduced over the course of treatment in both groups (Online Supplemental Table 2). There were no cases of nasal mucosal ulceration or nasal septal perforation.

Vital Signs and Laboratory Assessments

Laboratory parameters showed no clinically relevant increases or decreases in either treatment group (Online Supplemental Table 3), and changes were similar between the groups and across the age strata. Similarly, there were no noteworthy findings in changes from baseline in vital signs in either group or for different age strata (Online Supplemental Table 4).

DISCUSSION

This study showed, for the first time to our knowledge, that MP-AzeFlu was safe and well tolerated during 3 months' continuous use in children ages 4 to 11 years with AR. MP-AzeFlu's good tolerability profile was confirmed in very young children (age group ≥ 4 to < 6 years) and older children (age groups ≥ 6 to < 9

Table 1 Demographic and baseline characteristics (safety population)

	All Age Strata		Ages ≥4 to <6 y		Ages ≥6 to <9 y		Ages ≥9 to <12 y	
	MP-AzeFlu (n = 304)	FP (n = 100)	MP-AzeFlu (n = 40)	FP (n = 11)	MP-AzeFlu (n = 128)	FP (n = 44)	MP-AzeFlu (n = 136)	FP (n = 45)
Age, mean ± SD, y	8.1 ± 2.1	8.1 ± 1.9	4.6 ± 0.5	4.6 ± 0.5	7.2 ± 0.8	7.2 ± 0.8	10.0 ± 0.8	9.9 ± 0.8
Boys, no. (%)	183 (60)	51 (51)	25 (63)	5 (45)	70 (55)	20 (45)	88 (65)	26 (58)
Race, no. (%)								
American Indian/Alaska Native	4 (1)	1 (1)	1 (3)	0 (0)	2 (2)	1 (2)	1 (<1)	0 (0)
Asian	12 (4)	1 (1)	2 (5)	0 (0)	4 (3)	1 (2)	6 (4)	0 (0)
Black/African American	62 (20)	21 (21)	12 (30)	3 (27)	24 (19)	11 (25)	26 (19)	7 (16)
Native Hawaiian/other	2 (1)	1 (1)	0 (0)	0 (0)	2 (2)	1 (2)	0 (0)	0 (0)
Pacific Islander								
White	237 (78)	80 (80)	26 (65)	9 (82)	100 (78)	31 (70)	111 (82)	40 (89)
Other	1 (<1)	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
TSS, mean ± SD	1.72 ± 0.76	1.77 ± 0.73	1.64 ± 0.76	1.50 ± 0.73	1.74 ± 0.73	1.76 ± 0.69	1.73 ± 0.81	1.84 ± 0.77
PRQLQ score, mean ± SD	1.84 ± 1.05	1.88 ± 1.15	—	—	1.84 ± 1.03	2.01 ± 1.23	1.84 ± 1.07	1.75 ± 1.06

MP-AzeFlu = Meda Pharma's azelastine hydrochloride and fluticasone propionate; FP = fluticasone propionate; SD = standard deviation; TSS = total symptom score; PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire.

Table 2 Duration of exposure and compliance with medication (safety population)

	All Age Strata		Ages ≥4 to <6 y		Ages ≥6 to <9 y		Ages ≥9 to <12 y	
	MP-AzeFlu (n = 304)	FP (n = 100)	MP-AzeFlu (n = 40)	FP (n = 11)	MP-AzeFlu (n = 128)	FP (n = 44)	MP-AzeFlu (n = 136)	FP (n = 45)
Exposure, mean ± SD, days	85.9 ± 14.4	85.2 ± 16.7	86.0 ± 18.3	87.5 ± 7.6	85.6 ± 14.9	83.4 ± 20.4	86.2 ± 12.7	86.3 ± 14.1
Total No. sprays, mean ± SD	333.7 ± 58.6	333.3 ± 65.9	338.6 ± 72.2	342.3 ± 30.1	330.9 ± 61.5	326.5 ± 81.3	334.9 ± 51.5	337.8 ± 55.3
Average No. sprays/day, mean ± SD	3.9 ± 0.2	3.9 ± 0.2	3.9 ± 0.1	3.9 ± 0.1	3.9 ± 0.3	3.9 ± 0.2	3.9 ± 0.2	3.9 ± 0.1
Compliance, mean ± SD, %	96.9 ± 5.2	97.5 ± 4.2	98.5 ± 2.4	97.8 ± 2.7	96.1 ± 6.9	97.1 ± 5.6	97.1 ± 3.7	97.9 ± 2.5
Subjects with 80% compliance overall, no. (%)	300 (99)	97 (97)	38 (95)	11 (100)	126 (98)	42 (95)	136 (100)	44 (98)

MP-AzeFlu = Meda Pharma's azelastine hydrochloride and fluticasone propionate; FP = fluticasone propionate; SD = standard deviation.

Table 3 Overview of adverse events (safety population)

	All Age Strata		Ages ≥ 4 to < 6 y		Ages ≥ 6 to < 9 y		Ages ≥ 9 to < 12 y	
	MP-AzeFlu (n = 304)	FP (n = 100)	MP-AzeFlu (n = 40)	FP (n = 11)	MP-AzeFlu (n = 128)	FP (n = 44)	MP-AzeFlu (n = 136)	FP (n = 45)
≥ 1 TEAE, no. (%)	124 (41)	37 (37)	18 (45)	5 (45)	51 (40)	15 (34)	55 (40)	17 (38)
≥ 1 TRAE, no. (%)	49 (16)	12 (12)	8 (20)	1 (9)	15 (12)	6 (14)	26 (19)	5 (11)
≥ 1 SAE, no. (%)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)
≥ 1 TEAE that led to discontinuation, no. (%)	6 (2)	4 (4)	2 (5)	1 (9)	0 (0)	1 (2)	4 (3)	2 (4)
Deaths, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

MP-AzeFlu = Meda Pharma's azelastine hydrochloride and fluticasone propionate; FP = fluticasone propionate; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; SAE = serious adverse event.

Table 4 TEAEs (safety population)*

	All Age Strata		Ages ≥ 4 to < 6 y		Ages ≥ 6 to < 9 y		Ages ≥ 9 to < 12 y	
	MP-AzeFlu (n = 304)	FP (n = 100)	MP-AzeFlu (n = 40)	FP (n = 11)	MP-AzeFlu (n = 128)	FP (n = 44)	MP-AzeFlu (n = 136)	FP (n = 45)
Any TEAE, no. (%)	124 (41)	37 (37)	18 (45)	5 (45)	51 (40)	15 (34)	55 (40)	17 (38)
Epistaxis	30 (10)	9 (9)	4 (10)	1 (9)	12 (9)	4 (9)	14 (10)	4 (9)
Headache	20 (7)	3 (3)	2 (5)	0 (0)	10 (8)	3 (7)	8 (6)	0 (0)
Cough	11 (4)	3 (3)	3 (8)	0 (0)	4 (3)	2 (5)	4 (3)	1 (2)
Pyrexia	10 (3)	2 (2)	2 (5)	0 (0)	4 (3)	0 (0)	4 (3)	2 (4)
Oropharyngeal pain	9 (3)	0 (0)	0 (0)	0 (0)	4 (3)	0 (0)	5 (4)	0 (0)
Otitis media	9 (3)	3 (3)	3 (8)	0 (0)	5 (4)	1 (2)	1 (< 1)	2 (4)
Vomiting	9 (3)	2 (2)	0 (0)	1 (9)	6 (5)	0 (0)	3 (2)	1 (2)
Upper abdominal pain	8 (3)	2 (2)	0 (0)	1 (9)	5 (4)	1 (2)	3 (2)	0 (0)
URTI	8 (3)	1 (1)	2 (5)	1 (9)	2 (2)	0 (0)	4 (3)	0 (0)
Diarrhea	4 (1)	4 (4)	0 (0)	2 (18)	1 (< 1)	1 (2)	3 (2)	1 (2)

TEAE = treatment-emergent adverse event; MP-AzeFlu = Meda Pharma's azelastine hydrochloride and fluticasone propionate; FP = fluticasone propionate; URTI = upper respiratory tract infection.

*TEAEs recorded are those reported by $\geq 3\%$ of the subjects in either treatment group.

years and ≥ 9 to < 12 years), with a low incidence of TRAEs, improvement in nasal examination findings, and no clinically relevant changes in vital signs or laboratory parameters. Epistaxis, headache, and cough were the most common AEs (consistent with a diagnosis of AR) and were generally mild and spontaneously resolving. The incidence of sedation or drowsiness with MP-AzeFlu was low ($< 1\%$), and taste problems were uncommon ($< 1\%$). Somewhat fewer children discontinued the study due to AEs with MP-AzeFlu (2%) than with FP (4%). Based on these and other study results,^{17,18} MP-AzeFlu was approved by the FDA in February 2015 for use in children 6 to 11 years of age at a dosage of one spray per nostril twice daily.²¹

The data obtained in this study were generalizable to the broad pediatric population because they were consis-

tent with similar safety findings in adults, adolescents, and children, both in randomized controlled trials and observational studies.^{15–17,22} The safety and tolerability profile of MP-AzeFlu was established in adults and adolescents in a large clinical trial program that involved > 4000 patients with SAR^{13,15} and almost 3000 patients in a real-life study.²² MP-AzeFlu was also evaluated in a 1-year safety trial in > 600 adult patients with chronic rhinitis (*i.e.*, PAR or non-AR).¹⁶ Similar to the present study, the 1-year safety trial found a low incidence of TRAEs with MP-AzeFlu (9.4%) or FP (11.1%) treatment for 52 weeks, with no evidence of late-occurring AEs.¹⁶ Nasal examinations improved over time, no ulcerations or septal perforations occurred, ocular examination findings were unremarkable, and hypothalamic pituitary adrenal axis suppression was not observed.¹⁶ The safety of

Table 5 TRAEs (safety population)*

	All Age Strata		Ages ≥ 4 to < 6 y		Ages ≥ 6 to < 9 y		Ages ≥ 9 to < 12 y	
	MP-AzeFlu (n = 304)	FP (n = 100)	MP-AzeFlu (n = 40)	FP (n = 11)	MP-AzeFlu (n = 128)	FP (n = 44)	MP-AzeFlu (n = 136)	FP (n = 45)
Any TRAE, no. (%)	49 (16)	12 (12)	8 (20)	1 (9)	15 (12)	6 (14)	26 (19)	5 (11)
Epistaxis	27 (9)	9 (9)	4 (10)	1 (9)	10 (8)	4 (9)	13 (10)	4 (9)
Headache	10 (3)	1 (1)	1 (3)	0 (0)	5 (4)	1 (2)	4 (3)	0 (0)

TRAE = Treatment-related adverse event; MP-AzeFlu = Meda Pharma's azelastine hydrochloride and fluticasone propionate; FP = fluticasone propionate.

*TRAEs recorded are those reported by $\geq 3\%$ of the subjects in either treatment group.

MP-AzeFlu in adults and adolescents has been comprehensively reviewed.²³

A recent randomized, double-blind, placebo controlled, parallel-group study confirmed the good safety and tolerability profile of MP-AzeFlu in 348 children (ages 4–11 years) with moderate-to-severe SAR.¹⁷ In that study, 16.2% of children who received MP-AzeFlu and 13.1% who received placebo reported one or more TEAEs, and, of these, 8.7% and 3.4%, respectively, were considered TRAEs. Epistaxis occurred at similar rates in the MP-AzeFlu (3.5%) and placebo (3.4%) groups. All TRAEs were considered mild, and no serious AEs were reported.¹⁷ Similar to the current study, MP-AzeFlu use for 14 days was not associated with any significantly focused nasal examination finding. The proportion of children with moderate or severe mucosal edema or nasal discharge decreased over time, and slight improvements in mucosal erythema were found with MP-AzeFlu.¹⁷

The superior symptom relief afforded by MP-AzeFlu in adults and adolescents^{13–15,22} has also been mirrored in the pediatric AR population.^{17,18} Children treated with MP-AzeFlu for 14 days experienced statistically superior and clinically relevant improvement in QoL by day 8 compared with those who received placebo.¹⁷ MP-AzeFlu also provided significantly better relief than placebo from nasal symptoms ($p = 0.002$) and ocular symptoms ($p = 0.009$).¹⁷ In addition, in efficacy data from the present study (published separately), children who received MP-AzeFlu for 3 months experienced significantly ($p = 0.0410$) better nasal symptom reduction than those who received FP.¹⁸ Furthermore, approximately 8 of 10 children treated with MP-AzeFlu in the pediatric study were symptom free or had mild symptoms within 1 month. This status was obtained up to 16 days faster with MP-AzeFlu versus FP.¹⁸ Achieving rapid symptom control should improve treatment compliance and improve school performance²⁴ and asthma control.²⁵

How MP-AzeFlu should be used in the pediatric AR population is a matter of both physician and patient preference. The choice for first-line use of MP-AzeFlu

reflects a “high to low” preference, starting with the pharmacologic treatment option with the best efficacy-to-safety ratio and then stepping down if tolerated. First-line use of MP-AzeFlu is supported by its rapid symptom relief (within minutes) and that it causes twice the ocular and nasal symptom control as an INS (specifically FP),¹⁸ with comparable safety, all of which should improve adherence. The growing evidence base that shows that mono and multiple AR treatment regimens provide insufficient symptom relief for many patients further supports first-line use of MP-AzeFlu.²⁶ Immunotherapy and strict environmental control measures are options; however, these steps are not always easily implemented for pediatric patients.²⁷

The choice for second-line use of MP-AzeFlu reflects a “low to high” preference, starting with a lower-efficacy treatment and stepping up when required. This step-up approach may be particularly challenging in children, in whom speed of effect and the degree of response directly influence treatment concordance. A step-up approach, therefore, should be carefully weighed against the potential for reduced compliance and treatment failure, the consequent delay in achieving disease control, and the increased medication and physician visit costs. For example, although second-generation oral antihistamines are a mainstay of AR treatment in children, they may not be adequate for relief of moderate-to-severe symptoms, especially nasal congestion.²⁸ Likewise, many children derive insufficient symptom relief from INS, with nasal sprays providing complete relief in only 17% of respondents of the Pediatric Allergies in America survey.⁵ Adding oral antihistamines to INS therapy offers no benefit over INS alone,^{29,30} whereas use of multiple treatments (such as intranasal antihistamine and INS) is likely to impair compliance and is associated with less homogeneous distribution within the nasal cavity and increased runoff (both anteriorly and posteriorly) compared with MP-AzeFlu.^{31,32}

There are some inherent limitations and constraints in conducting clinical trials in children with AR. Efficacy evaluations and AE reports in these studies reflected subjective assessments by the patient or the caregiver.

The reporting of AEs by children may be limited by their ability to verbalize or the parent's or caregiver's interpretation. However, in general, caregivers pay close attention to any event in their child that could be interpreted as an AE. Despite these potential limitations, the safety profile of MP-AzeFlu in the current pediatric study was favorable and generally similar to that seen with MP-AzeFlu in adults and adolescents.^{15,16,22}

CONCLUSION

MP-AzeFlu was safe and well tolerated after 3 months' continuous use in children with AR. Analysis of these data supported the effectiveness of MP-AzeFlu for the treatment of moderate-to-severe AR in the pediatric population.

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