

## A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis

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**Background:** Moderate-to-severe allergic rhinitis (AR) is a challenge to treat, with many patients using multiple therapies and achieving limited symptom control. More effective therapies must be developed and tested in well-controlled,

randomized, prospective studies with a direct comparison to current standards.

**Objectives:** The aim of these studies was to investigate the efficacy of MP29-02 (a novel formulation of azelastine and fluticasone propionate [FP]) in patients with moderate-to-severe seasonal allergic rhinitis (SAR) and to compare its efficacy with 2 first-line therapies (ie, intranasal azelastine and intranasal FP) in this population.

**Methods:** Three thousand three hundred ninety-eight patients (≥12 years old) with moderate-to-severe SAR were enrolled into 3 multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trials (MP4002 [NCT00651118], MP4004 [NCT00740792], and MP4006 [NCT00883168]). Each trial was conducted for 14 days during different allergy seasons. The primary efficacy variable was the sum of the morning and evening change from baseline in reflective total nasal symptom score (range, 0-24) over the treatment period. Outcomes for the meta-analysis included efficacy according to disease severity and time to response in relevant responder criteria.

**Results:** In the meta-analysis MP29-02 reduced the mean reflective total nasal symptom score from baseline (−5.7 [SD, 5.3]) more than FP (−5.1 [SD, 4.9],  $P < .001$ ), azelastine (−4.4 [SD, 4.8],  $P < .001$ ), or placebo (−3.0 [SD, 4.2],  $P < .001$ ). This benefit was observed from the first day of assessment, with improvement in each individual nasal symptom, even in the patients with the most severe disease. MP29-02 achieved response consistently days earlier and showed greater efficacy in patients with moderate-to-severe rhinitis than FP and azelastine.

**Conclusions:** MP29-02 represents a novel therapy that demonstrated superiority to 2 first-line therapies for AR. Patients with moderate-to-severe SAR achieved better control, and their symptoms were controlled earlier with MP29-02 than with recommended medications according to guidelines. (J Allergy Clin Immunol 2012;129:1282-9.)

**Key words:** Allergic rhinitis, azelastine, fluticasone propionate, MP29-02, moderate-to-severe

Allergic rhinitis (AR) occurs in more than 500 million persons around the world and is a global health problem that causes major illness and disability.<sup>1,2</sup> The effects of AR are far reaching and easily underestimated, with its negative effects affecting patient's quality of life (QoL)<sup>3</sup> and school and work performance.<sup>4,5</sup> It is also a costly disease, estimated at €4260 per patient per year in Europe,<sup>6</sup> and \$3.4 billion annually in the United States in direct medical costs alone.<sup>7</sup>

AR is a challenge to treat because many patients do not respond sufficiently to treatment. Furthermore, the disease severity is

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#### Abbreviations used

ANCOVA: Analysis of covariance  
AR: Allergic rhinitis  
FP: Fluticasone propionate  
iTNSS: Instantaneous total nasal symptom score  
QoL: Quality of life  
RQLQ: Rhinitis Quality of Life Questionnaire  
rTNSS: Reflective total nasal symptom score  
rTOSS: Reflective total ocular symptom score  
SAR: Seasonal allergic rhinitis

underestimated and, consequently, inadequately treated.<sup>8</sup> Most patients have moderate-to-severe disease,<sup>3,9</sup> frequently experience severe symptoms while receiving therapy, and are dissatisfied and noncompliant with currently available therapy.<sup>10,11</sup> Patients use multiple therapies (as many as 74.4% of patients) in an attempt to achieve symptom control,<sup>3,9,12-14</sup> despite the limited evidence to support this practice.<sup>2</sup>

Given this unmet medical need, more effective therapies for the management of AR are clearly required. Current guideline-based therapy for AR includes oral and intranasal antihistamines and intranasal corticosteroids. Although intranasal corticosteroids are considered the most effective therapy, especially for more severe cases,<sup>2,15</sup> they need some time to become effective. In contrast, intranasal H<sub>1</sub>-antihistamines, such as azelastine, have a rapid onset of action.

The recently updated Allergic Rhinitis and its Impact on Asthma guidelines<sup>15</sup> highlighted the need for high-quality, direct comparison studies to further substantiate the current treatment recommendations. Three randomized, placebo- and active-controlled, parallel-group trials were performed to directly compare the efficacy and safety of intranasal azelastine, intranasal fluticasone propionate (FP), and intranasal MP29-02 (a novel formulation of azelastine and FP), with all 3 medications using exactly the same formulation, in patients with moderate-to-severe seasonal allergic rhinitis (SAR). Each study aimed to demonstrate and replicate that MP29-02 demonstrated superiority to either monotherapy in a head-to-head fashion. Moreover, in the meta-analysis responder analyses were added to further address relevance in treatment efficacy.

## METHODS

### Protocol

Individual results and a meta-analysis of 3 phase III, multicenter, randomized, double-blind, parallel-group trials (MP4002 [NCT00651118], MP4004 [NCT00740792], and MP4006 [NCT00883168]) were assessed in patients with moderate-to-severe SAR to determine the efficacy of MP29-02 compared with intranasal H<sub>1</sub>-antihistamine (azelastine), corticosteroid (FP), and placebo using the same formulation. Placebo spray comprised exactly the same vehicle/formulation as the active treatments without any active agent. The same treatments and treatment periods and essentially similar protocols were used in the 3 studies. The studies were conducted in accordance with US Food and Drug Administration and European Medicines Agency recommendations,<sup>16,17</sup> and good clinical practice<sup>18</sup> during the 2008-2009 US Spring and Fall allergy seasons. After institutional review board approval, 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 response

to relevant pollen were randomized. All subjects had moderate-to-severe SAR defined by a reflective total nasal symptom score (rTNSS) of at least 8 of 12, with a congestion score of 2 or 3 during screening. Inclusion criteria for the duration of symptoms for the 3 studies were slightly different. For more information on this and exclusion criteria, see the [Methods](#) section in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). Excluded therapies and medications are summarized in [Table E1](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

### Planned interventions and timing

Each study comprised a 7-day, single-blind, placebo lead-in period and a 14-day treatment period with 3 study visits at days 1, 7, and 14. On visit 2 (day 1), eligible patients were randomized to 14 days of treatment (1 spray per nostril twice daily) with the following: (1) MP29-02 nasal spray (novel formulation of 137 µg of azelastine/50 µg of FP); (2) azelastine nasal spray (137 µg); (3) FP (50 µg) nasal spray; or (4) vehicle placebo nasal spray. Doses were separated by approximately 12 hours. Patients recorded application times and symptom scores in a diary. Compliance with treatment was assessed (see the [Methods](#) section in this article's Online Repository).

### Efficacy variables

The primary efficacy variable was the sum of the morning and evening overall change from baseline in 12-hour rTNSSs over the entire 14-day treatment period (sum of the individual nasal symptoms of congestion, itching, rhinorrhea, and sneezing).<sup>16,17</sup> All nasal and ocular symptoms were scored by patients twice daily on each treatment day according to a 4-point scale. For nasal symptoms, a score of 0 was defined as none (no symptoms present), a score of 1 was defined as mild (mild symptoms that do not interfere with any activity), a score of 2 was defined as moderate (slightly bothersome symptoms that slightly interfere with activity/nighttime sleep), and a score of 3 was defined as severe (bothersome symptoms that interfere with activity/nighttime sleep). Therefore the maximum rTNSS or instantaneous total nasal symptom score (iTNSS) was 24 (ie, 4 symptoms × score of 3 × 2 for morning + evening). See the [Methods](#) section in this article's Online Repository for calculation of baseline scores.

Secondary efficacy variables included overall change from baseline (treatment period, days 2-14) in the individual reflective nasal symptom score, iTNSS, and reflective total ocular symptom score (rTOSS). For the symptoms of itchy eyes and watery eyes, the same scale was used as for nasal symptoms. For the symptom of red eyes, the following scale was used: 0, none (no redness present); 1, mild (slightly dilated blood vessels and pinkish color compared with the subject's normal color); 2, moderate (more dilation of blood vessels and red color compared with subject's normal color); and 3, severe (large, numerous, dilated blood vessels and deep red color compared with the subject's normal color). The maximum rTOSS was 18 (ie, 3 symptoms × score of 3 × 2 for morning + evening). Onset of action was also determined clinically by means of assessment of iTNSS in the first 4 hours after administration.

### QoL

QoL was assessed before randomization and at the end of the study by using the 28-item Rhinitis Quality of Life Questionnaire (RQLQ) for subjects older than 18 years.<sup>19</sup> Total baseline RQLQ scores were used to categorize patients according to severity.

### Safety variables

Safety was assessed based on the incidence, type, and severity of adverse events coded with the Medical Dictionary for Regulatory Activities. At each visit, patients underwent a direct visual nasal examination to determine potential side effects to the nasal mucosa or otherwise clinically relevant intranasal conditions. Vital signs were also measured.

### Sample size

For studies MP4002 and MP4004, sample size was determined based on the results of a previously published proof-of-concept exploratory study,<sup>20</sup> which

suggested that MP29-02 and FP might reduce the rTNSS by  $-5.92$  and  $-4.19$ , respectively, and that a meta-analysis SD of 5 might be a conservative estimate. On the basis of these values, a 2-sided  $\alpha$  value of 5%, and a 10% dropout rate, 195 randomized subjects per treatment arm were sufficient to achieve 90% power. Sample size in study MP4006 was determined by excluding a treatment difference of less than 0.6 units in overall reduction in the rTNSS over a 14-day treatment period. Allowing for dropouts, a minimum of 450 subjects per group had to be randomized.

## Randomization

Patients were randomized and balanced by study site in blocks of 4. 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 blind to treatment assignment. The active controls comprised the individual components of MP29-02 in the same vehicle (ie, contained the same excipients assessed qualitatively and quantitatively), pump volume (0.137 mL per spray), and device (see the [Methods](#) section in this article's Online Repository). A blind 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

A hierarchical test procedure was implemented to maintain the overall 2-sided type I error level of .05 among the pairwise comparisons. As a first step, changes in combined rTNSSs were compared between patients receiving MP29-02 and placebo. If this was significant, MP29-02 was then compared with azelastine, and if this was also significant, it was then compared with FP.

As prespecified in trial protocols and statistical analysis plans before unblinding, efficacy analyses were performed on the intent-to-treat population of all randomized patients with at least 1 postbaseline observation. An analysis of covariance (ANCOVA) model was applied to the primary efficacy variable of absolute change in combined morning plus evening rTNSSs. The model included the treatment days from day 2 (first day with postdose morning score) 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 using the Satterthwaite approximation. Treatment differences are presented as differences in least squares means resulting from this applied ANCOVA (ie, estimates are corrected for influence of covariates, such as center or baseline severity [see [Methods](#) section in this article's Online Repository]), to account for the applied inferential statistical methods. Change from baseline in iTNSSs, individual reflective nasal symptom scores, rTOSSs, and RQLQ scores were assessed in the same way.

The meta-analysis on efficacy data was conducted *post hoc* and comprised all 3 studies. The statistical models used for the meta-analysis were similar to those used in the individual studies, with an additional fixed effect for study.

In addition, the rTNSS (overall and by day) was assessed based on patient severity. Patients were categorized into 2 severity groups according to their median baseline rTNSSs (ie,  $\leq 18.9$  or  $> 18.9$ ) or median baseline RQLQ scores (ie,  $\leq 3.9$  or  $> 3.9$ ). Moreover, time to response was analyzed by using Kaplan-Meier estimates. A change from baseline in (1) combined rTNSS of at least 50%<sup>17</sup> or (2) a score of 1 point or less for each nasal symptom (ie, complete or near-complete resolution of each symptom) were used to define response.

## RESULTS

### Patients

Study completion rates were high (approximately 95%) and similar across studies and across treatment groups (see [Table E2](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Dropout rates were negligible (see [Table E3](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). When data were pooled for meta-analysis, 848, 846, 847, and 857 patients received MP29-02, FP, azelastine, and placebo, respectively. The baseline characteristics of the 4 treatment groups were similar, both within and between studies ([Table I](#)). Patients' baseline rTNSSs were well matched and confirmed that the vast majority of these patients had moderate-to-severe AR.

## Outcomes

**Efficacy in individual studies (primary end point rTNSS).** In each study MP29-02 significantly reduced the mean rTNSS from baseline by a greater margin than FP, azelastine, or placebo ([Table II](#) and [Fig 1](#)). All individual nasal symptoms contributed to the effect (see [Tables E4](#) and [E5](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). In each study all active treatments were statistically significantly superior to placebo, whereas MP29-02 demonstrated superiority to all other treatment arms.

**Safety.** For each study, the proportion of subjects with a treatment-emergent adverse event was similar for the active groups (see [Table E6](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). The higher proportion of treatment-related adverse events observed in the MP29-02 and azelastine treatment groups was due primarily to the taste of azelastine coded as dysgeusia in these patients (2.1% to 4.7% of MP29-02-treated patients and 3.4% to 7.2% of azelastine-treated patients, see [Table E7](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), but no patient discontinued therapy because of this event. For all studies, changes in vital signs and nasal examination were similar in all groups.

**Meta-analysis. rTNSSs, iTNSSs, individual symptom scores, and rTOSSs: Change from baseline.** Patients treated with MP29-02 experienced significantly greater nasal symptom relief than those treated with either monotherapy. Over the entire 14-day treatment period, MP29-02 reduced the mean rTNSS from baseline ( $-5.7$  [SD, 5.3]) to a significantly greater degree than FP ( $-5.1$  [SD, 4.9],  $P < .001$ ), azelastine ( $-4.4$  [SD, 4.8],  $P < .001$ ), or placebo ( $-3.0$  [SD, 4.2],  $P < .001$ ; [Table II](#) and [Fig 1](#)). MP29-02 had an onset of action of 30 minutes, and the clinical benefit was observed during the first day of assessment and sustained over the entire course of treatment (see [Fig E1](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

MP29-02 reduced the overall iTNSS from baseline to a significantly greater extent than FP ( $P = .022$ ), azelastine ( $P < .001$ ), or placebo ( $P < .001$ ). MP29-02 targeted all of the symptoms of AR (see [Tables E4](#) and [E5](#)). Compared with FP or azelastine monotherapy, patients who received MP29-02 had greater relief from their symptoms of nasal congestion ( $P = .005$  vs FP and  $P < .001$  vs azelastine), nasal itch ( $P = .005$  vs FP and  $P = .001$  vs azelastine), rhinorrhea ( $P = .013$  vs FP and  $P < .001$  vs azelastine), and sneezing ( $P = .001$  vs FP and  $P < .001$  vs azelastine; see [Tables E4](#) and [E5](#)). Patients treated with MP29-02 also experienced superior relief from their ocular symptoms than those treated with FP alone. Over the entire 14-day treatment period, MP29-02 reduced the mean rTOSS from baseline ( $-3.2$  [SD, 4.0]) compared with FP ( $-2.8$  [SD, 3.6]), azelastine ( $-2.9$  [SD, 3.8]), or placebo ( $-1.8$  [SD, 3.4]), achieving statistical significance versus FP ( $P = .003$ ) and placebo ( $P < .001$ ; see [Tables E4](#) and [E5](#)).

**TABLE I.** Baseline characteristics of study participants included in 3 randomized trials (ITT population)

Study MP4002				
	MP29-02 (n = 207)	FP (n = 207)	Azelastine (n = 208)	Placebo (n = 209)
Age (y)	37.3 (14.1)	38.6 (14.1)	36.2 (14.6)	37.3 (16.0)
Male sex, no. (%)	65 (31.4)	80 (38.6)	78 (37.5)	77 (36.8)
White race, no. (%)	162 (78.3)	161 (77.8)	162 (77.9)	169 (80.9)
History of SAR (y)	21.7 (13.2)	21.3 (13.5)	21.6 (13.6)	21.2 (14.0)
Study MP4004				
	MP29-02 (n = 193)	FP (n = 189)	Azelastine (n = 194)	Placebo (n = 200)
Age (y)	38.8 (14.1)	37.0 (13.6)	38.2 (13.5)	37.2 (13.0)
Male sex, no. (%)	67 (34.7)	68 (36.0)	66 (34.0)	81 (40.5)
White race, no. (%)	154 (79.8)	140 (74.1)	153 (78.9)	164 (82.0)
History of SAR (y)	21.5 (13.5)	21.1 (13.7)	19.7 (13.1)	21.0 (12.8)
Study MP4006				
	MP29-02 (n = 448)	FP (n = 450)	Azelastine (n = 445)	Placebo (n = 448)
Age (y)	35.6 (14.5)	34.2 (14.5)	36.4 (14.8)	34.7 (14.1)
Male sex, no. (%)	171 (38.2)	170 (37.8)	174 (39.1)	179 (40.0)
White race, no. (%)	364 (81.3)	356 (79.1)	357 (80.2)	348 (77.7)
History of SAR (y)	20.4 (13.0)	19.6 (12.5)	19.5 (12.9)	19.6 (12.4)

Data are presented as means (SDs) unless otherwise stated.

ITT, Intent to treat.

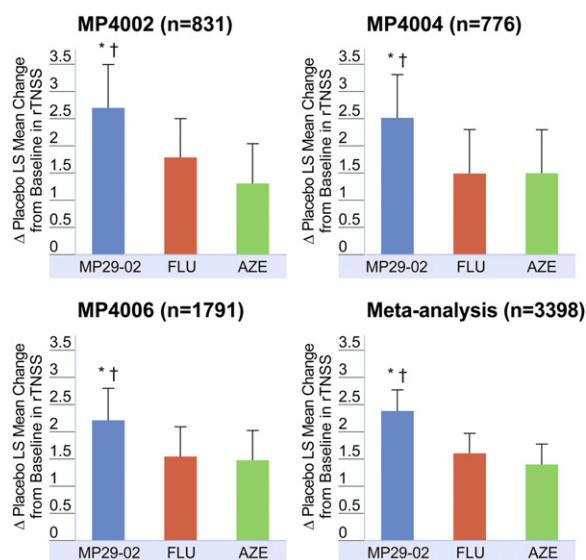
**TABLE II.** Total nasal symptom scores (baseline and change from baseline) for 3 randomized trials and the meta-analysis results (ITT population)

Treatment	No.	Baseline	Change from baseline	Difference	LS mean	95% CI	P value
Study MP4002							
MP29-02	207	18.3 (3.0)	−5.5 (5.2)	—	—	—	—
FP	207	18.2 (3.2)	−5.0 (4.7)	MP29-02, FP	−0.9	−1.74 to −0.07	.034
AZE	208	18.2 (3.5)	−4.1 (4.6)	MP29-02, AZE	−1.4	−2.22 to −0.54	.002
Placebo	209	18.6 (3.2)	−2.6 (3.9)	MP29-02, PLA	−2.7	−3.48 to −1.91	<.001
				FP, PLA	−1.8	−2.50 to −1.09	<.001
				AZE, PLA	−1.3	−2.04 to −0.60	.001
Study MP4004							
MP29-02	193	18.2 (3.3)	−5.6 (5.2)	—	—	—	—
FP	189	18.6 (2.9)	−5.0 (5.2)	MP29-02, FP	−1.0	−1.91 to −0.05	.038
AZE	194	18.5 (3.1)	−4.4 (4.6)	MP29-02, AZE	−1.0	−1.90 to −0.09	.032
Placebo	200	18.2 (3.1)	−2.8 (3.9)	MP29-02, PLA	−2.5	−3.33 to −1.67	<.001
				FP, PLA	−1.5	−2.34 to −0.69	.001
				AZE, PLA	−1.5	−2.31 to −0.71	.001
Study MP4006							
MP29-02	448	19.4 (2.4)	−5.6 (5.2)	—	—	—	—
FP	450	19.4 (2.4)	−5.1 (4.7)	MP29-02, FP	−0.6	−1.22 to −0.07	.029
AZE	445	19.5 (2.5)	−4.5 (4.8)	MP29-02, AZE	−0.7	−1.30 to −0.13	.016
Placebo	448	19.5 (2.4)	−3.2 (4.3)	MP29-02, PLA	−2.1	−2.70 to −1.57	<.001
				FP, PLA	−1.5	−2.03 to −0.95	<.001
				AZE, PLA	−1.4	−1.96 to −0.87	<.001
Meta-analysis (studies MP4002, MP4004, and MP4006)							
MP29-02	848	18.8 (2.9)	−5.7 (5.3)	—	—	—	—
FP	846	18.9 (2.8)	−5.1 (4.9)	MP29-02, FP	−0.8	−1.18 to −0.34	.001
AZE	847	18.9 (3.0)	−4.4 (4.8)	MP29-02, AZE	−0.9	−1.37 to −0.52	<.001
Placebo	857	19.0 (2.8)	−3.0 (4.2)	MP29-02, PLA	−2.3	−2.75 to −1.95	<.001
				FP, PLA	−1.6	−1.97 to −1.21	<.001
				AZE, PLA	−1.4	−1.78 to −1.02	<.001

Data are expressed as means (SDs). Difference from active treatment is given as LS mean treatment difference with associated 95% CIs and P values.

AZE, Azelastine (137 µg per nostril twice daily); FP, fluticasone propionate (50 µg per nostril twice daily); LS, least squares; MP29-02, azelastine/FP (137/50 µg/nostril twice daily); PLA, placebo.

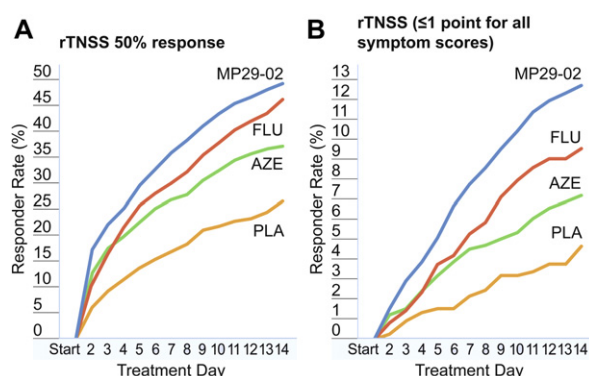




**FIG 1.** Effect of MP29-02, FP (FLU), and azelastine (AZE) on overall rTNSSs (morning plus evening) in patients with moderate-to-severe SAR. Data are presented as least squares (LS) mean change from baseline derived by means of ANCOVA minus placebo. The precision of these estimates are indicated by the upper bounds of the respective 95% CIs. Study MP4002:  $n = 831$ ,  $*P = .034$  versus FP;  $\dagger P = .001$  versus AZE; Study MP4004:  $n = 776$ ,  $*P = .038$  versus FP;  $\dagger P = .032$  versus AZE; Study MP4006:  $n = 1791$ ,  $*P = .029$  versus FP;  $\dagger P = .016$  versus AZE; Meta-analysis:  $n = 3398$ ,  $*P < .001$  versus FP;  $\dagger P < .001$  versus AZE.

**rTNSS responder analyses.** Fig 2, A, shows the proportion of patients in each treatment group who experienced a 50% or greater reduction in rTNSS over time. The results highlighted a time advantage of MP29-02 over FP (up to 3 days earlier) and azelastine (up to 5 days earlier) monotherapy in producing a clinically meaningful reduction in rTNSS, as well as an increased responder rate with MP29-02 (see Table E8 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). More patients treated with MP29-02 (12.4%) also exhibited complete or near-complete elimination of their symptoms (ie, reduction in all nasal symptoms scores to  $\leq 1$ ) than those treated with FP (9.3%), azelastine (7.1%), or placebo (4.2%; Fig 2, B). Moreover, this effect was also observed days earlier than either monotherapy: up to 5 days faster than FP ( $P = .033$ ) and up to 7 days faster than azelastine ( $P < .001$ ).

**rTNSS change from baseline by baseline patient severity.** MP29-02 provided benefits for all patients, providing significantly greater symptom relief than FP or azelastine monotherapy regardless of disease severity (Fig 3). When severity was split by median baseline rTNSS, MP29-02 was significantly superior to FP (difference,  $-0.6$ ;  $P = .033$  [95% CI,  $-1.16$  to  $-0.05$ ]) and azelastine (difference:  $-0.8$ ;  $P = .004$  [95% CI,  $-1.41$  to  $-0.27$ ]) in patients with less severe disease (ie, baseline rTNSS of  $\leq 18.9$ ), with a greater benefit observed in patients with more severe disease (ie, baseline rTNSS of  $>18.9$ ) compared with both FP (difference:  $-0.8$ ;  $P = .008$  [95% CI,  $-1.46$  to  $-0.23$ ]) or azelastine (difference:  $-1.1$ ;  $P = .001$  [95% CI,  $-1.71$  to  $-0.48$ ]). When severity was alternatively split by median baseline RQLQ score, MP29-02 was again superior to FP and azelastine monotherapy (in terms of rTNSS improvement) in patients with moderate rhinitis (ie, RQLQ:  $\leq 3.9$ ; difference of  $-0.4$  [ $P = .159$ ; 95% CI,  $-1.01$  to  $0.17$ ] vs FP and difference



**FIG 2.** Time-response curves showing the percentage of patients exhibiting 50% improvement in rTNSSs (A) or a score of 1 point or less (ie, complete or near-complete resolution) for each nasal symptom (B) by treatment day after treatment with MP29-02 ( $n = 834$ ), FP (FLU;  $n = 846$ ), azelastine (AZE;  $n = 847$ ), or placebo (PLA;  $n = 857$ ). Data are presented as mean proportion of patients for the meta-analysis dataset (studies MP4002, MP4004, and MP4006). Fig 2, A, MP29-02 versus FLU:  $P = .071$ ; MP29-02 versus AZE:  $P < .001$ ; MP29-02 versus PLA:  $P < .001$ . Fig 2, B, MP29-02 versus FLU:  $P = .033$ ; MP29-02 versus AZE:  $P < .001$ ; MP29-02 versus PLA:  $P < .001$ .

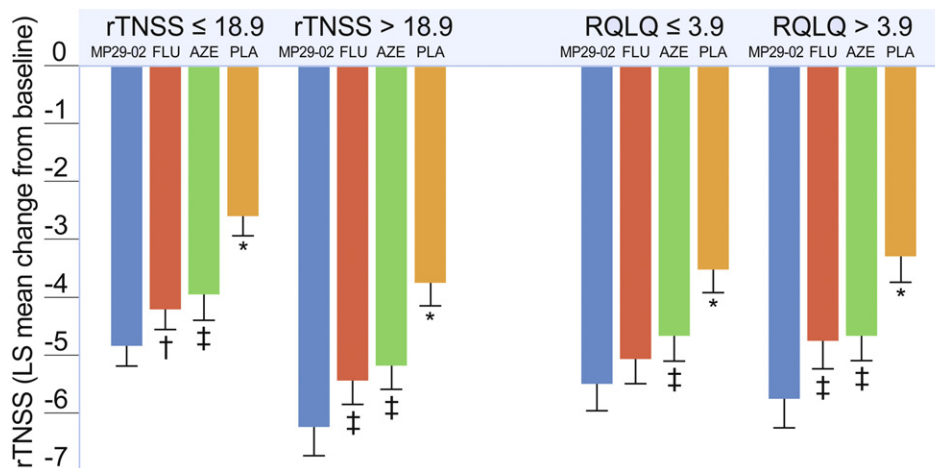
of  $-0.9$  [ $P = .006$ ; 95% CI,  $-1.46$  to  $-0.24$ ] vs azelastine) and significantly superior in patients with severe rhinitis (ie, RQLQ:  $>3.9$ ; difference of  $-1.0$  [ $P = .004$ ; 95% CI,  $-1.68$  to  $-0.33$ ] vs FP and difference of  $-1.1$  [ $P = .001$ ; 95% CI,  $-1.75$  to  $-0.44$ ] vs azelastine).

**QoL.** Patients were well matched for QoL impairment, with overall baseline RQLQ scores of 3.9 (SD, 1.0) in the MP29-02, azelastine, and placebo groups and 3.8 (SD, 1.0) in the FP group. By day 14, all active treatments significantly improved patient QoL (MP29-02:  $-1.6$  [SD, 1.3]; FP:  $-1.5$  [SD, 1.3]; azelastine:  $-1.4$  [SD, 1.3]) compared with placebo ( $-1.0$  [SD, 1.2],  $P < .001$ ).

## DISCUSSION

Before MP29-02, no clinical development program had demonstrated additional benefit over 2 currently recommended first-line AR therapies in patients with moderate-to-severe disease. In the present program MP29-02 demonstrated superior efficacy over intranasal FP and intranasal azelastine monotherapy in patients with AR in a set of 3 randomized, double-blind, placebo-controlled clinical studies with active controls by using the same device and formulation. This provides sound clinical evidence, for the first time, that intranasal antihistamines and corticosteroids have complementary pharmacologic effects on the pathogenesis of AR and satisfy the demands of the Allergic Rhinitis and its Impact on Asthma guidelines requesting high-quality direct comparison studies. The consistency of the results among the clinical trials and symptoms contributes to the robustness of the data. Adverse events were similar for all active groups, and only a few patients experienced mild dysgeusia.

The advancement in the treatment of SAR derives from MP29-02 providing consistent and uniform relief from each of the individual nasal symptoms of congestion, itching, rhinorrhea, and sneezing. Whether intranasal corticosteroids are also effective in treating ocular symptoms is an ongoing debate.<sup>21</sup> In this regard MP29-02 has been shown to be more effective than FP, as well as placebo, in alleviating ocular symptoms.



**FIG 3.** Effect of MP29-02, FP (FLU), azelastine (AZE), and placebo (PLA) on rTNSSs (morning plus evening) by severity in patients with SAR. Patients were classified as having more or less severe disease based on median baseline rTNSSs or baseline RQLQ scores (ie, baseline rTNSS score  $\leq 18.9$  [MP29-02:  $n = 425$ ; FP:  $n = 407$ ; AZE:  $n = 417$ ; PLA:  $n = 407$ ] or  $> 18.9$  [MP29-02:  $n = 423$ ; FP:  $n = 438$ ; AZE:  $n = 427$ ; PLA:  $n = 449$ ] or baseline RQLQ score  $\leq 3.9$  [MP29-02:  $n = 374$ ; FP:  $n = 382$ ; AZE:  $n = 382$ ; PLA:  $n = 364$ ] or  $> 3.9$  [MP29-02:  $n = 363$ ; FP:  $n = 356$ ; AZE:  $n = 365$ ; PLA:  $n = 373$ ]). Data are presented as least squares (LS) mean change from baseline for the meta-analysis dataset (studies MP4002, MP4004, and MP4006). The precision of these estimates are indicated by the lower bounds of the respective 95% CIs. \* $P \leq .001$  versus all active treatments. † $P < .040$  versus MP29-02. ‡ $P < .010$  versus MP29-02.

MP29-02 has a fast onset of action, demonstrating superiority immediately from the first day of treatment. Additionally, MP29-02 provided a clinically relevant 50% rTNSS reduction significantly earlier (and in a larger number of patients), with a time advantage over 2 standard therapies measured in days and not hours (up to 3 days earlier than FP and up to 5 days earlier than azelastine). 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.<sup>22</sup> Indirect evidence suggests that patients with SAR take their medication for 7 or fewer consecutive days.<sup>22,23</sup> Therefore a 3-day advantage to a 50% rTNSS reduction of MP29-02 over FP represents a substantial improvement within the personalized treatment cycle.

One of every 8 patients treated with MP29-02 exhibited complete or near-complete symptom resolution, which is surprising considering that the majority of patients had severe AR. This result might have significant socioeconomic implications when one considers that more than 500 million persons have AR. Extrapolating these 1 in 8 patients to the global situation, it would be expected that more than 60 million patients treated with MP29-02 could have no or minimal functional impairment days earlier at work or school and would require no additional health care visits.

Most patients with AR have moderate-to-severe disease.<sup>3,9</sup> The prerequisite in our studies of an rTNSS of at least 8 of 12, a congestion score of 2 or 3 during screening, and a significant QoL impairment ensured that included patients had moderate-to-severe AR. Although these patients are difficult to treat, they would also benefit most from any new treatment for AR, which provides added therapeutic value over recommended therapy. MP29-02 meets this requirement because it demonstrated superiority to the monotherapies in relieving all of the individual nasal symptoms associated with AR, including those associated with severe disease. The meta-analysis revealed, especially in patients with

more severe forms of AR who are currently difficult to treat, that the greater efficacy of MP29-02 compared with single components was rather more pronounced (Fig 3).

The generalizability of these data is an inherent limitation of all randomized trials because inclusion and exclusion criteria had to be in agreement with US Food and Drug Administration and European Medicines Agency guidelines. Thus it is possible that many patients seen in primary care are not in line with those included in the studies.<sup>24</sup> In particular, there are many patients who present with milder symptoms than those recruited.

Another limitation of the studies presented here was that, by virtue of the study design, patient QoL was only assessed on day 14, which, however, was sufficient to demonstrate that MP29-02 had clinically relevant superiority versus placebo. In follow-up research QoL assessments on day 7 might be considered, and daily visual analogue scale monitoring might help us better understand patients' views.<sup>25</sup> The mechanism of action of MP29-02 in conjunction with the provided evidence indicate at least an additive effect of MP29-02 over FP and azelastine alone. However, this study cannot demonstrate whether there is synergy. Challenge tests might be more appropriate.

When developing new combinations, potential drug-drug interactions are important to consider. A recent pharmacokinetic study proved that in the given case a drug-drug interaction could be excluded. However, at a very low level, a modest increase in systemic FP bioavailability compared with that of marketed FP could be detected. This may occur because the novel formulation characteristics of MP29-02 could result in a greater contact area for FP absorption with the nasal mucosal surface, thereby allowing improved local bioavailability and clinical efficacy.<sup>26</sup>

Consequently, the treatment difference of MP29-02 compared with a commercial FP formulation can be expected to be more pronounced than shown in the studies presented here. This has

been illustrated in a previously published study that showed that MP29-02 provided better and faster control of AR symptoms than observed in our studies when compared with a commercial FP spray.<sup>27</sup> However, that study could not distinguish formulation and pharmacologic effects and therefore was of limited scientific value when trying to define the complementary pharmacologic effects of intranasal antihistamines and corticosteroids in patients with AR.

In summary, to our knowledge, this is the largest body of evidence comparing the efficacy of different types of intranasal AR therapies. In nearly 3400 patients, MP29-02 was faster and more effective than established first-line therapies (with FP representing intranasal corticosteroids and azelastine representing intranasal antihistamines) in patients with moderate and severe AR. The results are consistent among different parameters, including ocular symptoms, and across various allergy seasons. Taken together, these results show that MP29-02 can be considered the drug of choice for AR therapy because it offers additional benefit to patients with AR, in particular with moderate-to-severe disease.

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**Clinical implications: Most patients with AR have moderate-to-severe disease, which is frequently poorly controlled. Topical MP29-02 provides rapid relevant relief for these patients with SAR.**

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## METHODS

### Detailed inclusion criteria for each of the 3 randomized controlled studies

All subjects were required to have moderate-to-severe AR, which was defined as rhinitis with 1 or more of the following: (1) sleep disturbance; (2) impairment of daily activities, leisure, and/or sport; (3) impairment of school or work; and (4) troublesome symptoms. Inclusion criteria for each of the 3 studies were slightly different. At the screening visit, all patients were required to have an rTNSS of 8 of a possible 12 for inclusion and a congestion score of 2 or 3. At the randomization visit, subjects entering study MP4002 or MP4004 were required to have a (1) 12-hour rTNSS (morning or evening) of 8 or greater on 3 separate symptom assessments during the lead-in period, (2) a morning or evening 12-hour reflective nasal congestion score of 2 or 3 on 3 separate symptom assessments, and (3) an iTNSS of 8 or greater at time point zero. Patients eligible for inclusion into study MP4006 were required to have a score of 56 or greater for the sum of 7 consecutive rTNSS (morning plus evening) assessments for 3 days before randomization and on the morning of randomization with a nasal congestion score of 14 or greater. At the time of randomization (before noon), MP4006 patients were also required to have an iTNSS of 8 or greater and a congestion score of 2 or greater at time point zero.

### Detailed exclusion criteria

Subjects were excluded if they had erosion, ulceration, or septal perforation or another disease (eg, sinusitis, rhinitis medicamentosa, polyposis, respiratory tract infection [within 14 days of screening], asthma [except intermittent asthma]), significant pulmonary disease, or symptomatic cardiac conditions or were taking concomitant medication that could interfere with the interpretation of study results. Smokers were not excluded from the study.

### Assessment of treatment compliance

Subjects recorded each dose (number of sprays) of twice-daily study medication in their subject diaries. On days 1, 7, and 14, the study site staff reviewed the amount of study medication returned and reviewed the amount of medication recorded in diaries. This information was used to assess the subject's compliance with the study dosing. Any discrepancies between the subject diary and the actual amount of returned study medication were resolved before the subject left the clinic.

### Settings and locations in which the data were collected

Study MP4002 was carried out in 44 sites in the United States from March 2008 to June 2008. Studies MP4004 (August–November 2008) and MP4006 (April 2009–August 2009) were carried out in 41 and 49 sites, respectively, in the United States.

### Baseline scores

Baseline scores were defined as the average of all nonmissing scores over the 7-day placebo lead-in period (studies MP4002 and MP4004) or during the 3 days before randomization (study MP4006), including the morning of day 1 (predose). The overall change from baseline to day 14 included assessments from day 1 in the evening through day 14 in the morning.

### Statistical analysis

ANCOVA was used to assess differences between treatment groups for the primary efficacy variable of absolute change in combined (morning plus evening) rTNSSs, as well as change from baseline in iTNSSs, individual reflective nasal symptom scores, rTOSSs, and RQLQ scores. ANCOVA is a general linear model with a continuous outcome variable (quantitative) and 2 or more predictor variables, in which at least 1 is continuous (quantitative and scaled) and at least 1 is categorical (nominal and nonscaled). ANCOVA methods are always based on least squares means and not on simple means. These least squares means provide estimates of treatment effects and treatment differences adjusted for other effects. It is a common scientific rule to adjust at least for all effects used in the randomization procedure (ie, center and baseline severity). Therefore least squares means are presented here for intergroup treatment differences.

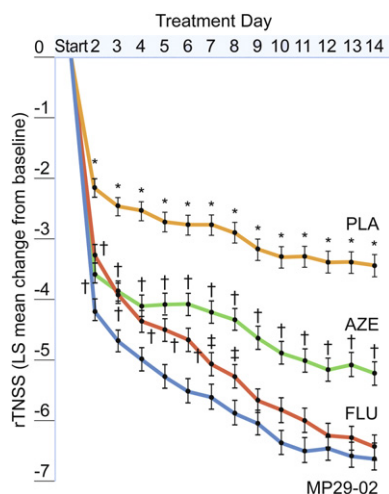
### Study blinding

It is acknowledged that bitter taste is a well-known side effect of azelastine nasal spray. However, only a small proportion of patients recognized a deviating taste. In the current studies dysgeusia was reported by only 2.1% to 4.7% of patients receiving MP29-02 and by 3.4% to 7.2% of patients receiving azelastine. Importantly, dysgeusia is not exclusive to azelastine use. Bitter taste has also been reported by patients after intranasal FP use (according to its own Summary of Product Characteristics) and implied in a reference by Meltzer and colleagues.<sup>E1</sup> They showed that the majority of patients (60%) preferred intranasal fluticasone furoate over FP because of the aftertaste induced by the latter. In the current studies up to 1% of patients reported dysgeusia after intranasal FP administration, as well as up to 0.5% of placebo-treated patients. Therefore a potential bias caused by unblinding by bitter taste can be excluded for the vast majority of patients.

The studies were designed to investigate, in a scientifically sound manner, the drug effects in identical vehicle. Therefore placebo was pharmaceutically identical to MP29-02 without FP and azelastine hydrochloride. Adding a bitter taste to placebo would have therefore introduced a new excipient and modified the formulation. In that case a formulation-based bias might have been introduced to all placebo-treated patients.

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**FIG E1.** Effect of MP29-02 ( $n = 848$ ), FP (*FLU*;  $n = 846$ ), azelastine (*AZE*;  $n = 847$ ), and placebo (*PLA*;  $n = 857$ ) on rTNSSs (morning plus evening) on each day of the treatment period in patients with moderate-to-severe SAR. Data are presented as least squares (LS) mean change from baseline  $\pm$  SE for the meta-analysis dataset (studies MP4002, MP4004, MP4006).  $*P < .001$  versus all active treatments.  $\dagger P \leq .015$  versus MP29-02.  $\ddagger P \leq .050$  versus MP29-02. Mean baseline values (SDs): MP29-02, 18.8 (2.86); FP, 18.9 (2.78); AZE, 18.9 (3.00); PLA, 19.0 (2.80).

**TABLE E1.** Excluded therapies and medications

Medication/therapy	Time before screening visit
Loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, azelastine nasal spray	5 days
Oral and intranasal anticholinergic agents	5 days
Antihistamines (including ophthalmic preparations, sleep and diet aids, and cold preparations)	5 days
Ephedrine or pseudoephedrine-containing products	5 days
Decongestants	5 days
Ocular steroids	7 days
Cromolyn compounds	14 days
Oral antibiotics	14 days
Leukotriene inhibitors	14 days
Inhaled (nasal) corticosteroids	14 days
Ocular mast cell stabilizers	14 days
Monoamine oxidase inhibitors	14 days
Inhaled (oral) corticosteroids	30 days
Systemic steroids (oral, injected, intravenous)	30 days
Tricyclic antidepressants	30 days
Immunosuppressives/immunomodulators (eg, anti-TNF agents)	30 days
IgE antagonist	130 days

**TABLE E2.** Disposition of subjects

Disposition summary	Study		
	MP4002	MP4004	MP4006
Screened subjects, no.	984	918	2415
All randomized subjects, no. (%)	832 (100.0)	779 (100.0)	1801 (100.0)
Completed, no. (%)	798 (95.9)	739 (94.9)	1728 (95.9)
Discontinued, no. (%)	34 (4.1)	40 (5.1)	73 (4.1)
Reason for discontinuation, no. (%)			
Adverse event	6 (0.7)	8 (1.0)	15 (0.8)
Abnormal test result(s)	0 (0.0)	1 (0.1)	0 (0.0)
Treatment failure	0 (0.0)	5 (0.6)	4 (0.2)
Protocol violation	12 (1.4)	3 (0.4)	21 (1.2)
Noncompliance	—	5 (0.6)	14 (0.8)
Consent withdrawn	3 (0.4)	2 (0.3)	6 (0.3)
Lost to follow-up	5 (0.6)	3 (0.4)	4 (0.2)
Administrative problem(s)	0 (0.0)	0 (0.0)	1 (0.1)
Other	8 (1.0)	13 (1.7)	8 (0.4)
Safety population,* no. (%)	832 (100.0)	778 (99.9)	1801 (100.0)
ITT population,† no. (%)	831 (99.9)	776 (99.6)	1791 (99.4)

ITT, Intent-to-treat.

\*Safety population includes all randomized subjects who took at least 1 dose of the study drug.

†Intent-to-treat population includes all subjects who were randomized and had at least 1 postbaseline efficacy observation.



**TABLE E3.** Reasons for discontinuation by treatment group

Reason, no. (%)	Study											
	MP4002				MP4004				MP4006			
	MP2902 (n = 207)	FP (n = 207)	AZE (n = 208)	PLA (n = 210)	MP2902 (n = 195)	FP (n = 189)	AZE (n = 194)	PLA (n = 201)	MP2902 (n = 451)	FP (n = 450)	AZE (n = 449)	PLA (n = 451)
Adverse event	4 (1.9)	0 (0.0)	1 (0.5)	1 (0.5)	3 (1.5)	1 (0.5)	1 (0.5)	3 (1.5)	3 (0.7)	3 (0.7)	4 (0.9)	5 (1.1)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	3 (1.5)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.4)
Protocol violation	2 (1.0)	2 (1.0)	6 (2.9)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.0)	6 (1.3)	4 (0.9)	7 (1.6)	4 (0.9)
Noncompliance	—	—	—	—	0 (0.0)	5 (2.6)	0 (0.0)	0 (0.0)	1 (0.2)	5 (1.1)	4 (0.9)	4 (0.9)
Subject withdrew consent	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
Lost to follow-up	2 (1.0)	0 (0.0)	1 (0.5)	2 (1.0)	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.5)	4 (1.9)	2 (1.0)	1 (0.5)	5 (2.6)	3 (1.6)	2 (1.0)	3 (1.5)	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)
Totals	9 (4.3)	7 (3.4)	11 (5.3)	7 (3.3)	12 (6.2)	9 (4.8)	8 (4.1)	11 (5.5)	17 (3.8)	19 (4.2)	19 (4.2)	18 (4.0)

AZE, Azelastine; PLA, placebo.

**TABLE E4.** iTNSSs, individual nasal symptom scores, and total ocular symptom scores (baseline and change from baseline) for 3 randomized trials and the meta-analysis results (ITT population)

Treatment	Study							
	MP4002		MP4004		MP4006		Meta-analysis	
	Baseline	CFB	Baseline	CFB	Baseline	CFB	Baseline	CFB
<b>iTNSS (morning plus evening)</b>								
MP29-02	17.1 (3.7)	−5.2 (5.3)*	17.1 (4.1)	−5.4 (5.3)*	17.9 (3.5)	−5.0 (5.3)*	17.6 (3.7)	−5.2 (5.4)*
FP	16.8 (4.2)	−4.6 (4.7)*	17.1 (3.8)	−4.6 (5.2)*, †	17.9 (3.4)	−4.8 (4.9)*	17.4 (3.7)	−4.8 (5.0)*, †
AZE	16.8 (4.2)	−3.7 (4.7)*, ‡	17.2 (4.1)	−3.9 (4.6)*, ‡	18.0 (3.7)	−4.2 (4.9)*, †	17.5 (4.0)	−4.1 (4.8)*, ‡
PLA	17.2 (4.2)	−2.4 (4.1)	16.8 (3.9)	−2.3 (4.2)	17.9 (3.5)	−2.8 (4.4)	17.5 (3.8)	−2.6 (4.3)
<b>Reflective nasal congestion score (morning plus evening)</b>								
MP29-02	5.1 (0.8)	−1.3 (1.4)*	5.1 (0.9)	−1.3 (1.3)*	5.3 (0.7)	−1.2 (1.4)*	5.2 (0.8)	−1.3 (1.3)*
FP	5.0 (0.9)	−1.2 (1.3)*	5.0 (0.8)	−1.1 (1.5)*, †	5.3 (0.7)	−1.1 (1.2)*	5.2 (0.8)	−1.1 (1.3)*, †
AZE	5.1 (0.8)	−0.9 (1.3)*, ‡	5.1 (0.8)	−1.0 (1.3)*	5.3 (0.7)	−1.0 (1.2)*, †	5.2 (0.8)	−0.9 (1.3)*, ‡
PLA	5.1 (0.8)	−0.6 (1.1)	5.2 (0.7)	−0.7 (1.1)	5.3 (0.7)	−0.7 (1.2)	5.2 (0.7)	−0.7 (1.1)
<b>Reflective nasal itch score (morning plus evening)</b>								
MP29-02	4.6 (1.0)	−1.3 (1.5)*	4.5 (1.1)	−1.3 (1.5)*	4.9 (0.9)	−1.3 (1.5)*	4.8 (1.0)	−1.3 (1.5)*
FP	4.5 (1.1)	−1.1 (1.3)*	4.8 (0.9)	−1.2 (1.4)*	4.9 (0.9)	−1.2 (1.3)*	4.8 (1.0)	−1.2 (1.3)*, †
AZE	4.5 (1.2)	−0.9 (1.3)*, ‡	4.7 (1.1)	−1.1 (1.3)*	4.9 (0.9)	−1.1 (1.4)*	4.8 (1.0)	−1.0 (1.4)*, ‡
PLA	4.7 (1.1)	−0.6 (1.1)	4.6 (1.1)	−0.6 (1.2)	5.0 (0.9)	−0.8 (1.3)	4.8 (1.0)	−0.7 (1.2)
<b>Reflective rhinorrhea score (morning and evening)</b>								
MP29-02	4.5 (1.0)	−1.5 (1.5)*	4.5 (1.1)	−1.4 (1.5)*	4.7 (1.0)	−1.4 (1.5)*	4.6 (1.0)	−1.4 (1.5)*
FP	4.6 (1.0)	−1.3 (1.4)*, †	4.6 (1.0)	−1.3 (1.5)*	4.8 (0.9)	−1.3 (1.4)*	4.7 (1.0)	−1.3 (1.4)*, †
AZE	4.5 (1.2)	−1.1 (1.4)*, ‡	4.5 (1.1)	−1.0 (1.3)*	4.8 (0.9)	−1.2 (1.4)*, †	4.7 (1.0)	−1.1 (1.4)*, ‡
PLA	4.7 (1.0)	−0.7 (1.2)	4.4 (1.0)	−0.7 (1.2)	4.8 (0.9)	−0.8 (1.3)	4.7 (1.0)	−0.7 (1.2)
<b>Reflective sneezing score (morning plus evening)</b>								
MP29-02	4.0 (1.3)	−1.6 (1.6)*	4.1 (1.3)	−1.7 (1.6)*	4.5 (1.2)	−1.7 (1.6)*	4.3 (1.2)	−1.7 (1.6)*
FP	4.1 (1.2)	−1.5 (1.4)*	4.2 (1.3)	−1.4 (1.5)*, †	4.5 (1.2)	−1.5 (1.5)*, †	4.3 (1.2)	−1.5 (1.5)*, ‡
AZE	4.0 (1.3)	−1.3 (1.3)*, ‡	4.2 (1.3)	−1.3 (1.5)*	4.5 (1.1)	−1.4 (1.5)*, †	4.3 (1.2)	−1.3 (1.4)*, ‡
PLA	4.2 (1.2)	−0.8 (1.3)	4.0 (1.3)	−0.7 (1.3)	4.5 (1.1)	−0.9 (1.4)	4.3 (1.2)	−0.9 (1.3)
<b>rTOSS (morning plus evening)</b>								
MP29-02	11.9 (3.9)	−3.2 (4.0)*	11.7 (4.2)	−3.6 (3.9)*	12.3 (4.0)	−3.0 (4.0)*	12.1 (4.0)	−3.2 (4.0)*
FP	11.4 (4.4)	−2.6 (3.5)*	12.0 (3.8)	−2.7 (3.6)*, †	12.3 (3.6)	−2.8 (3.5)*	12.0 (3.9)	−2.8 (3.6)*, †
AZE	11.5 (4.5)	−2.8 (3.8)*	11.8 (3.9)	−3.0 (3.3)*	12.4 (4.0)	−3.0 (3.8)*	12.0 (4.1)	−2.9 (3.8)*
PLA	12.1 (4.3)	−1.9 (3.3)	11.6 (4.1)	−2.0 (3.1)	12.2 (3.7)	−2.0 (3.5)	12.0 (4.0)	−1.8 (3.4)

Data are expressed as means (SDs).

Study MP4002: MP29-02 (n = 207); FP (n = 207); AZE (n = 208); PLA (n = 209); ANCOVA *P* values: \**P* ≤ .034 versus PLA; †*P* ≤ .043 versus MP29-02; ‡*P* ≤ .015 versus MP29-02.Study MP4004: MP29-02 (n = 193); FP (n = 189); AZE (n = 194); PLA (n = 200); ANCOVA *P* values: \**P* ≤ .050 versus PLA; †*P* ≤ .050 versus MP29-02; ‡*P* ≤ .029 versus MP29-02.Study MP4006: MP29-02 (n = 448); FP (n = 450); AZE (n = 445); PLA (n = 448); ANCOVA *P* values: \**P* ≤ .002 versus PLA; †*P* ≤ .026 versus MP29-02.Meta-analysis: MP29-02 (n = 848); FP (n = 846); AZE (n = 847); PLA (n = 857); ANCOVA *P* values: \**P* < .001 versus PLA; †*P* ≤ .022 versus MP29-02; ‡*P* < .001 versus MP29-02.

AZE, Azelastine (137 µg per nostril twice daily); CFB, change from baseline; FP, fluticasone propionate (50 µg per nostril twice daily); ITT, intent-to-treat; MP29-02, azelastine/FP (137/50 µg/nostril twice daily); PLA, placebo.

**TABLE E5.** Treatment difference of change from baseline in total instantaneous nasal symptom scores and individual nasal symptom scores for 3 randomized trials and the meta-analysis results (ITT population)

Comparison	Study			
	MP4002	MP4004	MP4006	Meta-analysis
<b>iTNSS (morning plus evening)</b>				
MP29-02, PLA	-2.6 <i>P</i> < .001 (-3.39 to -1.79)	-2.8 <i>P</i> < .001 (-3.61 to -1.94)	-1.9 <i>P</i> < .001 (-2.49 to -1.36)	-2.3 <i>P</i> < .001 (-2.66 to -1.85)
MP29-02, FP	-0.7 <i>P</i> = .100 (-1.55 to 0.14)	-0.9 <i>P</i> = .049 (-1.87 to 0.00)	-0.3 <i>P</i> = .348 (-0.87 to 0.31)	-0.5 <i>P</i> = .022 (-0.93 to -0.07)
MP29-02, AZE	-1.3 <i>P</i> = .003 (-2.09 to -0.43)	-1.0 <i>P</i> = .029 (-1.90 to -0.10)	-0.7 <i>P</i> = .026 (-1.25 to -0.08)	-0.9 <i>P</i> < .001 (-1.30 to -0.46)
<b>Reflective nasal congestion (morning plus evening)</b>				
MP29-02, PLA	-0.6 <i>P</i> < .001 (-0.76 to -0.34)	-0.5 <i>P</i> < .001 (-0.73 to -0.29)	-0.5 <i>P</i> < .001 (-0.60 to -0.30)	-0.5 <i>P</i> < .001 (-0.60 to -0.38)
MP29-02, FP	-0.2 <i>P</i> = .163 (-0.38 to 0.06)	-0.3 <i>P</i> = .022 (-0.52 to -0.04)	-0.1 <i>P</i> = .106 (-0.28 to 0.03)	-0.2 <i>P</i> = .005 (-0.27 to -0.05)
MP29-02, AZE	-0.3 <i>P</i> = .003 (-0.56 to -0.12)	-0.4 <i>P</i> = .002 (-0.60 to -0.14)	-0.2 <i>P</i> = .004 (-0.38 to -0.07)	-0.3 <i>P</i> < .001 (-0.39 to -0.17)
<b>Reflective nasal itch score (morning plus evening)</b>				
MP29-02, PLA	-0.6 <i>P</i> < .001 (0.85 to -0.40)	-0.6 <i>P</i> < .001 (-0.86 to -0.38)	-0.4 <i>P</i> < .001 (-0.53 to -0.27)	-0.5 <i>P</i> < .001 (-0.63 to -0.40)
MP29-02, FP	-0.2 <i>P</i> = .058 (-0.47 to 0.01)	-0.2 <i>P</i> = .070 (-0.50 to 0.02)	-0.1 <i>P</i> = .142 (-0.27 to 0.04)	-0.2 <i>P</i> = .005 (-0.28 to -0.05)
MP29-02, AZE	-0.3 <i>P</i> = .015 (-0.54 to -0.06)	-0.2 <i>P</i> = .093 (-0.47 to 0.04)	-0.29 <i>P</i> = .065 (-0.32 to 0.01)	-0.2 <i>P</i> < .001 (-0.32 to -0.08)
<b>Reflective rhinorrhea score (morning plus evening)</b>				
MP29-02, PLA	-0.76 <i>P</i> < .001 (-0.99 to -0.53)	-0.6 <i>P</i> < .001 (-0.84 to -0.35)	-0.6 <i>P</i> < .001 (-0.75 to -0.42)	-0.6 <i>P</i> < .001 (-0.75 to -0.52)
MP29-02, FP	-0.25 <i>P</i> = .043 (-0.50 to -0.01)	-0.2 <i>P</i> = .274 (-0.41 to 0.12)	-0.1 <i>P</i> = .170 (-0.29 to 0.05)	-0.2 <i>P</i> = .013 (-0.28 to -0.03)
MP29-02, AZE	-0.41 <i>P</i> < .001 (-0.66 to -0.17)	-0.3 <i>P</i> = .058 (-0.51 to 0.01)	-0.2 <i>P</i> = .006 (-0.41 to -0.07)	-0.3 <i>P</i> < .001 (-0.40 to -0.16)
<b>Reflective sneezing score (morning plus evening)</b>				
MP29-02, PLA	-0.78 <i>P</i> < .001 (-1.02 to -0.55)	-0.9 <i>P</i> < .001 (-1.10 to -0.59)	-0.8 <i>P</i> < .001 (-0.92 to -0.58)	-0.8 <i>P</i> < .001 (-0.90 to -0.70)
MP29-02, FP	-0.19 <i>P</i> = .144 (-0.44 to 0.06)	-0.3 <i>P</i> = .046 (-0.56 to -0.01)	-0.2 <i>P</i> = .014 (-0.40 to -0.04)	-0.2 <i>P</i> < .001 (-0.35 to -0.09)
MP29-02, AZE	-0.33 <i>P</i> = .010 (-0.59 to -0.08)	-0.3 <i>P</i> = .066 (-0.53 to 0.02)	-0.2 <i>P</i> = .012 (-0.40 to -0.05)	-0.3 <i>P</i> < .001 (-0.38 to -0.13)
<b>rTOSS (morning plus evening)</b>				
MP29-02, PLA	-1.17 <i>P</i> < .001 (-1.77 to -0.57)	-1.54 <i>P</i> < .001 (-2.16 to -0.92)	-1.07 <i>P</i> < .001 (-1.50 to -0.64)	-1.20 <i>P</i> < .001 (-1.51 to -0.90)
MP29-02, FP	-0.52 <i>P</i> = .097 (-1.14 to 0.10)	-0.88 <i>P</i> = .009 (-1.54 to -0.23)	-0.26 <i>P</i> = .247 (-0.69 to 0.18)	-0.47 <i>P</i> = .003 (-0.78 to -0.16)
MP29-02, AZE	-0.25 <i>P</i> = .457 (-0.90 to 0.41)	-0.6 <i>P</i> = .069 (-1.25 to 0.05)	-0.03 <i>P</i> = .912 (-0.47 to 0.42)	-0.21 <i>P</i> = .196 (-0.53 to 0.11)

Results are given as least squares mean treatment difference with associated *P* values and 95% CIs.

AZE, Azelastine; ITT, intent-to-treat; PLA, placebo.

**TABLE E6.** Overview of adverse events (safety population)

<b>Study MP4002</b>				
	<b>MP29-02 (n = 207)</b>	<b>FP (n = 207)</b>	<b>AZE (n = 208)</b>	<b>PLA (n = 210)</b>
No. (%) of subjects with any AE				
All treatment-emergent AEs	30 (14.5)	32 (15.5)	26 (12.5)	24 (11.4)
All treatment-related AEs	17 (8.2)	14 (6.8)	16 (7.7)	8 (3.8)
No. (%) of subjects with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Study MP4004</b>				
	<b>MP29-02 (n = 195)</b>	<b>FP (n = 189)</b>	<b>AZE (n = 194)</b>	<b>PLA (n = 200)</b>
No. (%) of subjects with any AE				
All treatment-emergent AEs	31 (15.9)	24 (12.7)	35 (18.0)	20 (10.0)
All treatment-related AEs	20 (10.3)	10 (5.3)	29 (14.9)	9 (4.5)
No. (%) subjects with Serious AEs	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Study MP4006</b>				
	<b>MP29-02 (n = 451)</b>	<b>FP (n = 450)</b>	<b>AZE (n = 449)</b>	<b>PLA (n = 451)</b>
No. (%) of subjects with any AE				
All treatment-emergent AEs	75 (16.6)	55 (12.2)	63 (14.0)	55 (12.2)
All treatment-related AEs	50 (11.1)	28 (6.2)	45 (10.0)	18 (4.0)
No. (%) of subjects with serious AEs	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

AE, Adverse event; AZE, azelastine; PLA, placebo.



**TABLE E7.** Overview of treatment-related, treatment-emergent adverse events (safety population)

Study MP4002				
	MP29-02 (n = 207)	FP (n = 207)	AZE (n = 208)	PLA (n = 210)
Any adverse event	17 (8.2)	14 (6.8)	16 (7.7)	8 (3.8)
Dysgeusia	5 (2.4)	2 (1.0)	7 (3.4)	1 (0.5)
Epistaxis	2 (1.0)	5 (2.4)	4 (1.9)	2 (1.0)
Headache	1 (0.5)	5 (2.4)	1 (0.5)	3 (1.4)
Nasal discomfort	2 (1.0)	2 (1.0)	4 (1.9)	0 (0.0)
Nausea	1 (0.5)	2 (1.0)	1 (0.5)	0 (0.0)
Sneezing	1 (0.5)	0 (0.0)	2 (1.0)	1 (0.5)
Study MP4004				
	MP29-02 (n = 195)	FP (n = 189)	AZE (n = 194)	PLA (n = 200)
Any adverse event	20 (10.3)	10 (5.3)	24 (14.9)	9 (4.5)
Dysgeusia	4 (2.1)	1 (0.5)	14 (7.2)	1 (0.5)
Epistaxis	3 (1.5)	3 (1.6)	3 (1.6)	5 (2.5)
Headache	5 (2.6)	4 (2.1)	4 (2.1)	1 (0.5)
Cough	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)
Nasal discomfort	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)
Nausea	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)
Oropharyngeal pain	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)
Mucosal erosion	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study MP4006				
	MP29-02 (n = 451)	FP (n = 450)	AZE (n = 449)	PLA (n = 451)
Any adverse event	50 (11.1)	28 (6.2)	45 (10.0)	18 (4.0)
Dysgeusia	21 (4.7)	1 (0.2)	23 (5.1)	0 (0.0)
Epistaxis	8 (1.8)	5 (1.1)	5 (1.1)	8 (1.8)
Headache	6 (1.3)	6 (1.3)	9 (2.0)	2 (0.4)
Somnolence	5 (1.1)	0 (0.0)	2 (0.4)	1 (0.2)
Mucosal erosion	2 (0.4)	5 (1.1)	0 (0.0)	1 (0.2)

Values are presented as numbers (percentages).

Occurring in 1% or more of subjects in any treatment group. A subject with multiple AEs was counted only once.

AZE, Azelastine; PLA, placebo.

**TABLE E8.** Time advantage of MP29-02: treatment day at which specific responder rates were achieved

Responder rate	Fifty percent reduction in rTNSSs achieved at treatment day			
	MP29-02	FP	AZE	PLA
15%	2	3	3	6
20%	3	4	4	9
25%	4	5	6	14
30%	6	7	9	—
35%	7	9	12	—
40%	9	12	—	—
45%	11	14	—	—

AZE, Azelastine (137 µg per nostril twice daily); FP, fluticasone propionate (50 µg per nostril twice daily); MP29-02, Azelastine/FP (137/50 µg per nostril twice daily); PLA, placebo.