

MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study

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ABSTRACT

Background: The European Union has prioritized allergic rhinitis (AR) control. *Contre les Maladies Chronique pour un Vieillissement Actif Allergic Rhinitis and its Impact on Asthma* has endorsed the visual analog scale (VAS) as the AR control language and incorporated it into a new AR treatment algorithm. Concurrently, the Respiratory Effectiveness Group and the European Academy of Allergy and Clinical Immunology are striving to improve the quality of published real-life AR research. Our aim was to assess the effectiveness of MP-AzeFlu by using a VAS in a well-designed, real-life, pan-European study.

Methods: A total of 2988 patients (aged ≥ 12 years) with Allergic Rhinitis and its Impact on Asthma defined moderate-to-severe AR from Germany, Sweden, Romania, United Kingdom, Denmark, and Norway were included. Patients (except from the United Kingdom) assessed symptom severity by using a VAS from 0 mm (not at all bothersome) to 100 mm (very bothersome) on days 0, 1, 3, 7, and the last visit (~day 14) in the morning before MP-AzeFlu use. Patients' perceived level of disease control was assessed on day 3. A VAS score cutoff on day 3 for "well controlled" was determined, and the proportion of patients who achieved this response was calculated.

Results: MP-AzeFlu was associated with a mean VAS score reduction from 73.7 mm at baseline to 23.4 mm by the last visit. This reduction was significant ($p < 0.001$) compared with baseline from day 1 and sustained until the last day of the study. By day 3, 50.3% of patients considered their symptoms well controlled; 18.2, 40.0, 66.6, and 75.9% of the patients achieved the ≤ 38 mm well-controlled VAS score cutoff on days 1, 3, 7 and the last day, respectively. The results were consistent across countries, age, phenotype, and severity.

Conclusion: MP-AzeFlu provided effective and rapid symptom control in a real-life pan-European setting and aligned with the European Union, *Contre les Maladies Chronique pour un Vieillissement Actif Allergic Rhinitis and its Impact on Asthma*, the Respiratory Effectiveness Group, and the European Academy of Allergy and Clinical Immunology objectives, supporting MP-AzeFlu as the drug of choice for the treatment of moderate-to-severe AR.

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Allergic rhinitis (AR) is the most prevalent chronic allergic disease that affects European citizens today. The prevalence rates vary, ranging from 15.7% in Denmark,^{1,2} 20% in Norway,^{3,4} 22.5% in Germany,⁵

24% in the United Kingdom,⁶ to 25% in Sweden.⁷ The numbers may be higher than this because many patients remain undiagnosed, with the disease sometimes mistreated or undertreated as a consequence.⁸ Irrespective of the prevalence; the symptom and societal burden is high everywhere. A recent U.K. survey showed that patients with moderate-to-severe AR experienced 4.1 days/y of absenteeism (a cost to payers of \$1.38 billion/y), 37.7 days/y presenteeism, and visited their general practitioner on average 1.6 times/y for their rhinitis.⁹ In Sweden, the total cost of AR has been reported as \$1.44 billion/y (\$1063.41/individual/y), with presenteeism responsible for 70% of that cost.¹⁰

The importance of AR control has now been prioritized at the European Union level.¹¹ An airway-specific integrated care pathway has been implemented in 25 European Union countries to facilitate more effective disease management.¹² Furthermore, an AR clinical decision support system has been developed and integrated within an updated AR guideline.¹³ This uses a simple visual analog scale (VAS) score to assess AR control and guide treatment decisions.¹⁴ The VAS has

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been incorporated into a free app for patients (*Allergy Diary*) to improve communication, facilitate control tracking, and guide treatment decisions. Previous research has shown that the VAS score can be used to assess the severity of AR¹⁵ and treatment efficacy.¹⁶ Furthermore, both the European Academy of Allergy and Clinical Immunology and the Respiratory Effectiveness Group have been working together to raise standards in real-life respiratory research.¹⁷ Data generated from well-designed real-life studies are valuable, generalizable to a broad patient population, provide evidence supplementary to that obtained from randomized controlled trials (RCT) and should help to qualify guideline recommendations.¹⁸

Providing more-effective pharmacologic therapies is another way to reduce AR symptoms. However, before the introduction of MP-AzeFlu (Dymista; Meda, Solna, Sweden), the treatment landscape had remained unaltered for many years. Second-generation antihistamines with little or no sedative effects were introduced, and new intranasal corticosteroids (INS) with lower systemic bioavailability (compared with the older INS) but with comparable efficacy provided.^{19,20} Increasing the dose of INS provided no additional symptomatic benefit due to the flat nature of their dose-response curves. Indeed, an INS efficacy threshold has now been established.²¹ Although, multiple AR therapy usage is widespread throughout Europe,^{9,22–24} adding oral antihistamines or leukotriene receptor antagonists to INS, provided little or no symptomatic benefit over INS monotherapy.^{25,26} Many patients remained symptomatic on monotherapies and multiple AR therapies^{27,28} and were dissatisfied with the symptomatic relief provided.²⁹

MP-AzeFlu is a new drug (ATC R01 AD58) for AR. It comprises an intranasal antihistamine (azelastine hydrochloride), an INS (fluticasone propionate), and a novel formulation in a single spray. Results from well-designed RCTs showed that patients with moderate-to-severe seasonal AR (SAR) treated with MP-AzeFlu experienced a rapid onset of relief (*i.e.*, within 30 minutes) and twice the overall nasal and ocular symptom relief of an INS or intranasal antihistamine.²¹ Moreover, more patients who used MP-AzeFlu experienced complete to near-complete symptom relief and many days faster than those on fluticasone propionate monotherapy.^{21,30} In addition, MP-AzeFlu has a sustained effect, which supports continuous use with improved concordance and has established its effectiveness in a large multicenter noninterventional study.³¹

It is increasingly recognized that conclusions drawn from classic clinical trials are not always useful aids for decision-making; assessing the value of a drug or technology requires an understanding of its impact on current management in a practical, real-life setting. According to a recent survey by the European Com-

mission, an increasing number of countries revisit the relative efficacy and effectiveness of a new treatment in comparison with standard therapy as part of their decision-making processes for reimbursement and pricing. This process takes place in addition to the EMEA assessment and aims at evaluating the added value offered by a new treatment. With a number of countries now moving into reference pricing for new treatments without added medical value, this additional effectiveness assessment has a major impact on a new drug's success in the market. RCT, although recognized as the criterion standard for establishing efficacy, operate in an idealized environment, and can only measure efficacy in limited populations. As such, they cannot provide a true indication of effectiveness, an area on which real-life studies are more suitable because data acquisition occurs from a more naturalistic environment. The aim of the present real-life study was to assess the effectiveness of MP-AzeFlu on achieving AR control in routine clinical practice across Europe. AR control was assessed by using a VAS, in line with the European Union, Contre les Maladies Chronique pour un Vieillissement Actif Allergique Rhinitis and its Impact on Asthma (MACVIA-ARIA), the Respiratory Effectiveness Group, and the European Academy of Allergy and Clinical Immunology initiatives.

METHODS

Protocol

This was a multinational (*i.e.*, Germany, Sweden, Norway, Denmark, Romania, and the United Kingdom), multicenter, prospective, noninterventional study. Individual country results and pooled data (*i.e.*, from each of the six countries) were assessed. The study consisted of an inclusion visit, when eligible patients were assigned MP-AzeFlu (1 spray/nosril twice a day) and an optional follow-up visit (not in the United Kingdom) after ~14 days. The study was carried out in accordance with current laws and guidelines in each country, and ethical approval was obtained from local independent investigational review boards. All the patients provided written informed consent before entering the study, and if <18 years old, their caregiver also provided signed consent.

Settings and Physicians

The study was carried out by practicing physicians in Germany, Sweden, Norway, Denmark, Romania, and the United Kingdom between April 2013 and August 2015. Physicians decided to include a patient into the study independently from and after the decision to prescribe MP-AzeFlu. The patients prescribed MP-AzeFlu assessed its effectiveness in their own home and/or environment.

Patients

Patients with ARIA-defined moderate-to-severe SAR and/or perennial AR (PAR) for whom monotherapy with either intranasal H₁ antihistamines or INS had been considered insufficient (in the opinion of the investigators) were included.³² Patients were required to be ≥ 12 years of age, with acute AR symptoms on the day of inclusion, defined as a recommended VAS score of >50 mm. However, patients could be enrolled into the study regardless of their VAS score if the physician rated their symptoms as moderate to severe. Patients with SAR were defined as those with a documented allergy to at least one pollen allergen (*i.e.*, spring, summer, and/or autumn pollen) but no nonpollen allergens. Patients with PAR were those with a documented allergy to at least one nonpollen allergen (*i.e.*, house-dust mites, animal dander, and/or mold) but no pollen allergens. Patients with both SAR and PAR had a documented allergy to at least one pollen and at least one nonpollen allergen. Rhinitis of unknown origin was defined as allergy to other allergens (*i.e.*, not one of the allergens listed above) or unknown allergens (*i.e.*, rhinitis indicated from history but no specific immunoglobulin E data). Patients were excluded from the study if they had a known hypersensitivity to MP-AzeFlu or any of its ingredients or if they were pregnant or breast-feeding. Apart from use of ritonavir, there were no restrictions regarding concomitant treatments during the study.

MP-AzeFlu Use in Routine Clinical Practice

At the inclusion visit, physicians recorded information on patient demographics, clinical symptoms, the number of previous clinical visits due to AR, previous AR treatments in the current calendar year, ARIA-defined disease severity, and AR phenotype (*i.e.*, SAR, PAR, SAR plus PAR, or unknown AR). Physicians identified their reason for the patient's visit and the reason for prescribing MP-AzeFlu (*e.g.*, other therapy was not sufficient in the past or not considered sufficient to treat acute symptoms). Data were recorded by the physicians in an electronic case report form (Trium Analysis Online GmbH, Munich, Germany) setup in the national language in Romania and Germany, and in the English language for the other countries.

Effectiveness Assessment

Patients from each country (except the United Kingdom) evaluated AR symptom severity on a simple 100 mm VAS in response to the statement, "please reflect on how bothersome your symptoms were within the previous 24 hours." The patients marked their response on the VAS from 0 (not at all bothersome) to 100 (very bothersome). VAS assessment was done in the morning, before MP-AzeFlu use, on days 0, 1, 3, 7, and

at treatment end (*i.e.*, after ~ 14 days). On day 3, the patients also recorded their perceived level of AR control as either well controlled, partly controlled, or uncontrolled, in response to the question, "how well controlled were your allergy symptoms within the previous 24 hours?" All effectiveness assessment information was recorded by patients on patient cards (provided in either German, Swedish, Norwegian, Danish, or Romanian), handed back to physicians during the follow-up visit or sent by mail and transcribed by physicians into an electronic case report form. Data were electronically signed by physicians and saved in the study data base located at Trium Analysis Online GmbH.

Safety

All suspected adverse drug reactions (ADR) and special situations were documented in the electronic case report form. An ADR was defined as an adverse event (AE) with a reasonable possibility that the event may have been caused by MP-AzeFlu. A special situation was recorded in the event of pregnancy, breast-feeding, any overdose, abuse, off-label use, misuse or medication error, or an ADR related to occupational exposure or lack of efficacy.

Statistics

All baseline data were based on the safety population (all patients who received ≥ 1 MP-AzeFlu dose and whose physician provided an electronic signature to confirm data accuracy). The effectiveness analyses were based on the VAS population, defined as for the safety population but with the exclusion of U.K. patients ($n = 193$). Effectiveness was not assessed in the United Kingdom because use of the VAS was considered interventional. However, these U.K. patients were included in the safety population and contributed to information on MP-AzeFlu use in routine clinical practice. Categorical data were described as the number and percentage of patients and continuous data as mean (standard deviation [SD]) by a clinical research organization (Syneed Medidata GmbH, Konstanz, Germany) by using the SAS statistical software package (version 9.1.3 or higher; SAS Institute, Cary, NC).

The mean (SD) VAS score on days 0, 1, 3, 7, and the last day were described for the whole VAS population in each country (except the United Kingdom) and as a pooled analysis. Mean VAS scores were also provided according to disease phenotype (*i.e.*, SAR, PAR, or SAR plus PAR), severity (*i.e.*, less severe, a mean baseline VAS score of 50–74 mm; more severe, a mean baseline VAS score of >75 mm), and patient age (*i.e.*, 12–17 years, 18–65 years, and >65 years) for the pooled data at the same time points. A change in the VAS score from baseline to days 1, 3, 7, and the last day was

Table 1 Patient demographic and baseline characteristics (N = 2988)

Descriptor	
Female patients, no. (%)	1655 (55.4)
Age, no. (%)	
<12 y	3 (0.1)
12–17 y	194 (6.5)
18–65 y	2548 (85.3)
>65 y	243 (8.2)
Duration of rhinitis, mean $\pm$ SD, y*	12.1 $\pm$ 11.0
Type of rhinitis, no. (%)	
SAR	1199 (40.1)
SAR + PAR	1085 (36.3)
PAR	352 (11.8)
Unknown	352 (11.8)
Severity of AR, no. (%)	
Troublesome symptoms	2140 (71.6)
Daily activities, leisure, sport	1905 (63.8)
Sleep disturbance	1445 (48.4)
School and/or work	1354 (45.3)
Predominant symptoms, no. (%)	
Nasal congestion	1570 (52.5)
Rhinorrhea	737 (24.7)
Sneezing	354 (11.9)
Nasal pruritus	261 (8.7)
Unknown	66 (2.2)
Concomitant ocular symptoms, no. (%)	1610 (53.9)

SD = Standard deviation; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; AR = allergic rhinitis.
**n* = 2188.

assessed as a contrast from repeated measurement analysis of covariance. The covariance matrix was left unspecified. A *p* value of <0.05 was judged to be significant. Patients' perception of disease control 3 days after starting treatment was calculated for the whole population and according to phenotype for the pooled data.

Post hoc Analyses

A weighted mean of the country-specific cutoffs (Youden index) to define "well-controlled" and "partly controlled" AR on day 3 were calculated for the pooled data. Responses were defined as achievement of these cutoffs and as a ≥ 23 -mm change from baseline in the VAS score (previously defined as a clinically meaningful improvement)³³ on days 0, 1, 3, 7, and the last day. Responder rates were derived from time to response analysis as Kaplan-Meier estimates.

Safety

AEs were coded by using the MedDRA coding system (version 16.1 or higher; MedDRA, McLean, VA).

Table 2 Previous allergic rhinitis treatment in the past year (N = 2988)

	No. (%)
Allergic rhinitis treatment	
Oral antihistamine	2000 (66.9)
Intranasal corticosteroid	1524 (51.0)
Intranasal antihistamine	866 (29.0)
Intranasal decongestant	558 (18.7)
Ocular antihistamine	528 (17.7)
Systemic corticosteroid	349 (11.7)
Any other AR treatment	229 (7.7)
Oral LTRA	193 (6.5)
Oral decongestant	164 (5.5)
None	158 (5.3)
Ocular mast cell stabilizer	115 (3.9)
Intranasal mast cell stabilizer	86 (2.9)
Unknown	86 (2.9)
No. AR treatments in current calendar year	
1	959 (32.2)
2	923 (30.9)
3	646 (21.6)
4	277 (9.3)
5	123 (4.1)
6	39 (1.3)
7	13 (0.4)
8	7 (0.2)
9	1 (0.0)
Immunotherapy	
In the past or currently ongoing	710 (23.8)

LTRA = Leukotriene receptor antagonist.

All documented AEs and special situations were processed by Meda's Drug Safety Department.

RESULTS

Patient Disposition

A total of 383 physicians enrolled 3120 patients into the study. A total of 132 patients were excluded from the safety population due to unconfirmed data documentation (*i.e.*, electronic signature of the treating physician was missing) except for the safety relevant information. The remaining 2988 patients were included in the safety population. The VAS population comprised 2795 patients (*i.e.*, which did not include U.K. patients).

Patient Demographics and Baseline Characteristics

Patient baseline characteristics are shown in Table 1. Of the patients, 84.5% had a baseline VAS score of >50 mm. A total of 2915 patients (97.6%) had moderate-to-severe AR according to ARIA classification. The

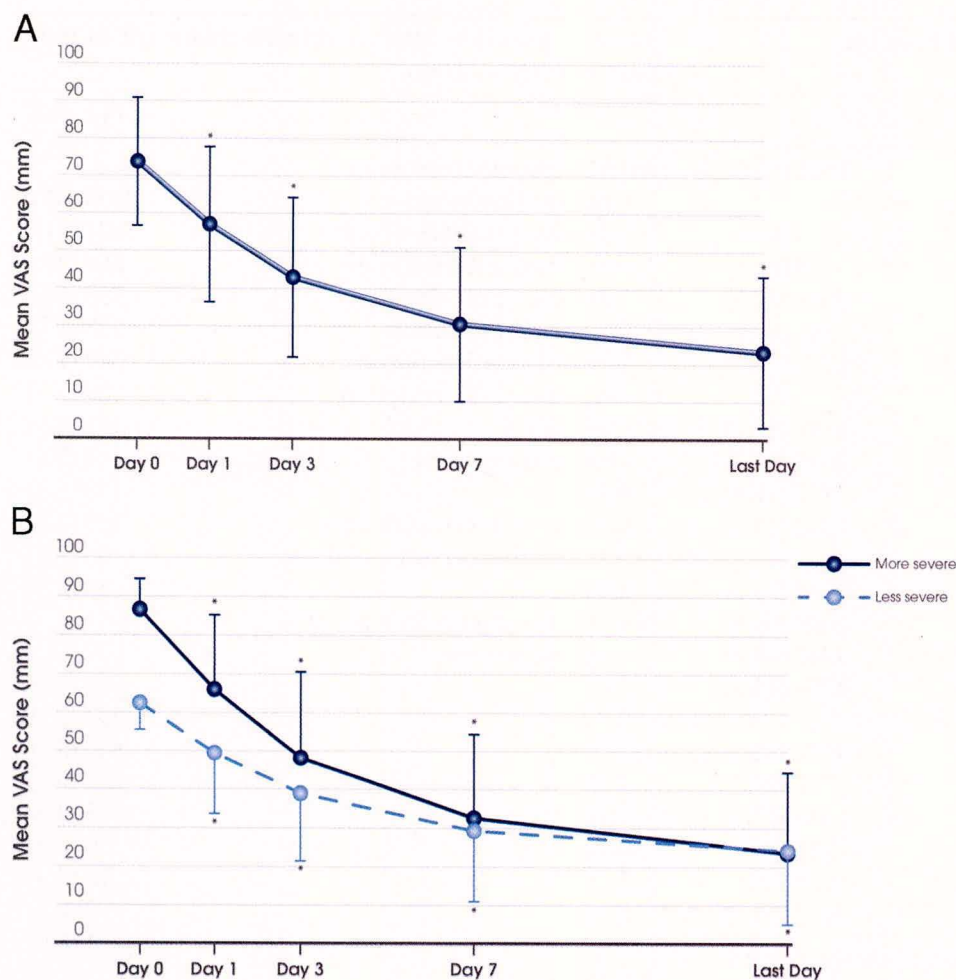


Figure 1. Effect of MP-AzeFlu on the visual analog scale (VAS) score over time in (A) the total population ($n = 2656$) and (B) according to baseline severity. Less severe, baseline VAS score of 50–74 mm ($n = 1129$); more severe, baseline VAS score of 75–100 mm ($n = 1398$). Data are presented as mean (standard deviation) for the pooled data. $*p < 0.001$ versus baseline.

mean $\pm$ SD of AR-specific physician visits in the current calendar year (before the MP-AzeFlu prescription) was 2.2 ± 2.8 . Overall, 617 patients (20.7%) visited their physician once before, 575 patients (19.2%) visited twice before, 383 (12.8%) visited three times before, and 538 (18.0%) visited four or more times prior to the current visit. The most-frequent reason for the physician visit was “acute AR symptoms” ($n = 2301$ [77.0%]), followed by “other” ($n = 501$ [16.8%]) and “expected allergen exposure in the near future” ($n = 359$ [12.0%]). The most common reason for prescribing MP-AzeFlu was that “other therapies were not sufficient in the past” ($n = 2045$ [68.4%]), followed by “other therapies are not considered sufficient to treat acute symptoms” ($n = 828$ [27.7%]), and “other” ($n = 290$ [9.7%]).

Previous AR Treatments in the Past Year

The most common AR medications used by patients were oral H_1 -antihistamines, INS and intranasal antihistamines (Table 2). Decongestants (either intranasal or oral) were used by 24.2% of patients ($n = 722$) and eye drops (either antihistamine or mast-cell stabilizers) by 21.5% of patients ($n = 643$). More than two-thirds of

patients ($n = 2029$ [67.9%]) had received multiple AR therapies in the past year; 14.2% of patients ($n = 425$) had received immunotherapy in the past, and 9.5% of patients ($n = 285$) were currently receiving immunotherapy (Table 2).

Effectiveness

For the analysis of the pooled data, the mean $\pm$ SD time period between the start of treatment and the VAS assessment on the last day of treatment (or on the day that patients returned their card) was 15.5 ± 8.0 days (median, 14 days; 1st quartile, 14 days, and 3rd quartile, 15 days). The symptom burden was high at baseline, with a mean $\pm$ SD reported VAS score of 73.7 ± 17.3 mm. MP-AzeFlu use was associated with an effective and rapid symptom reduction from baseline, average $\pm$ SD of 23.4 ± 20.3 mm by treatment end, a reduction of 50.4 ± 26.1 mm (Fig. 1 A). This VAS score reduction from baseline was significant ($p < 0.001$) from day 1 and sustained until the last day. Results were consistent for each of the countries (Table 3).

The results of the pooled analysis were also consistent, regardless of severity, with a rapid and significant ($p < 0.001$) symptom reduction from baseline observed

Table 3 Individual country results for the change from baseline in VAS score from baseline to the last day of MP-AzeFlu use and patient perception of disease control on day 3 of MP-AzeFlu use*

Country	Day	VAS Score, mean $\pm$ SD, mm	CFB to Last Day in VAS Score, $\pm$ SD, mm
Germany (N = 1781)	0	75.4 $\pm$ 17.2	
	1	56.7 $\pm$ 20.7#	54.1 $\pm$ 24.6
	3	41.1 $\pm$ 20.6#	
	7	27.9 $\pm$ 19.3#	
	Last	21.3 $\pm$ 18.3#	
Sweden (N = 431)	0	67.9 $\pm$ 16.1	
	1	56.3 $\pm$ 20.3#	36.1 $\pm$ 24.0
	3	47.5 $\pm$ 21.0#	
	7	38.3 $\pm$ 21.9#	
	Last	32.1 $\pm$ 22.8#	
Norway (N = 160)	0	68.1 $\pm$ 16.4	
	1	57.5 $\pm$ 20.1#	30.8 $\pm$ 27.2
	3	50.4 $\pm$ 20.9#	
	7	42.9 $\pm$ 23.1#	
	Last	37.4 $\pm$ 25.9#	
Denmark (N = 170)	0	67.1 $\pm$ 19.3	
	1	52.7 $\pm$ 23.0#	38.8 $\pm$ 27.3
	3	42.6 $\pm$ 24.2#	
	7	33.2 $\pm$ 22.6#	
	Last	28.4 $\pm$ 23.7#	
Romania (N = 253)	0	78.4 $\pm$ 15.1	
	1	62.9 $\pm$ 21.0#	63.6 $\pm$ 20.4
	3	45.3 $\pm$ 24.0#	
	7	28.4 $\pm$ 20.6#	
	Last	14.7 $\pm$ 15.1#	

VAS = Visual analog scale; SD = standard deviation; CFB = change from baseline.

*Data from the United Kingdom are not included because the patients did not record VAS scores in the United Kingdom.

$p < 0.001$ vs day 0.

in those with more-severe disease and those with less-severe disease, which ended at nearly the same VAS score (Fig. 1 B). Rapid and sustained symptom control was also observed for those patients, irrespective of phenotype (*i.e.*, SAR, PAR, and SAR plus PAR) (Fig. 2A) or age (*i.e.*, 12–17 years, 18–65 years, >65 years) (Fig. 2 B). For all subgroups, the VAS score reduction associated with MP-AzeFlu use was significantly ($p < 0.001$) reduced from baseline starting from day 1 and sustained until the last day. Three days after the start of MP-AzeFlu treatment, one in two patients (50.3%) with known control status considered their symptoms well

controlled (Fig. 3). This patient-perceived feeling of well-controlled AR was observed across the phenotype spectrum as well as in those patients for whom a sensitizing allergen was not documented (Fig. 3). Patients in the United Kingdom and patients with unknown symptom control were not included in the patient perception of control analysis at Day 3.

Response

The perception of well-controlled symptoms at day 3 corresponded to a VAS score cutoff of 38 mm; 18.2% of patients achieved this cutoff on day 1, 40.0% on day 3, 66.6% on day 7, and 75.9% of patients on the last day (Fig. 4). Similarly, the feeling of partly controlled symptoms at day 3 corresponded to a VAS score cutoff of 55 mm. Of the patients, 44.2, 73.4, 90.3, and 93.0% achieved this cutoff on days 1, 3, 7, and the last day, respectively (Fig. 4). This response was independent of phenotype. A similar proportion of patients with SAR, PAR, and SAR plus PAR (as well as those with unknown phenotype) achieved these well-controlled and partly controlled VAS score cutoffs on days 1, 3, 7 and the last day. The patients treated with MP-AzeFlu also achieved a rapid clinically relevant response (*i.e.*, ≥ 23 mm change from baseline in the VAS score); with approximately one-fourth of the patients (26.4% [$n = 688$]) achieving a clinically relevant symptom reduction at day 1, half of patients by day 3 (58.4% [$n = 1495$]), and ~ 8 of 10 patients after 1 week of MP-AzeFlu treatment (79.3% [$n = 2017$]).

Safety

During the course of this study, 20 patients (0.67%) reported 35 AEs. Fourteen patients (0.47%) reported 17 special situations. A causal relationship to treatment with MP-AzeFlu was assumed by the reporting physicians for 33 AEs, with the most frequent ADRs being dysgeusia ($n = 4$), nausea ($n = 3$), sneezing ($n = 3$), nasal discomfort ($n = 3$), rhinorrhea ($n = 2$), application site pain ($n = 2$), and epistaxis ($n = 2$). No AE or ADR was considered serious. Eleven of 2988 patients discontinued treatment with MP-AzeFlu due to one or more AEs, including dysgeusia, nausea, or nasal discomfort (each $n = 3$); rhinorrhea or sneezing (each $n = 2$); and nasal dryness, migraine, visual impairment, eye burning, application site pain, cough, asthma, nasal congestion, or rhinitis (each $n = 1$).

DISCUSSION

These data are a valuable addition to the real-life evidence base in terms of effectiveness and safety, and confirmed the rapid and sustained effectiveness of MP-AzeFlu under conditions of routine care around Europe, complementing the evidence gathered in RCTs.^{21,30,34} The trial is well designed (*e.g.*, effective-

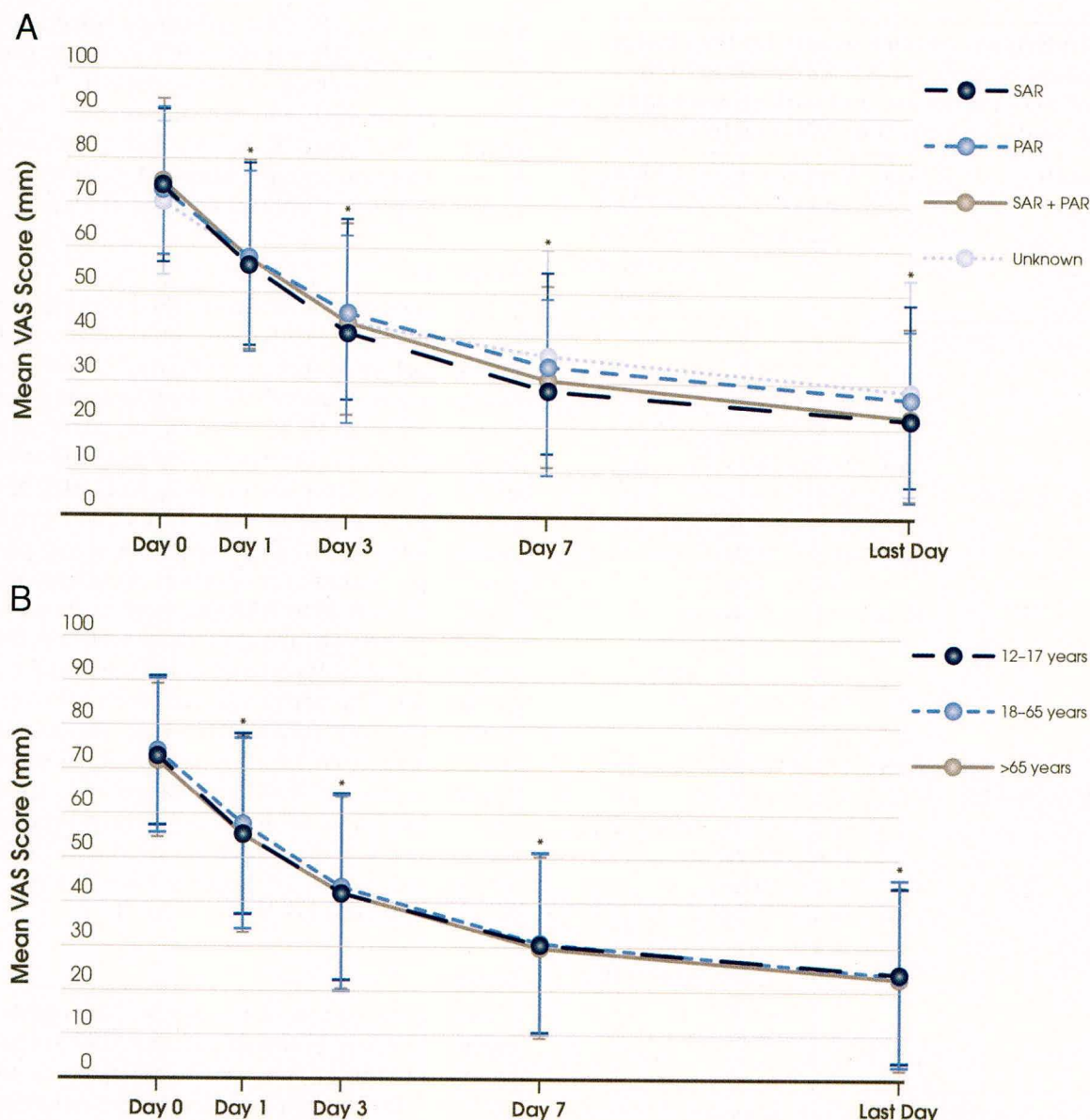


Figure 2. Effect of MP-AzeFlu on the visual analog scale (VAS) score over time according to (A) allergic rhinitis phenotype (i.e., seasonal allergic rhinitis [SAR] [$n = 1179$], perennial allergic rhinitis [PAR] [$n = 316$], SAR + PAR [$n = 1017$]), unknown [$n = 283$], and (B) age (i.e., 12–17 years [$n = 172$], 18–65 years [$n = 2393$], >65 years [$n = 227$]). Data are presented as mean (standard deviation) for the pooled data. * $p < 0.001$ versus baseline for each subgroup.

ness assessed by patients themselves and data recorded by physicians experienced in the treatment of AR), reported in line with the Respiratory Effectiveness Group/European Academy of Allergy and Clinical Immunology recommendations,¹⁷ and control was assessed by using a VAS, as endorsed by MACVIA-ARIA.¹³ Conducting real-life studies is an important part of the evidence base for any pharmacologic intervention (complementing the evidence from RCTs) because these studies include a broad and heterogeneous patient population, the results from which are generalizable to the AR population at large, which is not the case with RCTs. Furthermore, the level of clinical care in real-life studies is closer to that of everyday practice

than in RCTs, which follow up patients more intensively. Results from the current study, therefore, were those that one might expect to achieve in routine care.

MP-AzeFlu was associated with a rapid and clinically relevant reduction in patients' AR symptoms, achieving significance compared with baseline on day 1, which was sustained for the study duration of ~14 days. One of every two patients perceived that their symptoms were well controlled after only 3 days of treatment. The effect was consistent, regardless of phenotype (even those of unknown phenotype), severity, or age, and MP-AzeFlu was well tolerated. Some inter-country variability was noted in VAS score reduction, ranging from a 30.8–38.8 mm reduction in the Scandi-

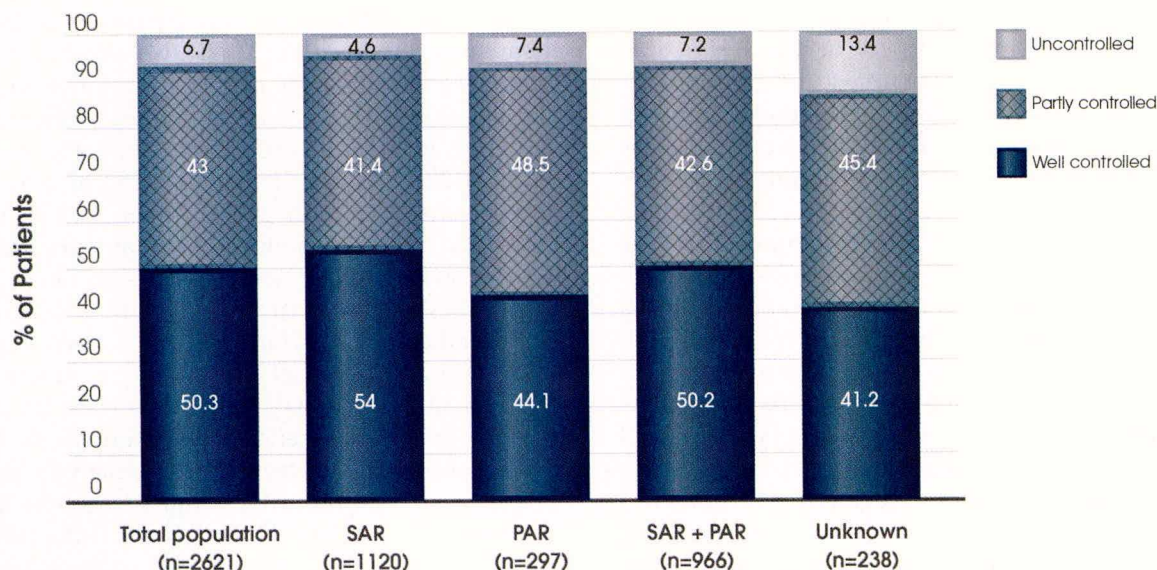


Figure 3. Patient perception of disease control on day 3 according to allergic rhinitis (AR) phenotype ($n = 2621$). SAR = seasonal allergic rhinitis, PAR = perennial allergic rhinitis.

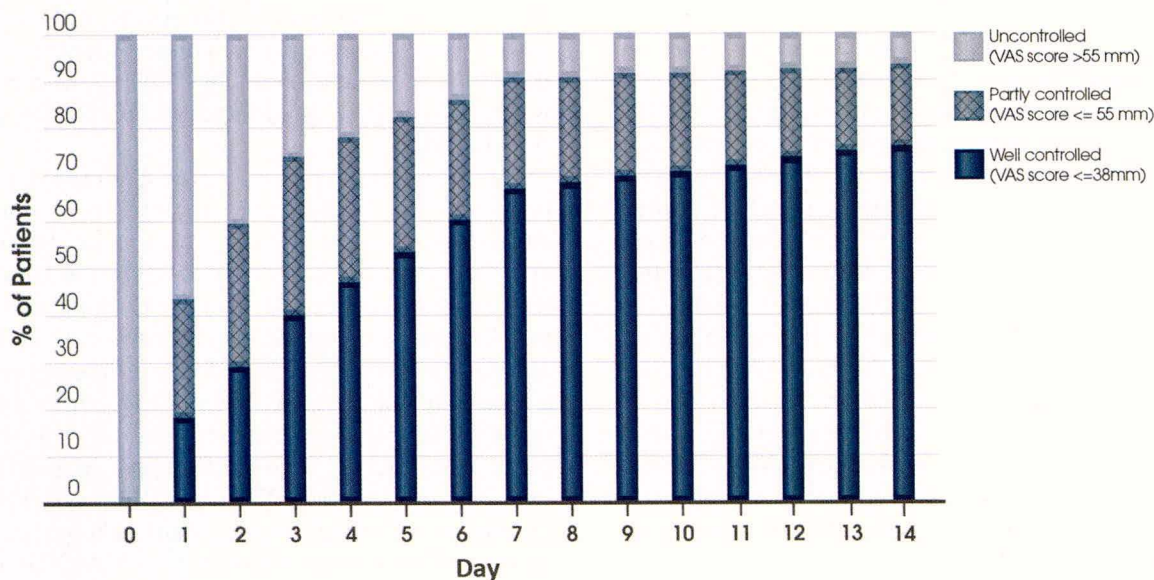


Figure 4. Proportion of patients treated with MP-AzeFlu who had well-controlled (i.e., visual analog scale [VAS] score, ≤ 38 mm), partly controlled (i.e., VAS score, ≤ 55 mm), and uncontrolled allergic rhinitis over time. Data are presented as Kaplan-Meier estimates for the pooled data on Days 1, 3, 7 and 14, and interpolated for the other days.

navian countries, 54.1 mm in Germany, to 63.6 mm in Romania, possibly due to higher baseline VAS scores in the German and Romanian studies. However, irrespective of country, the VAS score reduction was always rapidly clinically relevant (i.e., ≥ 23 mm change from baseline),³³ occurring within the first few days of treatment.

The effectiveness observed in this real-life study was better than the efficacy reported in RCTs, in which MP-AzeFlu provided complete to near-complete symptom control in one of six patients with moderate-to-severe SAR by day 14 and complete relief in seven of

ten patients with mild-to-moderate PAR in the first month, achieving these responses about a week faster than an INS.^{21,30} In this real-life study, one in two patients on MP-AzeFlu believed that their AR was well controlled after only 3 days. By using the VAS score to more objectively define AR control, approximately three-fourths of patients achieved a well-controlled VAS cutoff score of 38 mm by the last day. The discrepancy among the results from the different study designs highlights the importance of real-life studies in obtaining information about the effectiveness of a treatment (because patients included in these studies

are different from those in RCTs) and the importance of using patient-defined cutoffs of disease control rather than arbitrary ones identified in RCTs.

The VAS has been proposed as the new language of AR control and the basis of the AR control concept by MACVIA-ARIA.¹⁴ A VAS score of 50 mm (previously used to define patients with AR unresponsive to guideline-directed treatment)²⁸ has been proposed as the cutoff to define control and to guide treatment decisions as part of a treatment algorithm called a clinical decision support system. This MACVIA-ARIA cutoff agrees very well with the VAS score cutoff for partly controlled AR defined in the present study by patients themselves (*i.e.*, 55 mm). Of the patients, 90.3% treated with MP-AzeFlu in real life achieved this VAS score control threshold after 7 days. MACVIA-ARIA has also incorporated the VAS into a patient app (*Allergy Diary*) to track symptom control,³⁵ thus linking patients, physicians, and guidelines with a common language of AR control.

Data collected from patients during this study before prescribing MP-AzeFlu highlighted the high burden of AR around Europe and the need for a more-effective pharmacologic therapy. The societal burden of AR was evident from the high physician consultation rate (2.2 times per calendar year) and frequency of polypharmacy practices, with more than two-thirds of patients reporting use of multiple therapies, which is neither recommended^{36,37} nor proven.^{25,26,38,39} Both of these practices inflate costs associated with AR management and indicate dissatisfaction with therapy, a common finding from other AR surveys.^{29,40} The symptomatic burden of AR was evident, not only from high baseline VAS scores reported despite multiple therapy use by many patients, but also the high frequency of troublesome symptoms, activity impairment, sleep disturbance, and incidence of ocular symptoms reported, which can impair patients' quality of life to a greater degree than nasal congestion.⁴¹

Nasal congestion was reported by one of every two patients and was associated with a high reported use of decongestants (oral or intranasal, both of which carry significant AEs). Systemic corticosteroids were used previously in one of eight subjects, probably to relieve severe symptoms and unblock the nose. In an RCT setting, MP-AzeFlu provided three times the nasal congestion relief as an INS in patients with predominant congestion.²¹ In the current real-life study, MP-AzeFlu was associated with fast and effective symptom control in these patients with previously uncontrolled disease, which provided an opportunity for cost reduction due to unnecessary physicians visits and coprescriptions.

Evidence of insufficient symptomatic relief provided by previous AR treatments was also apparent by the fact that the most common reason for MP-AzeFlu prescription was that "other therapies were not sufficient

in the past" (68.4%) or "considered not sufficient to treat acute symptoms" (27.7%). MP-AzeFlu, therefore, was prescribed both as first-line treatment in patients for whom it was considered that monotherapy, with either an intranasal antihistamine or INS, would provide insufficient symptom relief, and also as second-line treatment in those patients who had a history of previous treatment failure. Both approaches are in keeping with the indication for MP-AzeFlu in Europe: first-line MP-AzeFlu treatment for the best chance of rapid and complete symptom control, then step down, or second-line MP-AzeFlu after INS treatment failure.

The main limitations of this study were the lack of a control group and random assignment. A head-to-head comparison between patient-centered cutoffs and response cutoffs from RCTs were not conducted. Furthermore, study data were derived from clinical records and patients themselves, and so the accuracy and completeness of data relied on the quality of these records and the ability of patients to recall information. Missing data could be a potential source of bias in the study results. However, in this study, data were complete for most demographic variables, and the missing data for the patient card, including VAS assessment, was 5%, which is considered acceptable for observational studies.

The strength of the evidence is derived from the inclusion of a large number of patients, considered sufficiently large to draw a general conclusion on use, effectiveness, and safety of MP-AzeFlu in routine clinical practice, coupled with a good study design and pan-European coverage. The consistency of findings among the countries provided confidence in the robustness of the data. A further strength of this study was the use of a simple VAS to assess effectiveness, the same VAS that is used in the new MACVIA-ARIA treatment algorithm.¹³ The patient-defined VAS score for partly controlled disease reported here (*i.e.*, 55 mm) and the 50-mm cutoff advocated by MACVIA-ARIA to gauge control and to guide decisions were in good agreement and provide valuable information to physicians on how patients who use MP-AzeFlu may respond within the context of the updated guideline.

CONCLUSION

Before MP-AzeFlu prescription, patients with AR throughout Europe had uncontrolled disease, with high polypharmacy and physician visit rates reported. MP-AzeFlu was associated with effective and rapid symptom control in a real-life setting of patients throughout Europe; assessed by using a VAS, the MACVIA-ARIA-endorsed language of AR control. The results were consistent regardless of disease phenotype, severity, or patient age. The responder rates observed in real life were higher than those observed in

RCTs. These results support MP-AzeFlu as the drug of choice for moderate-to-severe AR treatment in real life.

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