Efficacy of a Novel Intranasal Formulation of Azelastine Hydrochloride and Fluticasone Propionate, Delivered in a Single Spray, for the Treatment of Seasonal Allergic Rhinitis: Results from Russia

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Keywords

Allergic rhinitis · Azelastine · Fluticasone propionate · Intranasal · MP-AzeFlu · Moderate-to-severe rhinitis · Russia · Seasonal

Abstract

Background: The novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) in a single spray (MP-AzeFlu) was compared with a first-line intranasal antihistamine spray (AZE) in Russian seasonal allergic rhinitis (SAR) patients. **Methods:** Moderate-to-severe SAR/rhinoconjunctivitis patients ($n = 149$; aged 18–65 years) were randomized to receive MP-AzeFlu (137/50 μg AZE/FP per spray) or AZE (137 μg /spray), both as 1 spray/nostril twice daily, in a multicenter, open-label, 14-day, parallel-group trial. The primary outcome was change from baseline in morning and evening reflective total nasal symptom score (rTNSS). Secondary end points included: change from baseline in reflective total ocular symptom score (rTOSS), reflective total

of 7 symptom scores (rT7SS), 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) overall score, and Euro-QoL-5D (EQ-5D) questionnaire score. **Results:** When compared with AZE-treated patients, those treated with MP-AzeFlu experienced significantly greater reductions in rTNSS (difference: -2.47 ; 95% confidence interval [CI] -3.65 to -1.30 ; $p < 0.001$), rTOSS (difference: -1.62 ; 95% CI -2.32 to -0.92 ; $p < 0.001$), and rT7SS (difference: -4.34 ; 95% CI -5.98 to -2.70 ; $p < 0.001$). Superior relief observed on day 2 with MP-AzeFlu versus AZE was sustained throughout the study. MP-AzeFlu-treated patients experienced a greater improvement in QoL than AZE-treated patients as measured by overall RQLQ score (mean $\pm$ SD 2.91 ± 1.08 vs. 2.05 ± 1.15) and EQ-5D score (mean $\pm$ SD 87.4 ± 10.3 vs. 83.0 ± 12.8). MP-AzeFlu was well tolerated. **Conclusions:** MP-AzeFlu was superior to AZE in reducing moderate-to-severe SAR symptoms, providing earlier and more complete symptom relief.

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Introduction

Allergic rhinitis (AR) is a global health problem affecting as many as 500 million people worldwide [1]. A recent epidemiological study in 12 regions of the Russian Federation found AR symptoms in 18% of the population, among whom only 6.5% had a prior diagnosis of AR [2]. From the perspective of patients, AR causes significant morbidity, has a considerable impact on quality of life (QoL) [3, 4], and affects school and work attendance and productivity [5, 6]. The symptoms of AR and allergic rhinoconjunctivitis in Russian patients are found to impair health-related QoL to the same extent as patients in westernized countries, by adversely impacting sleep, daily activities, physical and mental status, and social functioning [7]. AR results in considerable healthcare costs [1] and, if untreated, may have considerable economic and QoL implications [8–10]. The impact of AR on productivity is higher than that of asthma, diabetes, or heart disease [9, 10].

Intranasal antihistamines are considered the first-line therapy for AR in both the USA and Russia [1, 2]. Currently, intranasal corticosteroids (INS) are the first-line treatment for AR according to the US Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1]. INS are recommended for use in patients with mild, mild-to-moderate, and moderate-to-severe disease [1, 11–13]. However, current treatments for AR provide insufficient control for many patients. In both clinical trials and real-life studies, many patients experience inadequate symptom relief while on INS due to their slow onset of action, symptom breakthrough [14], and an efficacy ceiling of a 60% reduction from baseline in reflective total nasal symptom score (rTNSS) [15]. This leads to patient dissatisfaction and poor compliance with INS therapy [16].

Switching INS type is not an effective solution, as different types have comparable efficacy [17, 18]. Consequently, many patients use multiple therapies [19] while searching for better and faster symptom relief [19], or simply “something that works” [20]. However, such multiparmacotherapy is not evidence-based [21–23] and therefore is not recommended by the guidelines [1, 13].

MP-AzeFlu (Dymista®, Mylan Inc., Canonsburg, PA, USA) is a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) delivered as a single spray, i.e., comprising 2 active ingredients from 2 different medication classes (INS and intranasal antihistamines) with complementary effects. MP-AzeFlu encompasses all of the treatment principles in ARIA [1, 13] (i.e., antihistamine, antileukotriene, mast-cell stabilizing, and anti-inflammatory) in a single puff [24]. More-

over, the efficacy and safety of MP-AzeFlu has been established in pivotal randomized controlled trials in the USA [15, 25], an open-label study in India [26, 27], and in real-life noninterventional studies conducted in Germany [28], the UK [28], Sweden [29], Norway [30], Denmark [31], and Romania [32].

MP-AzeFlu has previously been described as the drug of choice for the treatment of AR and a major breakthrough in the treatment of this disease [33]. The objective of this study was to assess the efficacy and safety of MP-AzeFlu in comparison with an AZE metered-dose nasal spray in a population of Russian seasonal AR (SAR)/rhinoconjunctivitis patients.

Material and Methods

This was a multicenter, randomized, open-label, parallel-group, phase 3 clinical study, carried out at 7 investigational sites in Russia between 25 April and 26 July 2014. The protocol and other study materials were approved by the Ministry of Healthcare of the Russian Federation and local ethics committees from the study centers, and the study was conducted in accordance with good clinical practice. Informed consent was obtained prior to the initiation of any study-related procedure.

Participants

Subjects aged 18–65 years, with a minimum 2-year history of moderate-to-severe SAR or rhinoconjunctivitis, current clinical rhinitis symptomatology, and a positive skin prick test to tree and grass pollens within the last year, were randomized. All subjects met ARIA criteria for moderate-to-severe SAR and had at least 1 of the following complaints: sleep disturbance, impairment of daily leisure and/or sports activities, impairment of study or work abilities, and bothersome symptoms. In addition, all subjects had to have an rTNSS of at least 8/12, with a congestion score of 2 or 3 during screening (day –3). At the start of treatment, subjects were required to have a 12-h nasal congestion score of 2 or 3 measured by a minimum of 2 separate symptom assessments (morning or evening [a.m. or p.m.]) during the washout period, with at least 1 of the 2 assessments recorded within 2 days of day 1 (which could include the a.m. assessment on day 1).

Exclusion criteria included the presence of nasal mucosa ulcerations or nasal septum perforation, nasal or sinus surgery or episodes of acute rhinosinusitis within the last year, chronic rhinosinusitis or nasal polyposis, hypersensitivity to antihistamines and INS, bronchial asthma (mild intermittent allowed), immunotherapy within the last 6 months, and certain previous medications within a prespecified period (e.g., INS within the last 14 days or a systemic corticosteroid within the last 30 days).

Planned Interventions and Timing

The study comprised a 3-day washout period and a 14-day treatment period, with study visits at randomization (day 1), on day 8, and at the end of the trial (day 14). On day 1, eligible patients were randomized in a 1:1 ratio to 14 days of treatment with either MP-AzeFlu nasal spray (137/50 µg AZE/FP per spray) or AZE (137

Fig. 1. Patient disposition. MP-AzeFlu, a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in a single spray.

µg/spray), both administered as 1 spray/nostril twice daily, separated by approximately 12 h (total daily dose: AZE, 548 µg; FP [MP-AzeFlu only], 200 µg). Patients recorded nasal and ocular symptom scores twice daily in a diary. On day 1, the a.m. assessment was before the treatment (included in baseline) and p.m. assessment upon treatment.

Efficacy End Points

The primary efficacy end point was the average change from baseline in combined (a.m. + p.m.) 12-h rTNSS for 13 days (days 2–14) of the 14-day treatment period. Secondary end points included average change from baseline for this 13-day period in rTOSS, rT7SS (rT7SS = rTNSS + rTOSS), reflective individual nasal (congestion, itching, rhinorrhea, and sneezing) and ocular (itching, redness, and watering) symptom scores, daily change from baseline in 12-h (a.m. + p.m.) rTNSS, rTOSS, and rT7SS, time to 50% response, time to a near-to-complete resolution of symptoms (time to achieve a score of ≤1 for each individual nasal symptom), an overall score for the 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and a visual analogue scale (VAS) score of health status taken from the EuroQol-5D (EQ-5D) questionnaire. The scoring systems for rTNSS and rTOSS are described in the online supplementary data (for all online suppl. material, see www.karger.com/doi/10.1159/000494507).

Safety End Points

Safety end points included the incidence, intensity, and description of all adverse events (AEs) throughout the study, a focused nasal examination, and vital signs (blood pressure and heart rate).

Statistical Analyses

Change from baseline in rTNSS, rTOSS, rT7SS, and each individual nasal and ocular symptom for each treatment over time as well as treatment comparisons were assessed using baseline-adjusted analyses of variance.

Time to response was analyzed by Kaplan-Meier estimates and log-rank tests. Response was defined as change from baseline in a.m. + p.m. rTNSS of at least 50% and ≤1 point remaining in each symptom score. A ≥50% rTNSS response was considered a substantial response, halving the patient's nasal symptom burden. The ≤1-point score remaining for each symptom score of the rTNSS ensured complete/near-to-complete symptom relief from all nasal symptoms. This criterion is extremely strict, as it required each nasal symptom to be categorized as no more than mild severity, meaning that patients would effectively feel symptom-free. RQLQ and EQ-5D VAS results were summarized descriptively.

Results

Patients

In total, 155 patients were screened, 149 of whom were enrolled, randomized, and treated (Fig. 1). The study population consisted of these 149 patients, 75 of whom were allocated to receive MP-AzeFlu and 74 to receive AZE. One AZE-allocated patient dropped out due to “protocol violation including noncompliance,” as their diary was not complete. The intention-to-treat population comprised the 148 study completers.

Treatment duration was a minimum of 11 days, with a mean (standard deviation [SD]) of 14.4 (±1.1) days in the MP-AzeFlu group and 14.1 (±1.0) days in the AZE group.

Patients in both treatment groups were comparable with regard to their baseline characteristics as presented in Table 1. The moderate-to-severe disease classification

Fig. 2. a Average change of combined (a.m. + p.m.) 12-h reflective total nasal symptom score (rTNSS) during 14 days of treatment compared with baseline. **b** Daily change from baseline in combined rTNSS. AZE, azelastine hydrochloride; CI, confidence inter-

val; LS, least squares; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single spray. ^a rTNSS (a.m. + p.m.) data may not have been available for all patients at all time points. * $p < 0.001$.

Table 1. Baseline characteristics of study participants

	MP-AzeFlu (n = 75)	AZE (n = 73)
Mean age, years ($\pm$ SD)	37.0 ($\pm$ 12.0)	34.9 ($\pm$ 10.0)
Male gender, n	40 (53.3%)	31 (42.5%)
Caucasian, n	75 (100%)	73 (100%)
Mean height, cm ($\pm$ SD)	172.8 ($\pm$ 9.6)	171.2 ($\pm$ 9.2)
Mean weight, kg ($\pm$ SD)	76.4 ($\pm$ 13.9)	72.4 ($\pm$ 15.7)
Periods of disease manifestation, n		
Spring	57 (76.0%)	46 (63.0%)
Summer	52 (69.3%)	51 (69.9%)
Autumn	13 (17.3%)	7 (9.6%)
Winter	2 (2.7%)	0 (0%)
Mean ($\pm$ SD) rTNSS (a.m. + p.m.)	19.9 ($\pm$ 2.2)	19.3 ($\pm$ 2.3)
Mean ($\pm$ SD) rTOSS (a.m. + p.m.)	9.2 ($\pm$ 5.1)	8.1 ($\pm$ 5.0)
Mean ($\pm$ SD) overall RQLQ score	3.5 ($\pm$ 1.1)	3.1 ($\pm$ 1.1)
Mean ($\pm$ SD) time since diagnosis, years	7.8 ($\pm$ 6.7)	7.0 ($\pm$ 6.5)
Patients previously treated within last 30 days, n	16 (21.3%)	17/74 (23.0%) ^a

AZE, azelastine hydrochloride; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single device; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS, reflective total nasal symptom score; rTOSS, reflective total ocular symptom score; SD, standard deviation.

^a $n = 74$.

was confirmed by ARIA criteria as well as by high baseline rTNSS, rTOSS, and overall RQLQ scores. Polysensitization was evident, with up to 11 sensitizing allergens reported per patient, though patients were most commonly

allergic to 4 allergens ($n = 32$; 22%). The most frequent sensitizing allergens were cock's-foot ($n = 83$; 56%), Timothy grass ($n = 81$; 55%), fescue ($n = 69$; 47%), and a mixture of herb pollens ($n = 66$; 45%).

Fig. 3. a Average change of combined (a.m. + p.m.) 12-h reflective total ocular symptom score (rTOSS) during 14 days of treatment compared with baseline. **b** Daily change from baseline in combined rTOSS. AZE, azelastine hydrochloride; CI, confidence inter-

val; LS, least squares; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single spray. ^a rTOSS (a.m. + p.m.) data may not have been available for all patients at all time points. * $p < 0.001$.

Table 2. Mean change from baseline during 14 days of treatment in individual nasal and ocular symptom scores

	MP-AzeFlu (<i>n</i> = 75)		AZE (<i>n</i> = 73)		Difference	95% CI	<i>p</i> value
	baseline	change from baseline	baseline	change from baseline			
Individual nasal symptoms							
Rhinorrhea	4.58	−2.91	4.44	−2.20	−0.71	−1.04 to −0.39	<0.001
Congestion	5.80	−3.59	5.76	−2.83	−0.76	−1.11 to −0.41	<0.001
Itching	4.79	−3.23	4.60	−2.65	−0.58	−0.89 to −0.27	<0.001
Sneezing	4.72	−3.27	4.50	−2.61	−0.66	−0.97 to −0.35	<0.001
Individual ocular symptoms							
Itching	3.38	−2.20	3.04	−1.62	−0.58	−0.85 to −0.31	<0.001
Redness	3.12	−2.03	2.68	−1.45	−0.58	−0.83 to −0.33	<0.001
Watering	2.72	−1.76	2.36	−1.35	−0.41	−0.66 to −0.15	0.002

AZE, azelastine hydrochloride; CI, confidence interval; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single device.

Outcomes

Primary Efficacy End Point

Baseline rTNSS (a.m. + p.m.) was 19.88 ± 2.24 and 19.30 ± 2.30 in the MP-AzeFlu and AZE groups, respectively. Patients treated with MP-AzeFlu experienced significantly better relief from their overall nasal symptoms. The least-squares (LS) mean reduction in rTNSS (a.m. + p.m.) across 13 days of treatment (days 2–14) was 12.83 for MP-AzeFlu-treated patients and 10.35 for AZE-treated patients (difference: -2.47 ; 95% confidence interval [CI] -3.65 to -1.30 ; $p < 0.001$) (Fig. 2a).

The superiority of MP-AzeFlu over AZE was observed on day 2 and was sustained to day 14 (Fig. 2b). In addition, significantly better relief was observed for each individual nasal symptom with MP-AzeFlu than with AZE ($p < 0.001$) (Table 2).

Secondary Efficacy End Points

Baseline rTOSS (a.m. + p.m.) was 9.22 ± 5.08 in the MP-AzeFlu group and 8.07 ± 5.03 in the AZE group. Patients treated with MP-AzeFlu experienced significantly better relief from their overall ocular symptoms. MP-

Fig. 4. **a** Average change of combined (a.m. + p.m.) 12-h reflective total of 7 symptom scores (rT7SS) during 14 days of treatment compared with baseline. **b** Daily change from baseline in combined rT7SS. AZE, azelastine hydrochloride; CI, confidence inter-

val; LS, least squares; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single spray. ^a rT7SS (a.m. + p.m.) data may not have been available for all patients at all time points. * $p < 0.001$.

Fig. 5. **a** Percentage of patients exhibiting a 50% improvement in rTNSS (a.m. + p.m.) by treatment day. **b** Percentage of patients with a near-to-complete resolution of nasal symptoms (score ≤ 1 point for each nasal symptom) by treatment day. AZE, azelastine

hydrochloride; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single spray; rTNSS, reflective total nasal symptom score.

AzeFlu-treated patients experienced a 5.96-point reduction in rTOSS (a.m. + p.m.) compared with the 4.34-point reduction in the AZE-treated group for days 2–14 of treatment (difference: -1.62 points; 95% CI -2.32 to -0.92 ; $p < 0.001$) (Fig. 3a). The superiority of MP-AzeFlu over AZE was observed on day 2 of treatment and was sustained to day 14 (Fig. 3b). Significantly better relief with MP-AzeFlu was also observed for each individual ocular symptom ($p < 0.01$) (Table 2).

Overall, MP-AzeFlu provided significantly better relief from the entire reflective rhinoconjunctivitis symptoms than AZE (18.79-point vs. 14.44-point reductions in rT7SS score [a.m. + p.m.], respectively; difference: -4.34 ; 95% CI -5.98 to -2.70 ; $p < 0.001$) (Fig. 4a). The superiority of MP-AzeFlu over AZE developed on day 2 of treatment and was sustained to day 14 (Fig. 4b).

Nearly all MP-AzeFlu-treated patients experienced at least a 50% reduction from baseline in their nasal symp-

Fig. 6. Mean change from baseline in quality of life measured with the adult RQLQ for overall change and each of the 7 subscores for MP-AzeFlu versus AZE. AZE, azelastine hydrochloride; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single spray; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

toms after 14 days of treatment, and they responded faster ($p < 0.0001$) than those treated with AZE (a median time to response of 3 and 6 days, respectively) (Fig. 5a). Approximately two-thirds of patients treated with MP-AzeFlu achieved near-to-complete nasal symptom relief with MP-AzeFlu after 14 days of treatment compared with approximately one-third of AZE patients, and patients treated with MP-AzeFlu achieved this response up to 6 days faster than AZE-treated patients ($p < 0.0001$; Fig. 5b).

Quality of Life

Patients treated with MP-AzeFlu experienced a greater improvement than patients treated with AZE in overall RQLQ score (2.91 ± 1.08 and 2.05 ± 1.15 , respectively) and each of the 7 individual domain scores (Fig. 6). The difference was clinically relevant [34]. Similar to RQLQ scores, EQ-5D VAS scores increased more for patients treated with MP-AzeFlu than for those treated with AZE. Scores increased from 61.0 ± 16.6 at baseline to 87.4 ± 10.3 on day 14 in the MP-AzeFlu group and from $63.5 \pm$

17.1 to 83.0 ± 12.8 in the AZE group. The increase in VAS score from baseline to day 14 was 26.4 for the MP-AzeFlu group and 19.5 for the AZE group.

Safety

The proportion of subjects with an AE was similar in the 2 treatment groups: 11/75 (14.7%) patients reported a total of 16 events in the MP-AzeFlu group and 11/74 (14.9%) patients reported a total of 24 events in the AZE group. The most frequent AE was headache, reported by 5 patients in each treatment group (Table 3); headache was found to be unlikely related to treatment in 2 patients in the MP-AzeFlu group and 3 in the AZE group. All treatment-related AEs were mild-to-moderate in severity, and no serious AEs were recorded in the study.

No clinically significant changes in patients' vital signs or blood chemistry were observed throughout the study. Anterior rhinoscopy did not reveal any nasal mucosa damage throughout the study.

Table 3. Most frequently reported adverse events

	MP-AzeFlu, <i>n</i> (%) (<i>n</i> = 75)	AZE, <i>n</i> (%) (<i>n</i> = 74)
Headache	5 (6.7)	5 (6.8)
Dysgeusia	1 (1.3)	3 (4.1)
Somnolence	2 (2.7)	1 (1.4)
Sneezing	1 (1.3)	2 (2.7)

Adverse events were reported in at least 3 patients. AZE, azelastine hydrochloride; MP-AzeFlu, novel intranasal formulation of AZE and fluticasone propionate in a single device.

Discussion

The results of this study provide, for the first time, important evidence of the efficacy of MP-AzeFlu in Russian patients with moderate-to-severe SAR or rhinoconjunctivitis. The efficacy of MP-AzeFlu has been established using traditional measures as well as newly defined clinically relevant ones (as recommended by the European Medicines Agency). The superiority of MP-AzeFlu over AZE was apparent in both nasal and ocular symptom relief, the clinically relevant response, and the QoL, with both treatments equally well tolerated.

MP-AzeFlu was shown to be significantly more effective than first-line treatment with an antihistamine (AZE) for SAR. In our study, the efficacy of MP-AzeFlu was assessed in a clinically relevant way, i.e., in a way that means something to patients and physicians, and answers the question “How much better will I feel and how quickly will I get better?” Almost all patients treated with MP-AzeFlu in this study experienced a clinically relevant regress of their nasal symptom burden in 2 weeks. After just 5 days, more than three-quarters of the patients developed a 50% response to MP-AzeFlu.

Assuming similar results across practices, physicians treating AR could see more than twice as many MP-AzeFlu-treated patients than AZE-treated patients experiencing complete/near-to-complete symptom relief, and many days sooner. This is important because the time to achieve significant symptom reduction is crucial for patients with AR and is a trigger for maintaining patient compliance [20].

The findings of this study are consistent with those of previous randomized controlled trials of MP-AzeFlu carried out in the USA [15, 25]. Data from US placebo-controlled studies show that MP-AzeFlu provided twice the overall nasal and ocular symptom relief than either FP or AZE monotherapy. Point estimates for treatment differenc-

es in the Russian study were even higher than in the US studies, confirming the high efficacy of MP-AzeFlu. As in this study, more US MP-AzeFlu-treated patients achieved a 50% reduction from baseline in rTNSS and complete/near-to-complete symptom relief (and this occurred about a week faster) than those treated with commercially available active comparators intranasal FP or AZE [15]. MP-AzeFlu also provided greater symptom relief, irrespective of disease severity, most effectively treating the entire spectrum of nasal and ocular symptoms, and targeted patients' most bothersome symptoms [15]. Of note, MP-AzeFlu was 3 times more effective than FP for congestion [15].

MP-AzeFlu also demonstrated a consistent response across seasons and large geographic regions (i.e., Europe, the USA, and Asia) [25]. In real-life studies, MP-AzeFlu was found to provide effective and rapid symptom control in all age groups (adults and adolescents) of patients with SAR or perennial AR, and in those with more or less severe disease, with responder rates higher than those observed in controlled clinical trials [28].

The open-label study design remains the main limitation of this study. The generalizability of these data is an inherent limitation of all randomized trials [35] since inclusion and exclusion criteria have to be in agreement with the US FDA and European Medicines Agency guidelines.

In conclusion, MP-AzeFlu provided significantly better, more rapid, and more complete symptom control than AZE in a Russian cohort with moderate-to-severe SAR or rhinoconjunctivitis, supporting its position as an effective treatment for these patients.

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