

Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis

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ABSTRACT

Intranasal corticosteroids are considered the most effective therapy for moderate-to-severe seasonal allergic rhinitis (SAR) and recommended first line in guidelines. It is uncertain whether intranasal antihistamines have comparable efficacy. This study was designed to compare the efficacy of azelastine (AZE; 137 µg/spray) and fluticasone propionate (FP; 50 µg/spray), both given as 1 spray/nostril bid (i.e., approved dosing regimen in the United States), in SAR via a post hoc analysis of data from a previously published direct-comparison study. Six hundred ten moderate-to-severe SAR patients (≥12 years old) were randomized into a double-blind, placebo-controlled, parallel-group trial. The primary efficacy variable was change from baseline in reflective total nasal symptom score (rTNSS (morning and evening), over 14 days. Reflective total ocular symptom score (rTOSS) was a key secondary variable. Reflective total of seven symptom scores (rT7SS [nasal plus ocular symptoms]) and time to ≥50% reduction from baseline in these key parameters were also analyzed. AZE and FP reduced rTNSS from baseline by a similar degree (−3.25 versus −3.84; $p = 0.2014$). Patients experienced comparable improvement in rTOSS (−2.62 versus −2.17; $p = 0.2371$) and rT7SS (−5.83 versus −6.05; $p = 0.7820$). FP was superior to AZE in alleviating rhinorrhea (−1.15 versus −0.87; $p = 0.0433$), but AZE showed comparable efficacy for all other nasal and ocular symptoms. There was no clinically or statistically significant difference between AZE (−1.17) and FP (−1.43) for reduction in the overall rhinitis quality of life questionnaire score (although FP, but not AZE, significantly differed from placebo). A similar proportion of patients in the AZE and FP groups achieved a 50% reduction in rTNSS. However, more AZE patients (53.0%) exhibited a 50% reduction in rTOSS by day 14 versus FP (39.6%), and ≤3 days faster ($p = 0.028$). Intranasal AZE (137 micrograms/spray) and intranasal FP (50 micrograms/spray), both 1 spray/nostril b.i.d., had comparable efficacy in symptom control in moderate-to-severe SAR.

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Allergic rhinitis (AR) is a prevalent disease in the United States associated with significant burden,

comorbidities, and health care costs.^{1,2} Guidelines recommend intranasal corticosteroids (INSs) as the most effective medication for controlling the symptoms of AR.^{3,4} Intranasal azelastine (AZE) has been shown to be effective for patients who had previously failed oral antihistamine therapy.^{5,6} However, the studies available are insufficient to place intranasal antihistamines properly into a comprehensive pharmacotherapeutic algorithm.³ Moreover, there is a paucity of high-quality, direct head-to-head comparison studies between intranasal antihistamines and INSs. There is a need for

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such studies to inform future AR treatment recommendations.

Comparisons between medications are best done with head-to-head trials to control the variability that may exist between different clinical trials. Four large, parallel group, placebo-controlled, randomized trials have compared intranasal AZE and fluticasone propionate (FP) in a head-to-head fashion.^{7–9} The first study assessed the efficacy and safety of MP29-02 (a novel intranasal AZE/FP formulation) versus commercially available intranasal AZE (Astelin; MedaPharmaceuticals, Somerset, NJ), generic intranasal FP (Roxane Laboratories, Columbus, OH), and placebo in moderate-to-severe seasonal AR (SAR) patients during the Texas mountain cedar season.⁷ The results showed that patients treated with MP29-02, AZE, or FP experienced significantly greater relief from their overall nasal symptoms compared with placebo patients and that MP29-02 was significantly superior to both AZE and FP.⁷ However, a direct statistical comparison between AZE and FP was not reported. A meta-analysis of the remaining three studies⁸ also compared the efficacy of MP29-02, AZE, FP, and placebo, but in this instance all comparators had exactly the same formulation. MP29-02 was again found to be significantly more effective than AZE, FP, or placebo. However, when interpreting the results of this meta-analysis, one should consider that the formulation of the products differed from that of commercial products.¹⁰

We present the results of a direct comparison between intranasal AZE and intranasal FP in patients with moderate-to-severe SAR using commercially available products. The primary efficacy measure of change from baseline in overall reflective total nasal symptom score (rTNSS; morning [A.M.] and evening [P.M.]) is presented, as well as change from baseline in reflective total ocular symptom score (rTOSS). Other end points not previously published are also presented such as change from baseline in overall reflective total of seven symptom scores (rT7SS; comprising all nasal and ocular symptoms) as well as Kaplan-Meier plots showing the proportion of patients achieving a 50% reduction in rTNSS, rTOSS, and rT7SS and the time taken to achieve this response.

The aim of this *post hoc* analysis is to assess the efficacy of intranasal AZE (137 μ g/spray) versus intranasal fluticasone (50 μ g/spray), both 1 spray/nostril b.i.d., in a direct, sensitive, head-to-head, randomized, double-blind, placebo-controlled study design. This may provide additional evidence to solve the current discrepancy between the positioning of intranasal antihistamines in European and U.S. rhinitis treatment guidelines.

MATERIALS AND METHODS

Protocol

This phase III, multicenter, randomized, double-blind, parallel group, trial (MP4001 [NCT00660517]) was performed at eight investigational sites during the 2007–2008 U.S. spring mountain cedar allergy season. The original analysis has been published by Hampel and colleagues.⁷ Its primary aim was to determine the efficacy and safety of MP29-02 compared with a commercially available intranasal H₁-antihistamine (AZE; Astelin), corticosteroid (FP; generic FP nasal spray), and placebo in patients with moderate-to-severe SAR. Here, we present the results of a *post hoc* analysis that further statistically assessed differences between intranasal AZE and FP in this patient population. The study was conducted in accordance with the Food and Drug Administration and European Medicines Agency recommendations^{11,12} and good clinical practice.¹³ After Institutional Review Board approval was obtained (clinical trial registration NCT00660517), written informed consent was obtained from all patients or legal guardians (subjects aged <18 years).

Participants

Subjects (≥ 12 years old) with a minimum 2-year history of SAR, significant current clinical rhinitis symptomatology, and a positive skin-prick test to relevant pollen were randomized. All subjects had moderate-to-severe SAR defined by an rTNSS of at least 8 of 12, with a congestion score of 2 or 3. A detailed description of inclusion and exclusion criteria have been previously published⁷ and are also provided in the online supplement.

Planned Interventions and Timing

The study comprised a 7-day, single-blind, placebo lead-in period, and a 14-day treatment period with three study visits at days 1, 7, and 14. On visit 2 (day 1), eligible patients were randomized (1:1:1:1) to 14 days of treatment with (i) MP29-02 nasal spray, (novel formulation of 137 μ g of AZE/50 μ g of FP); (ii) AZE nasal spray (137 μ g); (iii) FP (50 μ g) nasal spray; or (iv) vehicle placebo nasal spray, all 1 spray/nostril b.i.d. (*i.e.*, both approved dosing regimens in the United States) For the purpose of the current article we focused on the comparison between intranasal AZE and FP, the results of which have not been published previously. Doses were separated by ~ 12 hours. Patients recorded application times and symptom scores in a diary twice daily. Details of compliance assessment are provided in the online supplement.

Efficacy Variables

The primary efficacy variable was the sum of the A.M. and P.M. overall change from baseline for the

entire 14-day period in 12-hour rTNSS, which consisted of the four nasal symptoms of congestion, itching, rhinorrhea, and sneezing.^{11,12} All four nasal symptoms were scored by patients twice daily (A.M. and P.M.) on each treatment day according to a 4-point scale (0–3; maximum = 24).

Secondary efficacy variables included overall change from baseline (treatment period, days 2–14) in the individual reflective nasal symptom scores, instantaneous TNSS (iTNSS), and rTOSS, as well as the individual ocular symptoms of itching, watering, and redness. All three ocular symptoms were scored by patients twice daily (A.M. and P.M.) on each treatment day according to a 4-point scale (0–3; maximum rTOSS = 18). Details of scoring are provided in the online supplement.

Quality of Life

Quality of life was assessed before randomization and at the end of the study using the 28-item Rhinitis Quality of Life Questionnaire (RQLQ) for subjects >18 years old.¹⁴

Safety

Safety was assessed by patient-reported adverse events.

Sample Size

Sample size in the original analysis was determined to allow detection of a treatment difference in rTNSS of 1.71 points, assuming an SD of 5 points. Using a two-tailed test with an α -value of 0.05 and 80% power and allowing for a 10% dropout rate, ~150 subjects per treatment group were required for this study. The current *post hoc* analysis was not particularly powered to detect a difference between AZE and FP but proved to be large enough to identify both better and worse treatments,⁷ thus achieving assay sensitivity.

Randomization

Patients were randomized balanced and by study site in blocks of four. Eligible subjects received the study site's next available randomization number in sequence.

Blinding

Individual nasal spray bottles were identity masked such that both patients and study personnel were blinded to treatment assignment. A blinded randomization code was maintained at a central site apart from the sponsor and study centers. Study blinding was preserved at the study sites until all subjects completed the study and the database had been locked.

Statistical Analyses

Efficacy analyses were performed on the intent-to-treat population of all randomized patients with at least one postbaseline observation. An analysis of covariance (ANCOVA) model was applied to the primary efficacy variable of absolute change in combined (A.M. and P.M.) rTNSS. The model included the treatment days from 1st day of assessment (day 2) to day 14. Fixed effects were treatment group, day, and center, with baseline as a continuous covariate. The covariance matrix of the error terms was left unspecified and allowed to differ among treatment groups, with degrees of freedom calculated by Satterthwaite approximation. Change from baseline in iTNSS, individual reflective nasal and ocular symptom scores, rTOSS, and overall RQLQ score were assessed in the same way. The absolute change in combined (A.M. and P.M.) rT7SSs (*i.e.*, rTNSS plus rTOSS) were assessed using the same ANCOVA model. In addition, time to response was analyzed by Kaplan-Meier estimates. A change from baseline in rTNSS, rTOSS, and rT7SS of at least 50% as recommended by current guidelines was used to define response.¹² The original analysis followed a hierarchical test procedure that found statistical significance in each single step. We now add *post hoc* the contrast between AZE and fluticasone.

RESULTS

Patients

The study completion rate was high and similar among treatment groups (Table 1). Dropout rates were negligible. Subject baseline characteristics of the three treatment groups were similar (Table 2). Patient baseline rTNSS confirmed that the vast majority of these patients had moderate-to-severe AR.

Outcomes

Efficacy. rTNSS, iTNSS, rTOSS, rT7SS, Individual Symptom Scores: Change from Baseline.

Patients treated with either intranasal AZE or FP exhibited significantly superior relief from both their nasal and ocular symptoms compared with patients in the placebo group. AZE patients experienced comparable nasal and ocular symptom relief as those treated with FP (Table 3). Over the entire 14-day treatment period, ANCOVA results revealed a treatment difference in reduction of rTNSS (A.M. and P.M.) from baseline between AZE and FP of -0.59 (95% CI, $-1.50, 0.32$; $p = 0.2014$). Intranasal AZE and FP treatment resulted in similar reductions from baseline in the iTNSS (Difference [Diff]: -0.44 ; 95% CI, $-1.36, 0.48$; $p = 0.3453$), rTOSS (Diff: 0.45 ; 95% CI, $-0.30, 1.21$; $p = 0.2371$), and rT7SS (Diff: -0.22 ; 95% CI, $-1.78, 1.34$; $p = 0.7820$; Table 3). The difference between AZE and FP for rTNSS improvement

Table 1 Subject disposition

	AZE	FP	Placebo
All subjects randomized	153	153	151
Completed, <i>n</i> (%)	144 (94.1)	144 (94.1)	144 (95.4)
Discontinued, <i>n</i> (%)	9 (5.9)	9 (5.9)	7 (4.6)
Primary reason for discontinuation, <i>n</i> (%)			
Adverse event	3 (2.0)	1 (0.7)	1 (0.7)
Treatment failure	1 (0.7)	1 (0.7)	0 (0.0)
Noncompliance	2 (1.3)	3 (2.0)	1 (0.7)
Subject withdrew consent	1 (0.7)	2 (1.3)	2 (1.3)
Lost to follow-up	0 (0.0)	2 (1.3)	0 (0.0)
Other	2 (1.3)	0 (0.0)	3 (2.0)
Intent-to-treat population	152 (99.3)	151 (98.7)	151 (100.0)
Safety population	152 (99.3)	153 (100.0)	151 (100.0)

AZE = azelastine; FP = fluticasone propionate.

Table 2 Patient baseline characteristics

Characteristics	AZE (<i>n</i> = 152)	FP (<i>n</i> = 151)	Placebo (<i>n</i> = 151)
Age (yr)	39.5 (14.1)	38.1 (14.2)	39.9 (14.7)
Range	12–74	12–74	12–75
Gender			
Female, <i>n</i> (%)	97 (63.8)	100 (66.2)	102 (67.5)
Race			
White, <i>n</i> (%)	135 (88.8)	130 (86.1)	131 (86.8)
rTNSS	18.1 (3.7)	18.3 (3.5)	18.7 (3.5)
rTOSS	11.8 (4.2)	11.8 (4.3)	12.2 (4.4)
RQLQ overall score*	3.8 (1.0)	3.8 (1.1)	3.9 (1.2)
Duration of SAR history (yr)	19.0 (12.9)	18.4 (11.5)	18.1 (12.2)

Data are presented as mean (SD) unless otherwise stated.

*AZE, *n* = 133; FP, *n* = 132; PLA, *n* = 126 (only adults completed the RQLQ).

AZE = azelastine; FP = fluticasone propionate; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; RQLQ = Rhinitis Quality of Life Questionnaire; SAR = seasonal allergic rhinitis.

was not significant on any day including day 14, with the exception of day 13 (Fig. 1 A). AZE was significantly superior to FP for the relief of overall ocular symptoms on day 2 (Fig. 1 B). There was no significant difference between AZE and FP on any day during the 14-day treatment period for the overall rhinitis symptom complex score (rT7SS; Fig. 1 C).

Both intranasal AZE and FP provided statistically superior relief to placebo for each of the nasal symptoms of itch, rhinorrhea, and sneezing, and for all ocular symptoms, over the 14-day treatment period (Table 4). Although FP was statistically significantly more effective for nasal congestion than placebo (*p* = 0.0101) and AZE was not (*p* = 0.0614), a direct comparison of AZE and FP revealed a comparable overall change from baseline for nasal congestion (Diff: −0.10; 95% CI, −0.34, 0.13; *p* = 0.3915), nasal itch (Diff: −0.09;

95% CI, −0.35, 0.16; *p* = 0.4582), and sneezing (Diff: −0.12; 95% CI, −0.40, 0.16; *p* = 0.4054). FP was superior to AZE in relieving rhinorrhea (Diff: −0.28; 95% CI, −0.55, −0.01; *p* = 0.0433; Table 4). There was no statistical difference between AZE and FP in terms of effectiveness in reducing the ocular symptoms of itching (Diff: 0.18; 95% CI, −0.09, 0.44; *p* = 0.1876), redness (Diff: 0.10; 95% CI, −0.17, 0.36; *p* = 0.4654), or watering (Diff: 0.17; 95% CI, −0.11, 0.44; *p* = 0.2367; Table 4).

rTNSS, rTOSS, and rT7SS: Time to First 50% Reduction from Baseline. Figure 2 shows the proportion of patients in each treatment group who experienced a ≥50% reduction in (A) rTNSS, (B) rTOSS, and (C) rT7SS over time. More patients in the AZE (37.4%) and FP (38.2%) treatment groups achieved a 50% reduction in rTNSS from baseline by day 14 compared with placebo pa-

Table 3 Effect of AZE, FP, and placebo (all 1 spray/nostril b.i.d.) on overall nasal and ocular symptoms in patients with moderate-to-severe AR

Treatment	Baseline	CFB	Difference	LS Mean	95% CI	p Value
rTNSS						
FP	18.34 (3.47)	−3.81 (4.76)	—	—	—	—
AZE	18.08 (3.66)	−3.00 (4.12)	FP − AZE	−0.59	−1.50, 0.32	0.2014
PLA	18.68 (3.45)	−1.91 (4.16)	FP − PLA	−1.64	−2.55, −0.73	0.0005
			AZE − PLA	−1.05	−1.89, −0.20	0.0152
iTNSS						
FP	17.09 (4.43)	−3.41 (4.81)	—	—	—	—
AZE	16.76 (4.54)	−2.64 (4.50)	FP − AZE	−0.44	−1.36, 0.48	0.3453
PLA	17.76 (4.08)	−1.62 (4.17)	FP − PLA	−1.78	−2.69, −0.88	0.0001
			AZE − PLA	−1.34	−2.22, −0.47	0.0028
rTOSS						
FP	11.77 (4.27)	−2.10 (3.71)	—	—	—	—
AZE	11.80 (4.21)	−2.38 (3.75)	FP − AZE	0.45	−0.30, 1.21	0.2371
Placebo	12.16 (4.35)	−1.31 (2.89)	FP − PLA	−0.85	−1.51, −0.19	0.0123
			AZE − PLA	−1.30	−1.99, −0.61	0.0002
rT7SS						
FP	30.10 (7.16)	−5.91 (8.05)	—	—	—	—
AZE	29.88 (7.22)	−5.38 (7.33)	FP − AZE	−0.22	−1.78, 1.34	0.7820
PLA	30.84 (7.20)	−3.22 (6.66)	FP − PLA	−2.50	−3.97, −1.03	0.0009
			AZE − PLA	−2.28	−3.69, −0.86	0.0017

Data are presented as mean (SD) unless otherwise stated.

AZE, *n* = 152; FP, *n* = 151; PLA, *n* = 151.

AR = allergic rhinitis; CFB = change from baseline; LS = least squares; rTNSS = reflective total nasal symptom score; FP = fluticasone propionate; AZE = azelastine; PLA = placebo; iTNSS = instantaneous nasal symptom score; rTOSS = reflective total ocular symptom score; rT7SS = reflective total of 7 symptom scores.

tients (28.3%) and achieved this response up to 5 days faster ($p = 0.050$ versus AZE; $p = 0.044$ versus FP). There was no statistical difference between AZE and FP in this regard ($p = 0.905$; Fig. 2 A). Conversely, more patients treated with AZE (53.0%) achieved a 50% reduction from baseline in their ocular symptoms by day 14 compared with patients in either the FP (39.6%) or the placebo (41.5%) groups and achieved this response up to 3 days earlier than FP ($p = 0.028$) and up to 5 days earlier than placebo ($p = 0.020$; Fig. 2 B). FP did not significantly differentiate from placebo for this parameter ($p = 0.950$). The proportion of patients who experienced a $\geq 50\%$ reduction in their overall nasal and ocular symptoms combined (*i.e.*, rT7SS) was similar in the AZE and FP groups after 14 days of treatment; 39.6 and 36.9%, respectively, with no significant difference between AZE and FP in speed of this response ($p = 0.5858$; Fig. 2 C).

Quality of Life. Patients were well matched for quality-of-life impairment, with overall baseline RQLQ scores of 3.8 in each of the AZE (SD = 1.0) and FP groups (SD = 1.1) and 3.9 (SD = 1.2) in the placebo group. By day 14, FP (−1.43) but not AZE (−1.17)

significantly improved patients' overall RQLQ score compared with placebo (−1.01; $p = 0.0063$ versus FP). However, there was no clinically or statistically significant difference between AZE and FP in this regard (Diff: −0.27; 95% CI, 0.57, 0.04; $p = 0.0848$).

Safety. Both AZE and FP were well tolerated. Safety results have previously been published by Hampel and colleagues and are presented in the online supplement (online supplement Table E1).⁷

DISCUSSION

The results of the present *post hoc* analysis of this large, multicenter, randomized, double-blind, placebo-controlled trial show that intranasal AZE and FP for 14 days have efficacy of comparable magnitude in patients with moderate-to-severe SAR. The trial was adequately powered (for MP29-02 versus FP and AZE comparisons) and was proven to be sensitive. Among others, significant differences of FP versus MP29-02 and placebo were achieved. Despite this documented assay sensitivity, it was unable to detect a statistical difference between AZE and FP for the traditional

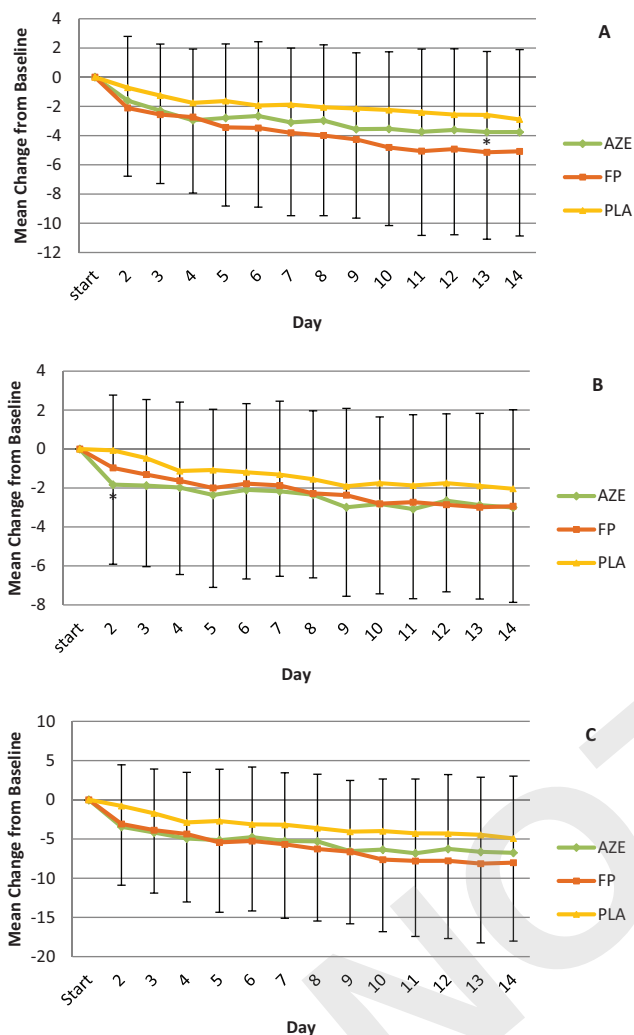


Figure 1. Effect of 14 days treatment with intranasal fluticasone propionate (FP; $n = 151$), intranasal azelastine (AZE; $n = 152$), or placebo (PLA; $n = 150$; all 1 spray/nostril b.i.d.) on (A) reflective total nasal symptom score (rTNSS), (B) reflective total ocular symptom score (rTOSS), and (C) reflective total of seven symptom score (rT7SS) in patients with moderate-to-severe seasonal allergic rhinitis (SAR). Data are presented as mean change from baseline with SD. * $p < 0.05$ versus FP.

efficacy measures of change from baseline in rTNSS and rTOSS. However, it should be noted that this was a superiority study by design and not a formal noninferiority study with prespecified noninferiority margins.

Patients experienced similar relief from their individual nasal symptoms of congestion, itch, and sneezing and from their ocular symptoms of itch, watering, and redness, whether treated with AZE or FP. Indeed, an assessment of rT7SS, which comprises all nasal and ocular symptoms, showed that there was no significant difference between AZE and FP, both being equally effective in controlling the overall disease symptom complex of these patients during the 14-day trial. The

responder analyses for rTNSS and rT7SS agree with the primary efficacy variable result and provide confidence that there is no clinically relevant difference between intranasal AZE and FP for the control of all of the symptoms of SAR over a treatment period of 14 days. This is a relevant time period because the average duration of an SAR episode for patients with moderate-to-severe disease is just 12.5 days.¹⁵ Safety results from the original trial reported that both AZE and FP were well tolerated; epistaxis (2.6%) being the most commonly reported adverse event in the AZE group, followed by dysgeusia (2.0% versus 0% for FP group). Epistaxis and headache were the adverse events most commonly reported in the FP group (both 3.9% versus 2.6% and 1.3% in the AZE group, respectively).⁷

Although in the present analysis FP was statistically more effective than AZE in relieving rhinorrhea, patients treated with AZE exhibited similar improvements in all other nasal symptoms, including nasal congestion, widely recognized as the most bothersome chronic symptom for AR patients. AZE appeared to offer more relief from ocular symptoms than FP, as evidenced by its consistent numerical advantage for each and every ocular symptom, and the significant and clinically relevant 50% reduction from baseline in rTOSS days earlier (up to 3 days) than FP. Other studies that have investigated the ocular effect of INSs in SAR showed substantial inconsistency of the effect of some INSs across and within trials.¹⁶ Conflicting or even negative effects on ocular symptoms have been observed for most INSs examined, including FP.¹⁶

The results of this *post hoc* analysis are important for many reasons. Of the many clinical studies published in AR, only a small proportion has compared different active molecules head-to-head. To adequately evaluate these molecules, it is necessary to conduct such studies to generate robust comparative data. The presented *post hoc* analysis presents data from a large, well-powered, high-quality trial (*i.e.*, randomized, double-blind, placebo- and active-controlled, direct comparison, parallel group) using commercially available therapies. It shows clearly that SAR patients treated with FP or AZE experience comparable relief from their total nasal and ocular symptoms. These data are robust because the clinical trial was sufficiently powered and proven to be sensitive to detect clinical differences between active and placebo groups and between active groups within the same trial.

These findings have been confirmed by another direct *post hoc* statistical comparison of an independent smaller study (MP428), which assessed the efficacy of intranasal AZE, FP, and the loose combination of FP plus AZE in 151 moderate-to-severe SAR patients after 2 weeks of treatment.¹⁷ This time, AZE was administered as 2 sprays/nostril b.i.d. and FP as 2 sprays/nostril once daily. In agreement with the current *post*

Table 4 Effect of AZE, FP, and placebo (all 1 spray/nostril b.i.d.) on individual nasal and ocular symptoms in patients with moderate-to-severe AR

Treatment	Baseline	CFB	Difference	LS Mean	95% CI	<i>p</i> Value
Reflective nasal congestion score (A.M. + P.M.)						
FP	4.97 (0.93)	−0.83 (1.28)	—	—	—	—
AZE	5.04 (0.88)	−0.70 (1.11)	FP − AZE	−0.10	−0.34, 0.13	0.3915
PLA	5.15 (0.78)	−0.52 (1.15)	FP − PLA	−0.32	−0.55, −0.08	0.0101
			AZE − PLA	−0.21	−0.44, 0.01	0.0614
Reflective nasal itch score (A.M. + P.M.)						
FP	4.54 (1.17)	−0.94 (1.28)	—	—	—	—
AZE	4.52 (1.21)	−0.81 (1.24)	FP − AZE	−0.09	−0.35, 0.16	0.4582
PLA	4.63 (1.25)	−0.48 (1.21)	FP − PLA	−0.40	−0.65, −0.15	0.0017
			AZE − PLA	−0.30	−0.55, −0.06	0.0153
Reflective rhinorrhea score (A.M. + P.M.)						
FP	4.70 (0.94)	−1.17 (1.47)	—	—	—	—
AZE	4.62 (1.15)	−0.82 (1.23)	FP − AZE	−0.28	−0.55, −0.01	0.0433
PLA	4.72 (1.01)	−0.55 (1.23)	FP − PLA	−0.57	−0.84, −0.29	<0.0001
			AZE − PLA	−0.29	−0.54, −0.04	0.0238
Reflective sneezing score (A.M. + P.M.)						
FP	4.14 (1.27)	−1.02 (1.41)	—	—	—	—
AZE	3.90 (1.40)	−0.78 (1.45)	FP − AZE	−0.12	−0.40, 0.16	0.4054
PLA	4.18 (1.31)	−0.46 (1.20)	FP − PLA	−0.52	−0.78, −0.25	0.0002
			AZE − PLA	−0.40	−0.66, −0.13	0.0036
Reflective ocular itch score (A.M. + P.M.)						
FP	4.31 (1.40)	−0.73 (1.27)	—	—	—	—
AZE	4.42 (1.28)	−0.86 (1.35)	FP − AZE	0.18	−0.09, 0.44	0.1876
PLA	4.46 (1.42)	−0.49 (1.14)	FP − PLA	−0.26	−0.50, −0.03	0.0283
			AZE − PLA	−0.44	−0.68, −0.19	0.0005
Reflective ocular redness score (A.M. + P.M.)						
FP	3.54 (1.66)	−0.67 (1.36)	—	—	—	—
AZE	3.40 (1.79)	−0.70 (1.31)	FP − AZE	0.10	−0.17, 0.36	0.4654
PLA	3.69 (1.79)	−0.37 (1.07)	FP − PLA	−0.34	−0.58, −0.11	0.0042
			AZE − PLA	−0.44	−0.68, −0.20	0.0003
Reflective ocular watering score (A.M. + P.M.)						
FP	3.91 (1.56)	−0.79 (1.41)	—	—	—	—
AZE	3.98 (1.57)	−0.91 (1.41)	FP − AZE	0.17	−0.11, 0.44	0.2367
PLA	4.01 (1.56)	−0.53 (1.11)	FP − PLA	−0.29	−0.54, −0.04	0.0236
			AZE − PLA	−0.46	−0.72, −0.20	0.0006

Data are presented as mean (SD) unless otherwise stated.

AZE, *n* = 152; FP, *n* = 151; PLA, *n* = 151.

AR = allergic rhinitis; CFB = change from baseline; LS = least squares; FP = fluticasone propionate; AZE = azelastine; PLA = placebo.

hoc analysis, there was no significant difference between AZE and FP in rTNSS reduction from baseline (Diff FP-AZE: 0.03; 95% CI, −1.46, 1.53; *p* = 0.9638).¹⁸ AZE was not significantly inferior to FP in alleviating any of the individual nasal symptoms of congestion (Diff: 0.09; 95% CI, −0.33, 0.51; *p* = 0.6697), itchy nose (Diff: −0.13; 95% CI, −0.61, 0.35; *p* = 0.6014), sneezing (Diff: −0.10; 95% CI, −0.51, 0.32; *p* = 0.6395), and (in this case) rhinorrhea (−0.16, 95% CI, −0.58, 0.27; *p* = 0.4598). A similar proportion of AZE and FP patients achieved a

50% reduction in rTNSS (45.4% versus 49.3%, respectively), with no significant difference in the time taken to achieve this response (*p* = 0.9514).¹⁸ Although these results are meaningful, it is likely that the study presented here is more sensitive in detecting treatment differences because of larger sample sizes. Moreover, it provides a scientifically more precise comparison as it uses the same posology for both treatments.

These effect sizes may not be generalized to all doses or dosing regimens or all intranasal antihistamines or

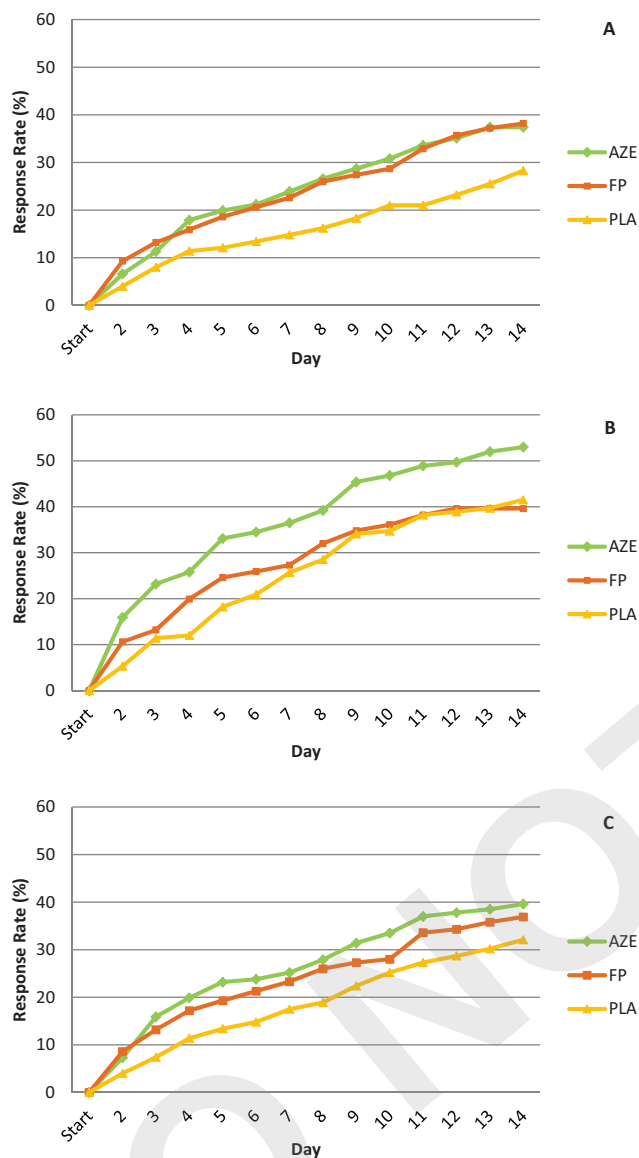


Figure 2. Mean percent of patients with moderate-to-severe seasonal allergic rhinitis (SAR) exhibiting time to first 50% improvement in (A) reflective total nasal symptom score (rTNSS), (B) reflective total ocular symptom score (rTOSS), and (C) reflective total of seven symptom score (rT7SS) after treatment with fluticasone propionate (FP), azelastine (AZE), or placebo (PLA). (A) AZE versus FP, $p = 0.9505$; FP versus PLA, $p = 0.0439$; AZE versus PLA, $p = 0.0503$. (B) AZE versus FP, $p = 0.0281$; FP versus PLA, $p = 0.9503$; AZE versus PLA, $p = 0.0202$. (C) FP versus AZE, $p = 0.5858$; FP versus PLA, $p = 0.2965$; AZE versus PLA, $p = 0.1094$.

topical corticosteroids. For example, a study by Lange and colleagues showed that intranasal mometasone furoate was significantly superior to intranasal levocabastine for the relief of all nasal symptoms, in terms of a global evaluation of efficacy and reduction in inflammatory mediator concentrations.¹⁹ However, because AZE has been reported to have, in addition to its

well-established antihistamine effects, anti-inflammatory and mast cell-stabilizing properties,^{20–24} this could serve to explain the magnitude of its efficacy as shown in this direct comparison study. Therefore, studies of the same size would be needed with other intranasal antihistamines to potentially reach similar conclusions.

As already mentioned previously, a limitation of the current *post hoc* analysis was that the original study was not designed as a noninferiority or therapeutic equivalence trial for AZE versus FP with prespecified noninferiority margins. However, the study was powered to detect relevant differences among active treatments and was able to detect treatment differences between placebo and active treatment groups. Intranasal AZE and FP were both statistically superior to placebo, and MP29-02 was statistically superior to both FP and AZE, with treatment differences much larger than that between AZE and FP, thus confirming study sensitivity. The robustness of the steroid-comparable efficacy of AZE is also confirmed by an estimation of the number of patients needed to treat to detect a statistical difference between groups. Based on the obtained estimates, a total of 1538 patients would be required (769 per treatment group) to achieve 80% power. This large sample size required is an indicator of the difficulty of achieving a statistically significant difference between groups and supports the fact that there is no clinically relevant difference in efficacy between AZE and FP at these doses. A further limitation is that the comparison between AZE and FP was not a primary objective of the trial and is *post hoc*. Moreover, the argumentation is based on nonsignificance, *i.e.*, on argumentation with the type II error level (in contrast to type I error levels for superiority proofs). Ideally, one may conduct a noninferiority study. However, the consistency of small treatment difference sizes among end points and showed assay sensitivity provide recognizable evidence for the comparability of AZE and FP presented here. To determine the effect of AZE compared with fluticasone, for a longer duration and for other indications (e.g., perennial AR and vasomotor rhinitis) further head-to-head studies need to be performed.

In conclusion, the results of this head-to-head comparison show that INSs can no longer be confirmed as the sole most effective therapy for symptom control in patients with moderate-to-severe SAR. Rather, intranasal AZE can be considered just as effective for symptom control as intranasal fluticasone. Because of this, intranasal AZE could be considered as first-line therapy in guidelines for SAR.

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