

Clinically Relevant Effect of a New Intranasal Therapy (MP29-02) in Allergic Rhinitis Assessed by Responder Analysis

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Key Words

Allergic rhinitis · Azelastine · Fluticasone · MP29-02 · Responder analysis · Severe chronic upper airway disease

Abstract

Background: It is unclear what constitutes a clinically meaningful response for allergic rhinitis (AR) outcomes. The objectives of these post hoc analyses were (1) to define a clinically meaningful response using novel efficacy analyses (including a responder analysis), and (2) to compare the efficacy of MP29-02 [a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP)] with commercially available FP, AZE and placebo in seasonal AR (SAR) patients, using these novel analyses. **Methods:** 610 moderate-to-severe SAR patients (≥ 12 years old) were randomized into a double-blind, placebo-controlled, 14-day, parallel-group trial. Change from baseline in the reflective total nasal symptom score (rTNSS) over 14 days was the primary outcome. Post hoc endpoints included the sum of nasal and oc-

ular symptoms (rTSS), efficacy by disease severity and by predominant nasal symptom, and a set of responder analyses. **Results:** MP29-02 most effectively reduced rTSS (relative greater improvement: 52% to FP; 56% to AZE) and both nasal and ocular symptoms irrespective of severity. More MP29-02 patients achieved a ≥ 30 , ≥ 50 , ≥ 60 , ≥ 75 and $\geq 90\%$ rTNSS reduction, which occurred days faster than with either active comparator; MP29-02 alone was superior to placebo at the $\geq 60\%$ (or higher) threshold. One in 2 MP29-02 patients achieved a $\geq 50\%$ rTNSS reduction and 1 in 6 achieved complete/near-to-complete response. Only MP29-02 was consistently superior to placebo for all patients, whatever their predominant symptom. **Conclusions:** MP29-02 provided faster and more complete symptom control than first-line therapies. It was consistently superior irrespective of severity, response criteria or patient-type, and may be considered the drug of choice for moderate-to-severe AR. These measures define a new standard for assessing relevance in AR.

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Introduction

The treatment of allergic rhinitis (AR) is well defined [1]. Most patients seen by physicians present with moderate/severe disease [2, 3]. Treatment-resistant phenotypes (e.g. severe chronic upper airways disease) have been described [4, 5] in around 20% of treated patients. AR impacts on quality of life [6–8] and is costly [9]. Any treatment providing substantial or near-to-complete symptom relief will have a considerable socioeconomic impact.

Intranasal corticosteroids (INS) are the most effective monotherapy for AR [1, 10, 11], but many patients are dissatisfied with treatment [12] and experience breakthrough symptoms [2, 3], and consequently most patients are seeking a new medication [13]. Nasal obstruction and ocular symptoms represent the most bothersome symptoms [14, 15] and are often difficult to control. Most physicians treat patients using multiple therapies [2, 3, 16, 17] to achieve quicker and more profound symptom relief [18], despite limited evidence to support this practice [10, 11].

Statistical significance over placebo is a proof of clinical efficacy. However, clinical relevance is more difficult to judge, particularly when comparing active therapies, and cannot be expressed by a single endpoint or analysis. Rather, clinical relevance is influenced by patient-related factors such as disease severity, the predominant symptom and conjunctivitis, and may be better expressed in terms of (1) the level of response (e.g. substantial or complete); (2) the time to achieve it; (3) an assessment of efficacy in treating the entire AR symptom complex, and (4) efficacy assessment irrespective of disease severity or the predominant symptom.

Background and Objectives

Scientific Background and Explanation of Rationale

Clinical trials should demonstrate a statistically significant improvement in the primary efficacy endpoint, but clinical relevance is not readily apparent from this analysis. One approach is to conduct a responder analysis [19] described in regulatory guidelines [20, 21] to define a level of response not achievable with available first-line therapy.

MP29-02, a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP), has previously been shown to be more effective than INS [22, 23]. We have taken the first of these studies, which compared MP29-02 to commercially available active comparators (i.e. Astelin® and generic Flonase®) [22] to assess the data in a more clinically relevant way using sev-

eral new analyses. Many of these analyses had not previously been developed at the time of study protocol submission and so were introduced post hoc.

Specific Objectives

This is a post hoc analysis of a phase III, multicenter, randomized, double-blind, parallel group trial [MP4001 (NCT00660517)] [22]. The aim was to firstly introduce new and more clinically meaningful efficacy analyses to gauge the efficacy of AR therapies, and secondly to assess the efficacy of MP29-02 and currently available first-line AR therapies using these new analyses. Specifically, this article investigates whether MP29-02 is more effective than commercially available active comparators (intranasal AZE, Astelin; Meda Pharmaceuticals, Somerset, N.J., USA), generic FP nasal spray (Roxane Laboratories, Columbus, Ohio, USA) and placebo in controlling overall nasal and ocular symptoms, irrespective of baseline severity and in those presenting with a predominant symptom. A responder sensitivity analysis defined a level of response not achievable with available first-line therapy. These post hoc parameters were defined a priori by an independent panel of experts (including J.B., W.C., C.B., D.P. and others), without having access to the data. The methods of the study have been previously published [22] and are presented in the online supplementary material (for all online supplementary material, see www.karger.com/doi/10.1159/000351404).

Material and Methods

Participants

Subjects (≥12 years old) with moderate-to-severe seasonal AR (SAR), with a minimum 2-year history, current rhinitis symptomatology, a positive skin prick test to mountain cedar pollen and who met all the study inclusion/exclusion criteria were randomized.

Planned Interventions and Timing

The study comprised a 7-day, single-blind, placebo lead-in period, and a 14-day treatment period with 3 study visits on days 1, 7 and 14. On visit 2 (day 1), eligible patients were randomized (1:1:1:1) to 14 days of treatment with (1) MP29-02 nasal spray [a novel intranasal formulation of AZE (137 µg) and FP (50 µg)]; (2) commercially available AZE nasal spray (137 µg); (3) commercially available FP (50 µg) nasal spray, or (4) vehicle placebo nasal spray. All sprays were given as 1 spray/nostril bid. Patients recorded symptom scores in a diary and concordance with treatment was assessed.

Efficacy Variables

The primary efficacy variable was change from baseline in morning and evening reflective total nasal symptom score

(rTNSS). Secondary endpoints included change from baseline in reflective total ocular symptom score (rTOSS), individual nasal and ocular symptom scores and the overall score from the 28-item Rhinitis Quality of Life Questionnaire (RQLQ; online suppl. text) [24].

Sample Size, Randomization and Blinding

Details on sample size, randomization and blinding are presented in the online supplementary text.

Statistical Analyses

Both rTNSS and rTOSS were assessed by patient severity using a baseline-adjusted analysis of covariance (ANCOVA) model (online suppl. text). Patients were categorized into two severity groups according to median baseline rTNSS (i.e. ≤ 18.9 or >18.9) and overall RQLQ score (i.e. ≤ 3.9 or >3.9). Those with a median baseline rTNSS ≤ 18.9 or an overall RQLQ score ≤ 3.9 were defined as less severe. Those patients with a median baseline rTNSS >18.9 or an overall RQLQ score >3.9 were defined as more severe. This analysis is pertinent since it is important to show efficacy in patients irrespective of symptom severity. A symptomatic subgroup of patients was defined with rTOSS baseline ≥ 8 to define patients with at least moderate ocular symptoms, since ocular symptoms are often not quantified even though they affect most subjects with SAR [25]. A reflective total of 5 symptom scores (rT5SS; rTNSS plus ocular itching) and a reflective total of 7 symptom scores (rT7SS; rTNSS plus rTOSS) were also determined, and change from baseline was assessed by the same ANCOVA model, as patients frequently present to clinic with both nasal and ocular symptoms.

Time to response in nasal symptoms was analyzed by Kaplan-Meier estimates and log-rank tests. A change from baseline in morning and evening rTNSS of at least (1) 30, 50 [20], 60, 75 or 90% and (2) ≤ 1 point remaining for each symptom score (i.e. complete/near-to-complete symptom resolution for both rTNSS and rT7SS) were used to define response. A $\geq 50\%$ rTNSS response was considered a substantial response, halving the patient's nasal symptom burden. Accordingly, an rTNSS $\geq 75\%$ response was considered an extensive response representing a symptom severity shift in our patients from moderate/severe to mild or less. The ≤ 1 point score remaining for each symptom score of the rTNSS or rT7SS ensured complete/near-to-complete symptom relief from all nasal symptoms (i.e. rTNSS) or all nasal plus ocular symptoms (i.e. rT7SS). This criterion is extremely strict as it required that each nasal or each nasal plus ocular symptom was categorized as of less than mild severity, meaning that patients would effectively feel symptom free. These responder sensitivity analyses were conceived in response to the EMA guideline (CHMP/EWP/2455/02) which questions the clinical relevance of a simple change from baseline in rTNSS and suggests a clinically meaningful response in symptom score [20].

Patients were characterized by predominant symptoms based on the maximum individual symptom scores at baseline (i.e. congestion, itching, rhinorrhea or sneezing). rTNSS and individual symptom reduction were assessed in patients categorized by their predominant symptom to show control of the entire disease symptom complex in these patients and to show relief of a patient's particular predominant symptom. An analysis of efficacy according to symptom predominance is clinically relevant since patients frequently present with a specific and most bothersome symptom.

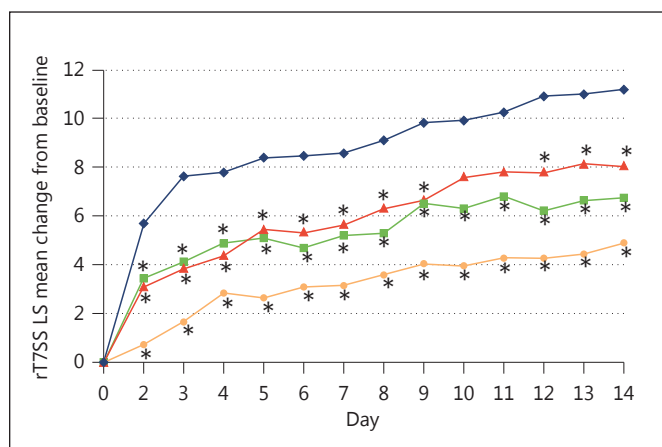


Fig. 1. Effect of MP29-02 (blue), FP (red), AZE (green) and placebo (yellow) on least squares (LS) mean change from baseline in rT7SS by treatment day (numbers and baseline data are provided in online suppl. table 6). * $p \leq 0.0336$ vs. MP29-02.

Results

Patients

The study was conducted during the 2007–2008 Texas mountain cedar allergy season at 8 investigational sites. Six hundred and ten patients were randomized, and 607 were included in the intend-to-treat population; 94.6% of patients completed the study. Completion rates were similar across all treatment groups (online suppl. table 1). Baseline characteristics of the four treatment groups were similar (online suppl. table 2) and confirmed that the vast majority of these patients had moderate-to-severe AR.

Outcomes

Original Analysis

MP29-02-treated patients experienced a significantly greater reduction in rTNSS (online suppl. fig. 1, 2), rTOSS and individual symptom scores compared to FP or AZE (online suppl. tables 3, 4). All active treatments were well tolerated (online suppl. table 5).

Post hoc Analyses

Rhinoconjunctivitis Symptoms (rT5SS and rT7SS)

MP29-02 patients had a significantly greater reduction in rT5SS and rT7SS than those treated with FP or AZE

Table 1. rTNSS response sensitivity analysis showing the proportion of patients achieving each response (at day 14) and the advantage (in days) of MP29-02 over active comparators and placebo

Response criteria ¹	MP29-02	AZE	FP	Placebo
≥30% reduction in rTNSS				
Patients at day 14, %	71.2	65.5	61.1	47.2
Advantage of MP29-02, days		≤5 (p = 0.1025)*	≤7 (p = 0.0225)*	≤10 (p<0.0001)
≥50 reduction in rTNSS				
Patients at day 14, %	49.1	37.4	38.2	28.3
Advantage of MP29-02, days		≤6 (p = 0.0223)	≤6 (p = 0.0284)*	≤10 (p<0.0001)
≥60% reduction in rTNSS				
Patients at day 14, %	35.6	26.0	25.1	20.9
Advantage of MP29-02, days		≤8 (p = 0.0404)	≤7 (p = 0.0496)	≤10 (p = 0.0029)
≥75% reduction in rTNSS				
Patients at day 14, %	25.5	16.4	17.7	12.9
Advantage of MP29-02, days		≤8 (p = 0.0242)	≤7 (p = 0.0848)	≤9 (p = 0.0032)
≥90% reduction in rTNSS				
Patients at day 14, %	14.5	3.5	5.4	6.0
Advantage of MP29-02, days		≤8 (p = 0.001)	≤6 (p = 0.012)	≤9 (p = 0.0126)

Bold data represent significance vs. placebo. * p < 0.05 vs. placebo derived by log-rank tests. Significance values provided are vs. MP29-02. Data in italics denote significance vs. placebo where lost.

¹ Derived by Kaplan-Meier curves estimating time to first response and considering censored data; days advantage refer to the maximal horizontal distances in the Kaplan-Meier curves.

monotherapies (online suppl. table 6). For rT7SS there was a relative greater improvement of 52 and 56% compared to FP (p = 0.0013) and AZE (p = 0.0004), respectively. The benefit was observed during the first day of treatment and was sustained over the entire course of treatment (fig. 1).

Reflective Total Nasal Symptom Score Change from Baseline Considering Severity

MP29-02 was significantly superior to both FP and AZE in alleviating patients' overall nasal symptoms regardless of disease severity (online suppl. table 6). For patients with less severe disease (median baseline rTNSS ≤18.9) the relative difference with MP29-02 was 42% compared to FP (p = 0.0188) and 64% compared to AZE (p = 0.0002), which increased to 49% (p = 0.0436) and 70% (p = 0.0035), respectively, for those with more severe disease (median baseline rTNSS >18.9; online suppl. fig. 3).

Reflective Total Ocular Score Change from Baseline Considering Severity

In patients with moderate-to-severe ocular symptoms at baseline (i.e. those with a median baseline rTOSS ≥8), MP29-02 was significantly superior to both FP and AZE,

with a relative difference of 63% versus FP and 42% versus AZE (p = 0.0012 and p = 0.0456; online suppl. table 6; online suppl. fig. 3).

rTNSS Responder Analyses

For all response cutoffs (i.e. ≥30, ≥50, ≥60, ≥75 and ≥90% response), more MP29-02 patients achieved these rTNSS reductions and did so days faster than both active comparators and placebo patients (table 1; fig. 2). The fraction of responders decreased when stricter response criteria were chosen, but the respective differences between MP29-02 and active comparators became more apparent (table 1). For the ≥60, ≥75 and ≥90% rTNSS reduction only MP29-02 could be statistically differentiated from placebo (table 1; fig. 2).

For the criterion of ≤1 point remaining in each nasal symptom score, 17.8% (or 1 in 6) of MP29-02 patients had a complete/near-to-complete nasal symptom resolution versus 9.2% of FP patients, 8.3% of AZE patients and 7.8% of placebo patients (fig. 2). MP29-02 patients achieved this response up to 8 days faster than either FP (p = 0.0262) or placebo (p = 0.0094) and up to 7 days faster than AZE (p = 0.0152). For the strictest response criterion of ≤1 point remaining for all symptoms (rT7SS), 14.2% (or 1 in 7) of MP29-02 patients achieved complete/

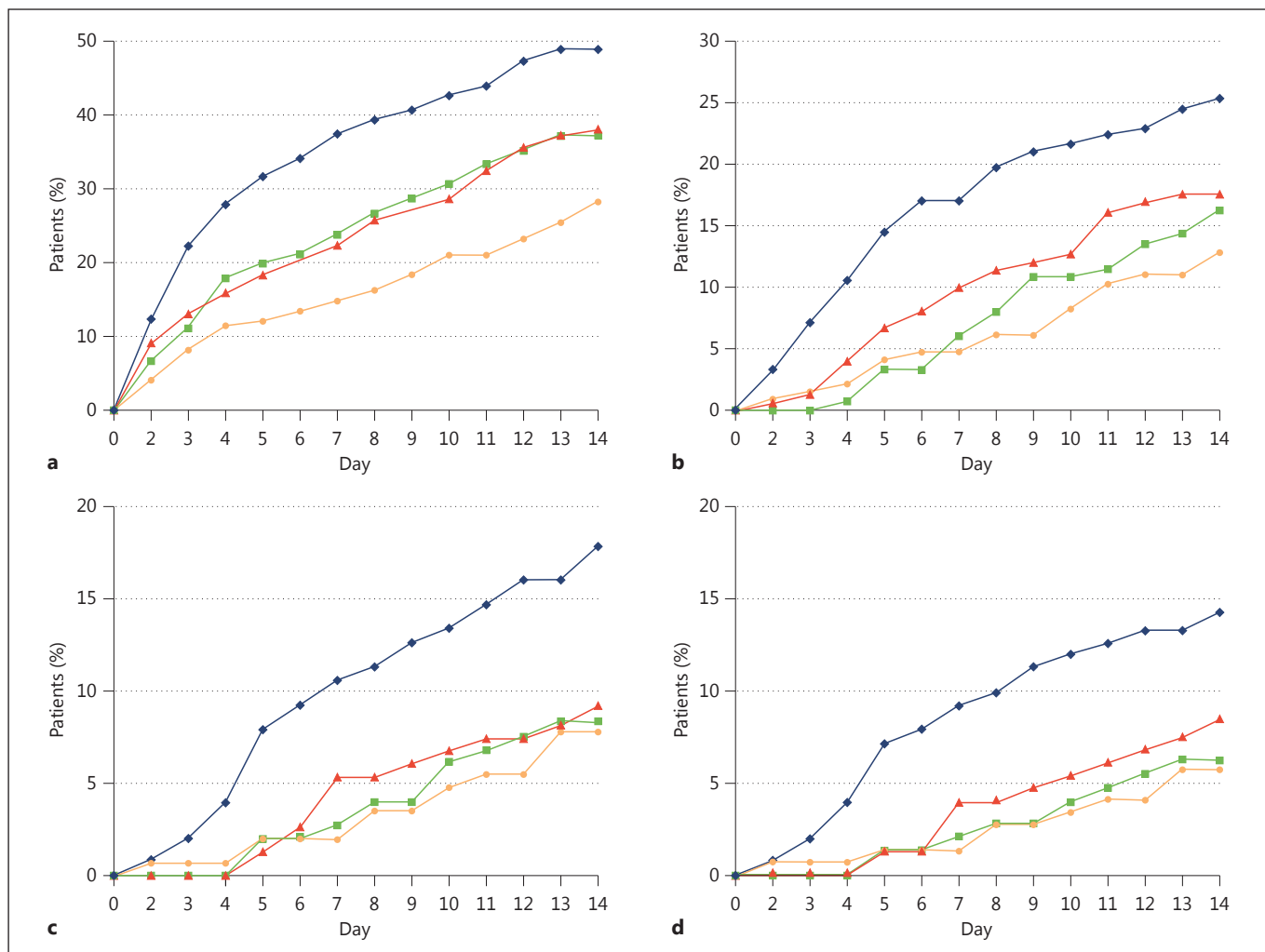


Fig. 2. Time to response curves following treatment for 14 days with MP29-02 (blue), FP (red), AZE (green) and placebo (yellow). **a** 50% response. **b** 75% response. **c** rTNSS: ≤ 1 point remaining for each symptom. **d** rT7SS: ≤ 1 point remaining for each symptom.

near-to-complete elimination from all their nasal and ocular symptoms compared to 8.5% of FP patients, 6.2% of AZE patients and 5.7% of placebo patients, achieving this response up to 8 days faster than patients in the FP ($p = 0.0929$), AZE ($p = 0.0204$) or placebo groups ($p = 0.0123$; fig. 2).

Predominant Symptom

Only MP29-02 was consistently statistically superior to placebo in reducing rTNSS for all patient types, whatever their leading symptom (table 2). FP was no better than placebo in reducing rTNSS for patients whose predominant symptom was nasal itching (table 2). Compared to FP, MP29-02 provided significantly better rTNSS

reduction for those patients mainly suffering from congestion (online suppl. fig. 4), nasal itching or sneezing. Compared to AZE, MP29-02 provided superior rTNSS reduction in those patients for whom congestion (online suppl. fig. 4) and rhinorrhea were the primary complaint.

Only MP29-02 consistently and significantly reduced the individual nasal symptom score compared to placebo corresponding to patients' predominant symptom (with the exception of nasal itching; $p = 0.0657$; table 3). By comparison, FP was no more effective than placebo in alleviating nasal congestion or nasal itching in patients presenting with these symptoms predominantly. MP29-02 was significantly superior to FP in relieving nasal congestion (online suppl. fig. 4), itching and sneezing in patients

Table 2. Reduction in overall nasal symptom score (rTNSS) by patient type

Treatment	Baseline rTNSS ¹	LS mean CFB	Relative difference ²	Absolute difference		95% CI	p value
rTNSS change from baseline in those patients whose predominant symptom is nasal congestion							
MP29-02 (n = 98)	19.56 (2.89)	-5.64	-	-	-	-	-
FP (n = 84)	18.57 (3.95)	-3.93	57%	MP-FP	-1.71	-3.00, -0.43	0.0093
AZE (n = 93)	18.20 (3.87)	-3.28	79%	MP-AZE	-2.36	-3.51, -1.21	<0.0001
PLA (n = 93)	18.85 (3.60)	-2.63	-	MP-PLA	-3.01	-4.14, -1.88	<0.0001
				FP-PLA	-1.30	-2.51, -0.09	0.0356
				AZE-PLA	-0.65	-1.69, 0.39	0.2185
rTNSS change from baseline in those patients whose predominant symptom is nasal itching							
MP29-02 (n = 40)	20.09 (3.36)	-5.48	-	-	-	-	-
FP (n = 45)	20.56 (3.06)	-3.01	100%	MP-FP	-2.47	-4.24, -0.69	0.0072
AZE (n = 45)	18.83 (3.77)	-3.80	68%	MP-AZE	-1.68	-3.55, 0.19	0.0781
PLA (n = 46)	20.63 (3.26)	-3.02	-	MP-PLA	-2.46	-4.27, -0.64	0.0088
				FP-PLA	0.01	-1.30, 1.32	0.9866
				AZE-PLA	-0.78	-2.29, 0.73	0.3096
rTNSS change from baseline in those patients whose predominant symptom is rhinorrhea							
MP29-02 (n = 41)	20.09 (3.55)	-5.46	-	-	-	-	-
FP (n = 45)	19.50 (3.43)	-4.89	17%	MP-FP	-0.57	-2.31, 1.16	0.5131
AZE (n = 38)	19.89 (3.60)	-3.65	55%	MP-AZE	-1.81	-3.44, -0.19	0.0294
PLA (n = 40)	19.91 (3.72)	-2.19	-	MP-PLA	-3.27	-4.89, -1.65	0.0001
				FP-PLA	-2.70	-4.30, -1.11	0.0011
				AZE-PLA	-1.46	-2.89, -0.03	0.0456
rTNSS change from baseline in those patients whose predominant symptom is sneezing							
MP29-02 (n = 25)	19.36 (4.19)	-5.21	-	-	-	-	-
FP (n = 27)	19.59 (4.06)	-2.96	51%	MP-FP	-2.25	-4.05, -0.44	0.0154
AZE (n = 22)	20.38 (3.52)	-4.46	17%	MP-AZE	-0.75	-2.66, 1.17	0.4401
PLA (n = 24)	20.35 (3.78)	-0.84	-	MP-PLA	-4.37	-6.12, -2.62	<0.0001
				FP-PLA	-2.12	-3.85, -0.40	0.0167
				AZE-PLA	-3.62	-5.34, -1.91	<0.0001

PLA = Placebo; LS = least squares; CFB = change from baseline; CI = confidence interval.

¹ Mean (SD); maximum baseline rTNSS = 24.

² $[1 - (\text{FP or AZE} - \text{PLA})/(\text{MP29-02} - \text{PLA})] \times 100$.

for whom these were the predominant symptoms. MP29-02 was also superior to AZE in relieving congestion (online suppl. fig. 4) and rhinorrhea in patients most bothered by these symptoms (table 3).

Discussion

MP29-02, a novel intranasal formulation of AZE and FP, is more effective than commercially available active comparators in providing relief from all symptoms, including ocular ones. The responder sensitivity analysis showed that more MP29-02 patients achieved each and every response threshold and did so days faster than intranasal FP or AZE, an important consideration since a

typical moderate-to-severe SAR episode lasts 12.5 days on average [18]. MP29-02 also provided the greatest relief, irrespective of disease severity, most effectively treated the entire nasal and ocular symptom complex, and targeted patients' most bothersome symptoms.

In this paper we define several new analyses which permit assessment of clinical relevance of treatments for the first time in AR. Regulatory authorities suggest measuring response to treatment using a responder analysis to demonstrate the magnitude of clinical effect [20, 21], but they are seldom reported. Here we assess clinically relevant response using novel time to response sensitivity analyses which included both relative and absolute response criteria. Both are important to patients, since the former assesses a clinically relevant response from baseline (e.g. a

Table 3. Reduction in individual nasal symptom scores by patient type

Treatment	Baseline symptom score ¹	LS mean CFB	Relative difference ²	Absolute difference		95% CI	p value
Change from baseline in nasal congestion score for those patients whose predominant symptom is nasal congestion							
MP29-02 (n = 98)	5.60 (0.47)	-1.41	-	-	-	-	-
FP (n = 84)	5.34 (0.78)	-0.90	71%	MP-FP	-0.51	-0.83, -0.19	0.0018
AZE (n = 93)	5.36 (0.77)	-0.83	81%	MP-AZE	-0.58	-0.88, -0.29	0.0001
PLA (n = 93)	5.47 (0.65)	-0.69	-	MP-PLA	-0.72	-1.02, -0.42	<0.0001
				FP-PLA	-0.21	-0.50, 0.09	0.1641
				AZE-PLA	-0.14	-0.40, 0.12	0.2894
Change from baseline in nasal itching score in those patients whose predominant symptom is nasal itching							
MP29-02 (n = 40)	5.56 (0.60)	-1.37	-	-	-	-	-
FP (n = 45)	5.59 (0.57)	-0.78	123%	MP-FP	-0.59	-1.08, -0.09	0.0214
AZE (n = 45)	5.35 (0.75)	-1.15	47%	MP-AZE	-0.22	-0.75, 0.31	0.4042
PLA (n = 46)	5.64 (0.61)	-0.90	-	MP-PLA	-0.47	-0.98, 0.03	0.0657
				FP-PLA	+0.11	-0.23, 0.46	0.5158
				AZE-PLA	-0.25	-0.66, 0.16	0.2300
Change from baseline in rhinorrhea score in those patients whose predominant symptom is rhinorrhea							
MP29-02 (n = 41)	5.57 (0.64)	-1.50	-	-	-	-	-
FP (n = 45)	5.42 (0.63)	-1.46	6%	MP-FP	-0.04	-0.57, 0.49	0.8671
AZE (n = 38)	5.49 (0.68)	-1.03	58%	MP-AZE	-0.48	-0.94, -0.02	0.0424
PLA (n = 40)	5.49 (0.69)	-0.67	-	MP-PLA	-0.83	-1.32, -0.34	0.0012
				FP-PLA	-0.78	-1.29, -0.28	0.0029
				AZE-PLA	-0.35	-0.77, 0.07	0.0992
Change from baseline in sneezing score in those patients whose predominant symptom is sneezing							
MP29-02 (n = 25)	5.27 (0.87)	-1.89	-	-	-	-	-
FP (n = 27)	5.33 (0.82)	-0.98	61%	MP-FP	-0.91	-1.40, -0.43	0.0004
AZE (n = 22)	5.45 (0.68)	-1.47	28%	MP-AZE	-0.42	-0.94, 0.09	0.1065
PLA (n = 24)	5.38 (0.79)	-0.40	-	MP-PLA	-1.49	-1.95, -1.04	<0.0001
				FP-PLA	-0.58	-1.02, -0.14	0.0101
				AZE-PLA	-1.07	-1.51, -0.64	<0.0001

PLA = Placebo; LS = least squares; CFB = change from baseline; CI = confidence interval.

¹ Mean (SD); maximum symptom score = 6.

² $[1 - (\text{FP or AZE} - \text{PLA}) / (\text{MP29-02} - \text{PLA})] \times 100$.

halving of symptom burden) and the later defines the symptoms remaining after treatment. Since clinical relevance is also influenced by patient-related factors such as disease severity, the predominant symptom and the presence of comorbidity, we also assessed efficacy in those patients with more and less severe disease, in those presenting with a predominant symptom, as well as the ability to treat the overall rhinitis symptom complex, incorporating the nasal and ocular symptoms most commonly associated with rhinoconjunctivitis. The only study to compare MP29-02 to commercially available active comparators was chosen to test these new efficacy analyses in order to ensure relevance to the real-world situation.

These analyses add important information not previously published [22]. A recent publication by Carr et al.

[23] on a different set of patients and using active comparators not commercially available also showed the treatment effect and consistent response of MP29-02 across seasons, symptoms and severity. However, treatment differences presented in that meta-analysis [23] were consistently less than those presented here, since the effect of formulation and device were eliminated.

Although the responder and other post hoc analyses reported here were not primary objectives of the trial, these parameters were defined as important by an independent panel of experts without having access to the data. The sensitivity analysis from ≥ 30 to $\geq 90\%$ rTNSS reduction from baseline incorporated a full range of improvement (from marginal to very important). One in 2 MP29-02 patients achieved the substantial response of

halving their nasal symptom burden (i.e. $\geq 50\%$) and 1 in 4 MP29-02 patients had mild or less symptoms after treatment (i.e. $\geq 75\%$ reduction in rTNSS) achieved days faster than with either active comparator.

The analysis showed the significant advantage of MP29-02 over the most effective medication class currently available to treat AR (i.e. INS) and also the responder criterion at which INS cease to benefit patients over the placebo response (i.e. $\geq 60\%$ rTNSS reduction from baseline). More MP29-02 patients also achieved the absolute response criterion of complete/near-to-complete nasal symptom resolution, which is clinically relevant considering both the severity of the patient population (i.e. rTNSS $\geq 8/12$ and nasal congestion $\geq 2/3$) and the strictness of the complete/near-to-complete criterion which means patients have less than mild symptoms across the rhinitis symptom complex spectrum. This was not the case with INS which did not differ from placebo in this regard.

In clinical practice, patients frequently present with a predominant symptom. Congestion is frequently reported as the most bothersome nasal symptom [15]. Not only was MP29-02 more effective than FP or AZE at providing targeted symptom relief per patient 'type' (e.g. more effectively reduced nasal congestion in patients whose predominant symptom was nasal congestion), it did so whilst maintaining overall control of the nasal symptom complex in all patient types. For nasal congestion-predominant patients, MP29-02 effectively reduced this symptom and patients' overall rTNSS, and thus may reduce the need for a nasal decongestant prior to MP29-02 administration.

However, for some patients the most bothersome symptoms of AR are from ocular origin [14, 17], which are usually less well controlled than nasal symptoms [26, 27]. Intranasal fluticasone furoate controls ocular symptoms [28], but its real efficacy compared to other INS is unclear since no head-to-head comparison has been made, and other INS also have some effect on these symptoms [29]. It cannot, therefore, be proposed that one INS is more effective than another. A novel treatment which more effectively controls ocular symptoms fills the gap for an important unmet need in AR. MP29-02 was clearly better at reducing ocular symptoms than FP and also AZE.

This clinical study did not include patients with mild AR who frequently self-medicate and are rarely seen in a clinic, but rather included patients with moderate-to-severe AR who represent the patient population most seen by GPs or respiratory specialists. The generalizability of

these data is an inherent limitation of all randomized trials [30] since inclusion and exclusion criteria has to be in agreement with FDA and EMA guidelines. However, the results of FP are representative for the entire class of INS, since FP and fluticasone furoate [31] and FP and mometasone furoate [32] have shown comparable efficacy in direct comparison studies.

MP29-02 has an excellent safety profile. Data captured from 4,022 patients recruited into four 14-day SAR studies confirmed that treatment-related adverse events (TRAEs) observed were those usually reported with AZE (dysgeusia) and FP (headache and epistaxis), did not exceed placebo in many instances and were 'mild' in the vast majority of cases [22, 23]. Furthermore, in a long-term (52-week) study in patients with chronic rhinitis the incidence of TRAEs was low, with no evidence of accumulation of TRAEs over time or evidence of cortisol suppression. Additionally, no nasal mucosal ulceration or perforations were seen and ocular examination findings were unremarkable [33].

MP29-02 also provided significant benefit over FP and AZE in reducing patients' global and individual nasal or ocular symptoms. The clinical benefit of MP29-02 was observed during the first day of assessment and was sustained over the entire course of treatment. This post hoc analysis may help physicians to better assess patients' phenotypes for treatment. Taken together, MP29-02 may be considered the drug of choice for moderate-to-severe AR patients. These measures could define a new standard for assessing clinical relevance in AR.

Acknowledgements

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Online Supplementary Material:

Clinically Relevant Effect of a New Intranasal Therapy (MP29-02) in Allergic Rhinitis Assessed by Responder Analysis

Methods

Protocol

The study was conducted in accordance with FDA and EMA recommendations [1, 2], and good clinical practice [3]. After Institutional Review Board approval, written informed consent was obtained from all patients or their legal guardians (subjects aged <18 years).

Participants

Inclusion Criteria

Subjects (≥ 12 years old) with a minimum 2-year history of seasonal allergic rhinitis (SAR), significant current clinical rhinitis symptomatology, and a positive skin prick test to mountain cedar pollen (within the past 12 months), who met all study inclusion/exclusion criteria, were eligible for randomization. All subjects had moderate-to-severe SAR defined by a reflective total nasal symptom score (rTNSS) of at least 8 out of 12, with a congestion score of 2 or 3 during screening. At randomization patients were required to have an rTNSS of at least 8 and a reflective nasal congestion score of ≥ 2 on 3 separate symptom assessments (one of which was within 2 days of day 1 and could include the morning of day 1) during the placebo lead-in period.

Exclusion Criteria

Subjects were excluded if they had erosion, ulceration or septal perforation, another disease [e.g. 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 which could interfere with the interpretation of study results. Excluded medications included oral or topical antihistamines, oral and intranasal anticholinergic agents, ephedrine- or pseudoephedrine-containing products and decongestants within 5 days; ocular steroids within 7 days; cromolyn compounds, oral antibiotics, leukotriene inhibitors, inhaled (oral or intranasal) corticosteroids, ocular mast cell stabilizers and monoamine oxidase inhibitors within 14 days; systemic corticosteroids (oral, intravenous), tricyclic antidepressant and immunosuppressives/immunomodulators within 30 days; IgE antagonists within 130 days, and sublingual immunotherapy within 6 months of screening.

Treatment Concordance

Subjects recorded each dose (number of sprays) of the twice daily study medication in their subject diary. On day 7 and 14 the study site staff reviewed the amount of study medication returned, and reviewed the amount of medication recorded in the patient's diary. 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.

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 [1, 2]. Each nasal symptom was scored by patients twice daily (a.m. + p.m.) on each treatment day from 0 to 3: 0 = none (no symptoms present); 1 = mild (mild symptoms which are noticeable and do not interfere with any activity); 2 = moderate (symptoms which are slightly bothersome and slightly interfere with activity or nighttime sleep), and 3 = severe (symptoms which are bothersome and interfere with activity or nighttime sleep). Therefore, the maximum score for rTNSS was 24 (i.e. 4 symptoms $\times$ score of 3 $\times$ 2 for a.m. + p.m.).

The reflective total ocular symptom score (rTOSS), which comprised the ocular symptoms of itching, watering and redness was a key secondary efficacy endpoint. Each ocular symptom was scored by patients twice daily (a.m. and p.m.) on each treatment day from 0 to 3. For the symptoms of itchy eyes and watery eyes the scale was the same as that used 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 to subject's normal color); 2 = moderate (more dilation of blood vessels and red color compared to subject's normal color), and 3 = severe (large, numerous dilated blood vessels and deep red color compared to subject's normal color). The maximum score for rTOSS was 18 (i.e. 3 symptoms $\times$ score of 3 $\times$ 2 for a.m. + p.m.).

Baseline Scores

Baseline scores were defined as the average of all combined scores over the 7-day placebo lead-in period, including the morning of day 1 (predose). The overall change from baseline to day 14 included assessments from day 1 p.m. through to day 14 a.m.

Rhinitis Quality of Life Questionnaire

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 older than 18 years [4]. The RQLQ consists of 7 domains (i.e. activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional) which are rated on a 7-point scale, with 0 being not troubled by allergy symptoms during the past week and 6 being extremely troubled. The overall RQLQ score was calculated by summing up the individual domain scores and change from baseline to day 14 recorded.

Safety

Safety was assessed by patient-reported adverse events.

Sample Size

Sample size was determined based on the results of a previously published proof of concept exploratory study [5], which suggested that MP29-02 [a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP)] and FP might reduce the rTNSS by -5.92 and -4.19 , respectively, and that a standard deviation of 5 might be a conservative estimate. Based on these values, a two-sided alpha of 5% and a 10% dropout rate, 95 randomized subjects per treatment arm were sufficient to achieve 90% power.

Randomization and Treatment Assignment

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. An interactive voice recognition system was utilized for assignment of subjects to treatment groups. Subjects were assigned two sets of study medication through the interactive voice recognition system: study drug (placebo) for the placebo lead-in period and randomized study drug for the treatment period. For either of these periods, the site staff were instructed to use the next available kit number at that site from a central randomization schedule that was designed to maintain treatment balance within each site. The randomization number and kit number were recorded on the source document, the case report form and the drug assignment record. The investigator or designee was responsible for instructing the subject regarding the exact dose of

study medications and the dosing schedule to be followed. The subject was also instructed to return with all used and unused medication supplies to the study site at each visit.

Blinding

Individual nasal spray bottles were identity-masked such that both patients and study personnel were blinded to treatment assignment. The active controls comprised commercially available AZE (Astelin[®], Meda) and FP (generic FP, Roxane Laboratories). Placebo comprised MP29-02 without any active constituents in the same vehicle (i.e. contained the same excipients assessed qualitatively and quantitatively), pump volume ($0.137 \mu\text{l}/\text{spray}$) and device. 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 Analysis

A hierarchical test procedure was implemented to maintain the overall two-sided type I error level of 0.05 among the pairwise comparisons. As a first step, changes in combined rTNSS were compared between MP29-02 and placebo. If this was significant, MP29-02 was then compared to AZE, and if significant, then to FP [6].

As prespecified, efficacy analyses were performed on the intent-to-treat (ITT) population of all randomized patients with at least one postbaseline observation. An analysis of covariance (ANCOVA) model was applied to the primary efficacy variable (rTNSS). 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 (i.e. estimates are corrected for influence of covariates, such as center or baseline severity, to account for the applied inferential statistical methods). Changes from baseline in rTOSS were assessed in the same way.

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Suppl. Table 1. Subject disposition

Disposition summary	MP29-02	AZE	FP	Placebo
All randomized subjects, n	153	153	153	151
Completed, n (%)	145 (94.8)	144 (94.1)	144 (94.1)	144 (95.4)
Discontinued, n (%)	8 (5.2)	9 (5.9)	9 (5.9)	7 (4.6)
Reason for discontinuation, n (%)				
Adverse event	1 (0.7)	3 (2.0)	1 (0.7)	1 (0.7)
Abnormal test result	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment failure	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Noncompliance	3 (2.0)	2 (1.3)	3 (2.0)	1 (0.7)
Withdrew consent	1 (0.7)	1 (0.7)	2 (1.3)	2 (1.3)
Lost to follow-up	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Administrative problem	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (2.0)	2 (1.3)	0 (0.0)	3 (2.0)
ITT population, n (%)	153 (100.0)	152 (99.3)	151 (98.7)	151 (100.0)
Safety population, n (%)	153 (100.0)	152 (99.3)	153 (100.0)	151 (100.0)

MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg.

Suppl. Table 2. Patient baseline characteristics (ITT population) [reprinted with permission, 6]

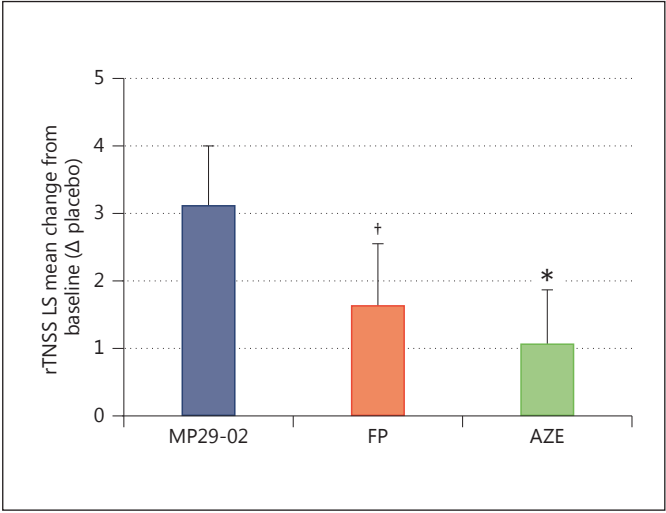
	MP29-02 (n = 153)	AZE (n = 152)	FP (n = 151)	Placebo (n = 151)
Age, years	39.5±14.2	39.5±14.1	38.1±14.2	39.9±14.7
Gender				
Female	97 (63.4)	97 (63.8)	100 (66.2)	102 (67.5)
Race				
White	132 (86.3)	135 (88.8)	130 (86.1)	131 (86.8)
Black	15 (9.8)	15 (9.9)	16 (10.6)	17 (11.3)
Asian	4 (2.6)	0 (0.0)	3 (2.0)	2 (1.3)
American Indian or Alaska native	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Other	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)
Duration of SAR, years	18.7±12.2	19.0±12.9	18.4±11.5	18.1±12.2
rTNSS	18.8±3.1	18.1±3.7	18.3±3.5	18.7±3.5
rTOSS	12.3±4.0	11.8±4.2	11.8±4.3	12.2±4.3
RQLQ overall score	3.90±1.06	3.81±1.04	3.82±1.07	3.87±1.17

Values represent mean ± SD or n (%). MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg.

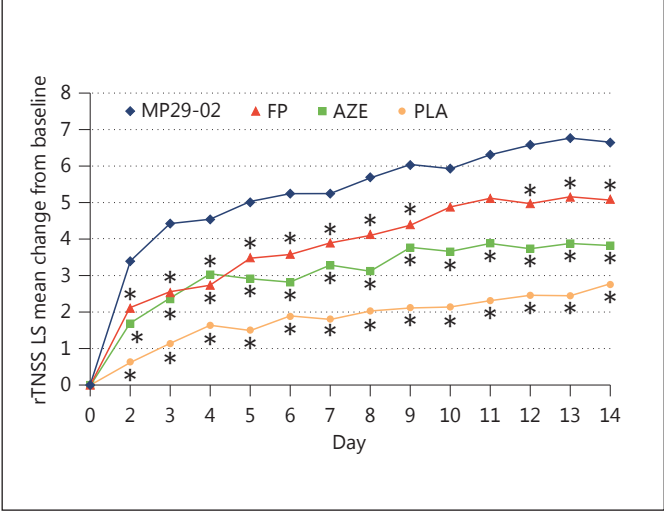
Suppl. Table 3. Overall LS mean change from baseline in the rTNSS and rTOSS following 14 days' treatment with MP29-02, intranasal FP, AZE and placebo in patients with moderate-to-severe seasonal allergic rhinitis (ITT population) [modified from fig. 1 and 4 in 6]

Treatment	Baseline (mean ± SD)	LS mean CFB	Relative difference ¹	Absolute difference	LS mean	95% CI	p value
rTNSS a.m. + p.m. (ITT)							
MP29-02	18.84±3.11	-5.31	-	-	-	-	-
FP	18.34±3.47	-3.84	47%	MP29-02-FP	-1.47	-2.44, -0.50	0.0031
AZE	18.08±3.66	-3.25	66%	MP29-02-AZE	-2.06	-2.98, -1.14	<0.0001
PLA	18.68±3.45	-2.20	-	MP29-02-PLA	-3.11	-4.03, -2.19	<0.0001
rTOSS a.m. + p.m. (ITT)							
MP29-02	12.31±4.03	-3.33	-	-	-	-	-
FP	11.77±4.27	-2.17	58%	MP29-02-FP	-1.17	-1.91, -0.42	0.0022
AZE	11.80±4.21	-2.62	35%	MP29-02-AZE	-0.72	-1.49, 0.06	0.0706
PLA	12.16±4.35	-1.32	-	MP29-02-PLA	-2.02	-2.70, -1.33	<0.0001

MP29-02: n = 153; FP: n = 151; AZE: n = 152; placebo: n = 151. MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg. PLA = Placebo; LS = least squares; CFB = change from baseline; CI = confidence interval.
¹ $[1 - (FP \text{ or } AZE - PLA)/(MP29-02 - PLA)] \times 100$.



Suppl. Fig. 1. Effect of MP29-02, FP and AZE on rTNSS (a.m. + p.m.) over the entire 14-day period. The precision of these estimates is indicated by the upper bounds of the respective 95% confidence intervals. MP29-02: n = 153; AZE: n = 152; FP: n = 151. * p < 0.0001 vs. MP29-02; † p = 0.0031 vs. MP29-02 [modified from fig. 1 in 6]. LS = Least squares.



Suppl. Fig. 2. Effect of MP29-02, FP and AZE on rTNSS (a.m. + p.m.) by treatment day. MP29-02: n = 153; AZE: n = 152; FP: n = 151; PLA: n = 151. * p ≤ 0.04 vs. MP29-02 [modified from fig. 3 in 6]. LS = Least squares.

Suppl. Table 4. Overall LS mean change from baseline in individual nasal and ocular symptom scores following 14 days' treatment with MP29-02, intranasal FP, AZE and placebo in patients with moderate-to-severe seasonal allergic rhinitis (ITT population) [modified from fig. 2 and 5 in 6]

Treatment	Baseline (mean ± SD)	LS mean CFB	Relative difference ¹	Absolute difference	LS mean	95% CI	p value
Nasal congestion (a.m. + p.m.)							
MP29-02	5.25±0.79	-1.24	-	-	-	-	-
FP	4.97±0.93	-0.86	54%	MP29-02-FP	-0.39	-0.65, -0.13	0.0034
AZE	5.04±0.88	-0.75	70%	MP29-02-AZE	-0.49	-0.74, -0.24	0.0001
PLA	5.15±0.78	-0.54	-	MP29-02-PLA	-0.70	-0.95, -0.45	<0.0001
Nasal itching							
MP29-02	4.66±1.10	-1.22	-	-	-	-	-
FP	4.54±1.17	-0.91	44%	MP29-02-FP	-0.31	-0.57, -0.04	0.0240
AZE	4.52±1.21	-0.82	56%	MP29-02-AZE	-0.40	-0.67, -0.13	0.0033
PLA	4.63±1.25	-0.51	-	MP29-02-PLA	-0.70	-0.97, -0.44	<0.0001
Rhinorrhea (a.m. + p.m.)							
MP29-02	4.80±0.93	-1.42	-	-	-	-	-
FP	4.70±0.94	-1.15	32%	MP29-02-FP	-0.27	-0.55, 0.02	0.0678
AZE	4.62±1.15	-0.87	65%	MP29-02-AZE	-0.54	-0.80, -0.28	<0.0001
PLA	4.72±1.01	-0.58	-	MP29-02-PLA	-0.83	-1.10, -0.56	<0.0001
Sneezing (a.m. + p.m.)							
MP29-02	4.14±1.35	-1.47	-	-	-	-	-
FP	4.14±1.27	-0.98	49%	MP29-02-FP	-0.48	-0.77, -0.20	0.0009
AZE	3.90±1.40	-0.86	61%	MP29-02-AZE	-0.60	-0.89, -0.32	<0.0001
PLA	4.18±1.31	-0.47	-	MP29-02-PLA	-1.00	-1.27, -0.73	<0.0001
Ocular itching (a.m. + p.m.)							
MP29-02	4.48±1.36	-1.23	-	-	-	-	-
FP	4.31±1.40	-0.70	67%	MP29-02-FP	-0.53	-0.79, -0.26	0.0001
AZE	4.42±1.28	-0.88	44%	MP29-02-AZE	-0.35	-0.63, -0.08	0.0127
PLA	4.46±1.42	-0.44	-	MP29-02-PLA	-0.79	-1.04, -0.54	<0.0001
Ocular watering (a.m. + p.m.)							
MP29-02	4.09±1.50	-1.13	-	-	-	-	-
FP	3.91±1.56	-0.82	51%	MP29-02-FP	-0.32	-0.59, -0.05	0.0218
AZE	3.98±1.57	-0.98	25%	MP29-02-AZE	-0.15	-0.43, 0.13	0.2923
PLA	4.01±1.56	-0.52	-	MP29-02-PLA	-0.61	-0.86, -0.35	<0.0001
Ocular redness (a.m. + p.m.)							
MP29-02	3.74±1.72	-1.05	-	-	-	-	-
FP	3.54±1.66	-0.66	53%	MP29-02-FP	-0.38	-0.65, -0.12	0.0044
AZE	3.40±1.79	-0.76	40%	MP29-02-AZE	-0.28	-0.55, -0.02	0.0372
PLA	3.69±1.79	-0.32	-	MP29-02-PLA	-0.73	-0.96, -0.49	<0.0001

MP29-02: n = 153; FP: n = 151; AZE: n = 152; placebo: n = 151. MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg. PLA = Placebo; LS = least squares; CFB = change from baseline; CI = confidence interval.

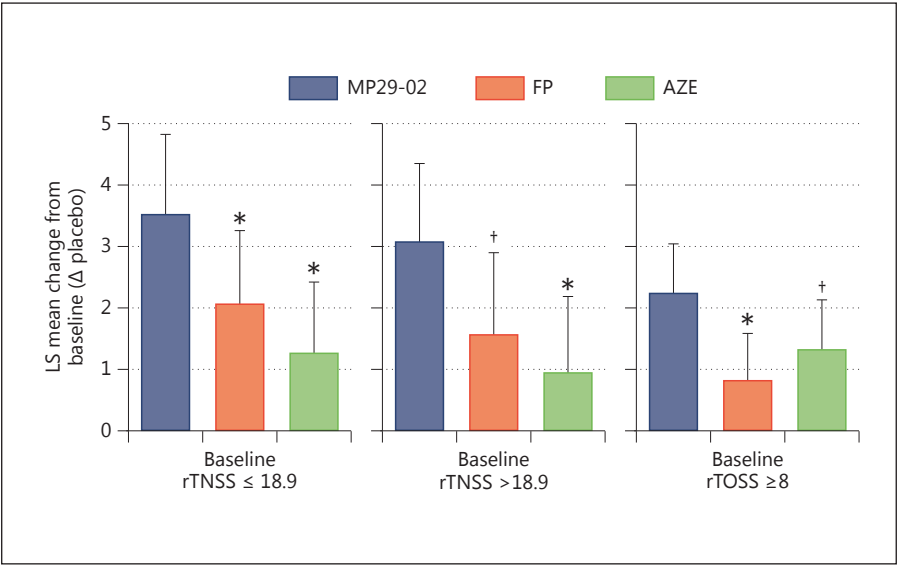
¹ $[1 - (FP \text{ or } AZE - PLA)/(MP29-02 - PLA)] \times 100$.

Suppl. Table 5. Commonly reported treatment emergent adverse events (safety population) [reprinted with permission, 6]

	Adverse events, n (%)			
	MP29-02 (n = 153)	AZE (n = 152)	FP (n = 153)	placebo (n = 151)
Dysgeusia (unpleasant taste)	11 (7.2)	3 (2.0)	0 (0.0)	0 (0.0)
Epistaxis	6 (3.9)	4 (2.6)	6 (3.9)	5 (3.3)
Headache	4 (2.6)	2 (1.3)	6 (3.9)	2 (1.3)
Pharyngolaryngeal pain	2 (1.3)	1 (0.7)	0 (0.0)	1 (0.7)
Nasal discomfort	2 (1.3)	0 (0.0)	1 (0.7)	0 (0.0)
Nausea	1 (0.7)	2 (1.3)	0 (0.0)	2 (1.3)
Mucosal erosion	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)
Somnolence	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)

A patient with multiple adverse events is counted only once in any row.
MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg.

Suppl. Fig. 3. Effect of MP29-02, FP and AZE on rTNSS and rTOSS over the entire 14-day treatment period by patient severity. The precision of these estimates is indicated by the upper bounds of the respective 95% confidence intervals. * $p \leq 0.0188$ vs. MP29-02; † $p \leq 0.0456$ vs. MP29-02. Numbers and baseline data provided in supplementary table 6. LS = Least squares.



Suppl. Table 6. Efficacy of MP29-02 compared to intranasal FP, AZE or placebo (ITT population) following 14 day's treatment in patients with more and less severe seasonal allergic rhinitis

Treatment	Baseline (mean ± SD)	LS mean CFB	Relative difference ¹	Absolute difference	LS mean	95% CI	p value
rTNSS a.m. + p.m. (baseline rTNSS ≤18.9)							
MP29-02 (n = 76)	16.25±1.85	-4.68	-	-	-	-	-
FP (n = 87)	15.86±2.16	-3.21	42%	MP29-02-FP	-1.46	-2.68, -0.25	0.0188
AZE (n = 84)	15.40±2.50	-2.41	64%	MP29-02-AZE	-2.26	-3.42, -1.10	0.0002
PLA (n = 75)	15.83±2.25	-1.16	-	MP29-02-PLA	-3.51	-4.78, -2.24	<0.0001
rTNSS a.m. + p.m. (baseline rTNSS >18.9)							
MP29-02 (n = 77)	21.40±1.62	-6.24	-	-	-	-	-
FP (n = 64)	21.71±1.51	-4.73	49%	MP29-02-FP	-1.52	-2.99, -0.04	0.0436
AZE (n = 68)	21.39±1.50	-4.11	70%	MP29-02-AZE	-2.13	-3.55, -0.71	0.0035
PLA (n = 75)	21.50±1.63	-3.18	-	MP29-02-PLA	-3.06	-4.34, -1.77	<0.0001
rTNSS a.m. + p.m. (RQLQ overall score ≤3.9)							
MP29-02 (n = 65)	17.64±2.84	-4.89	-	-	-	-	-
FP (n = 70)	17.72±3.19	-3.50	59%	MP29-02-FP	-1.39	-2.61, -0.18	0.0244
AZE (n = 71)	17.47±3.16	-3.29	68%	MP29-02-AZE	-1.61	-2.76, -0.45	0.0068
PLA (n = 64)	17.13±2.91	-2.54	-	MP29-02-PLA	-2.35	-3.64, -1.05	0.0005
rTNSS a.m. + p.m. (RQLQ overall score >3.9)							
MP29-02 (n = 72)	19.94±3.05	-5.95	-	-	-	-	-
FP (n = 63)	19.23±3.65	-4.10	49%	MP29-02-FP	-1.85	-3.40, -0.30	0.0194
AZE (n = 62)	18.90±3.97	-3.54	64%	MP29-02-AZE	-2.41	-3.86, -0.96	0.0013
PLA (n = 63)	20.08±3.32	-2.19	-	MP29-02-PLA	-3.76	-5.16, -2.36	<0.0001
rTOSS a.m. + p.m. (baseline rTOSS ≥8)							
MP29-02 (n = 128)	13.61±2.86	-3.89	-	-	-	-	-
FP (n = 125)	13.22±2.90	-2.47	63%	MP29-02-FP	-1.42	-2.27, -0.57	0.0012
AZE (n = 118)	13.50±2.91	-2.96	42%	MP29-02-AZE	-0.93	-1.83, -0.02	0.0456
PLA (n = 121)	13.77±2.95	-1.65	-	MP29-02-PLA	-2.23	-3.01, -1.46	<0.0001
rT5SS a.m. + p.m. (ITT)							
MP29-02 (n = 153)	23.32±4.12	-6.72	-	-	-	-	-
FP (n = 151)	22.65±4.57	-4.81	49%	MP29-02-FP	-1.91	-3.11, -0.71	0.0020
AZE (n = 152)	22.50±4.60	-4.23	64%	MP29-02-AZE	-2.49	-3.64, -1.33	<0.0001
PLA (n = 151)	23.14±4.54	-2.83	-	MP29-02-PLA	-3.88	-5.02, -2.74	<0.0001
rT7SS a.m. + p.m. (ITT)							
MP29-02 (n = 153) ²	31.15±6.62	-8.74	-	-	-	-	-
FP (n = 151)	30.10±7.16	-6.05	52%	MP29-02-FP	-2.69	-4.33, -1.06	0.0013
AZE (n = 152)	29.88±7.22	-5.83	56%	MP29-02-AZE	-2.91	-4.52, -1.31	0.0004
PLA (n = 151)	30.84±7.20	-3.55	-	MP29-02-PLA	-5.19	-6.71, -3.68	<0.0001

MP29-02: Novel intranasal formulation of AZE (137 µg) and FP (50 µg); AZE: 137 µg; FP: 50 µg. PLA = Placebo; LS = least squares; CFB = change from baseline; CI = confidence interval; rT5SS = reflective total of 5 symptom scores (rTNSS + ocular itching); rT7SS = reflective total of 7 symptom scores (rTNSS + rTOSS).

¹ $[1 - (\text{FP or AZE} - \text{PLA}) / (\text{MP29-02} - \text{PLA})] \times 100$.

² MP29-02 is twice as effective as FP or AZE in reducing overall nasal and ocular symptoms.

Suppl. Fig. 4. Effect of MP29-02, FP and AZE on rTNSS or nasal congestion score in those patients with predominantly nasal congestion. The precision of these estimates is indicated by the upper bounds of the respective 95% confidence intervals. * $p \leq 0.0001$ vs. MP29-02; $^{\dagger} p \leq 0.0093$ vs. MP29-02. Numbers and baseline data provided in supplementary tables 2 and 3. LS = Least squares.

