

A New Therapy (MP29-02) Is Effective for the Long-Term Treatment of Chronic Rhinitis

D Price,¹ S Shah,² S Bhatia,³ C Bachert,⁴ W Berger,⁵ J Bousquet,⁶ W Carr,⁵ P Hellings,⁷ U Munzel,⁸ G Scadding,⁹ P Lieberman¹⁰

¹University of Aberdeen, Aberdeen, UK

²Allergy and Asthma Consultants of NJ-PA, Colledgeville, Pennsylvania, USA

³IRL Clinical Research Centre, Mumbai, India

⁴Upper Airways Research Laboratory, Ghent University Hospital, Ghent, Belgium

⁵Allergy and Asthma Associates of Southern California, Mission Viejo, California, USA

⁶Hopital Arnaud de Villeneuve University Hospital, Montpellier and Inserm CESP1018, France

⁷University Hospitals Leuven, Leuven, Belgium

⁸MEDA Pharma GmbH & Co. KG, Bad Homburg, Germany

⁹The Royal National Throat Nose and Ear Hospital, London, UK

¹⁰University of Tennessee College of Medicine, Memphis, Tennessee, USA

■ Abstract

Background and objective: MP29-02 (Dymista), a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP), is significantly better than first-line therapy for the treatment of moderate-to-severe seasonal allergic rhinitis (SAR), and is well tolerated following 52 weeks of continuous use in chronic rhinitis. The aim of this study was to evaluate the long-term efficacy of MP29-02 versus FP in patients with chronic rhinitis.

Patients and methods: In total, 612 chronic rhinitis patients (perennial allergic rhinitis [PAR], n=424; nonallergic rhinitis, n=188) aged 12 years or older were enrolled into this open-label, parallel-group study and randomized to MP29-02 (1 spray/nostril bid) or FP nasal spray (2 sprays/nostril qd) for 52 weeks. Efficacy was assessed by change from baseline in $_{PM}$ reflective total nasal symptom score (rTNSS), time to first achieve 100% $_{PM}$ rTNSS reduction from baseline, and percentage of symptom-free days in the total and PAR populations posthoc.

Results: MP29-02 reduced patients' $_{PM}$ rTNSS from baseline significantly more than FP, from Day 1 up to and including week 28 (-2.88 vs -2.53; $P=.0048$), with treatment difference maintained for 52 weeks. Fluctuation in significance after week 28 might be explained, at least in part, by decreasing sample size, permitted according to ICH guidelines. By Day 1 almost twice as many MP29-02-patients were symptom free. After 1 month, 71.1% of MP29-02 patients experienced 100% rTNSS reduction (60.3% for FP), and did on a median of 9 days faster ($P=.0024$). Over 52 weeks MP29-02 patients experienced 8.4% more symptom-free days ($P=.0005$). These results were mirrored in the PAR subpopulation.

Conclusion: These results confirm MP29-02's wide therapeutic spectrum and assert its consistent superiority over an intranasal corticosteroid.

Key words: Dymista. Chronic rhinitis. Fluticasone propionate. Perennial allergic rhinitis. Long-term. Efficacy. Symptom-free days. Responder analysis.

■ Resumen

Antecedentes y objetivo: El MP29-02 (Dymista®) es una novedosa formulación de uso intranasal, compuesta por hidrocloreuro de azelastina y propionato de fluticasona (FP) que se ha demostrado significativamente superior al tratamiento de primera línea habitual de la rinitis alérgica estacional moderada o severa, y que presenta muy buena tolerancia por pacientes afectados de rinitis crónica, en su uso continuado durante un periodo de 52 semanas. El objetivo de este estudio era evaluar la eficacia a largo plazo del MP29-02 frente a FP, en pacientes afectados de rinitis crónica.

Pacientes y métodos: Realizamos un estudio aleatorizado, abierto y de grupos paralelos en el que se incluyeron 612 pacientes con rinitis crónica mayores de 12 años de edad, de los cuales 424 eran pacientes con rinitis alérgica perenne [PAR] y 188 con rinitis no alérgica.

Se administró MP29-02 (1 pulverización en cada fosa dos veces diarias) o FP (2 pulverizaciones en cada fosa una vez al día) durante 52 semanas. La eficacia del tratamiento se evaluó mediante el cambio con respecto al valor basal de la puntuación reflexiva total de síntomas vespertinos, (rTNSS), el tiempo a obtener una reducción del 100% en el rTNSS vespertino, y el porcentaje de días libres de síntomas en el total de los pacientes y en los afectados de rinitis alérgica perenne, en un análisis posthoc.

Resultados: MP29-02 redujo significativamente más el rTNSS vespertino, con respecto a su valor basal que el FP, desde el día 1 del estudio hasta inclusive la semana 28, manteniéndose las diferencias en el tratamiento hasta la semana 52. Las fluctuaciones en la significación de los resultados, a partir de la semana 28, pueden ser explicadas, al menos en parte, por la disminución de la muestra de pacientes estudiada, que las guías ICH permiten. Desde el día 1, casi el doble de pacientes en tratamiento con MP29-02 estaban libres de síntomas. Tras un mes de tratamiento, el 71.1% de los pacientes tratados con MP29-02 (7 de cada 10) experimentaron una reducción del 100% del rTNSS (60.3% de los tratados con FP), la cual se obtuvo 9 días antes (mediana) ($p=0.0024$). Tras 52 semanas los pacientes tratados con MP29-02 tenían un 8.4% más de días libres de síntomas ($p=0.0005$). Todos estos resultados fueron idénticos en la subpoblación de pacientes con PAR.

Conclusiones: Nuestros resultados demuestran que el MP29-02 posee un amplio espectro terapéutico y confirman una superioridad en eficacia sobre el corticoide intranasal.

Palabras clave: MP29-02. Dymista. Rinitis crónica. Propionato de fluticasona. Rinitis alérgica perenne. Largo plazo. Eficacia. Días libres de síntomas. Análisis de respuesta.

Introduction

Rhinitis can have an allergic origin (allergic rhinitis [AR]) or a nonallergic one (nonallergic rhinitis [NAR]) [1,2]. AR is a prevalent, underestimated, and undertreated condition [3,4], affecting 500 million people globally, and this figure is rising [1]. Although symptoms occurring during pollen seasons are easily distinguishable, year-round symptoms may be associated with AR and/or NAR, since the 2 diseases often coexist [5] and AR patients are also polysensitized [6,7]. In general practice, it is often difficult to differentiate between the two. A recent review estimated that approximately 2 of every 3 patients with rhinitis have AR (either seasonal AR [SAR] or perennial AR [PAR]) and that 1 in 3 have NAR [8]. As many as 42.5% of AR patients in Europe and 47% of those in the United States have persistent disease [9-11]. Therefore, there are many rhinitis patients who will need effective pharmacologic therapy for longer than 14 days. Unfortunately, overall effectiveness of marketed therapies has not improved in the past years [12,13]. Patients continue to cycle through multiple medications without experiencing additional improvement in their disease. Clearly, more effective therapies for the management of chronic rhinitis are needed.

MP29-02 (Dymista), a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP), is superior to established first-line AR therapies, intranasal FP, and intranasal AZE for the treatment of moderate-to-severe SAR, as shown in the largest direct head-to-head clinical development program to date [14-16]. In these SAR studies, MP29-02 significantly reduced patients' overall nasal symptom burden, and did so faster and better than either FP or AZE. Furthermore, it was more effective regardless of symptom, severity, or season over a 14-day treatment period [14-16].

MP29-02 is well tolerated in chronic rhinitis patients following 52 weeks of continuous use [17]. However, a statistical assessment of its long-term efficacy has not previously been published.

This study was primarily designed as a long-term safety trial [17]. It is a posthoc analysis of a phase III, 1-year

multicenter, randomized, open-label, parallel-group, active-controlled trial (MP4000 [EudraCT number: 2011-001368-23]) [17]. The primary aim was to assess whether the efficacy of MP29-02 is superior to standard AR therapy (FP) in patients with chronic rhinitis in a head-to-head fashion. Additionally, 100% responder analyses and percentage of symptom-free days were included as endpoints to further address relevance in treatment efficacy from a patient perspective both in the intent-to-treat (ITT) population and the PAR subpopulation. The parameters assessed in this posthoc analysis were defined a priori by an independent panel of experts without access to the data.

Materials and Methods

Protocol

This was a randomized, open-label, active-controlled, parallel-group study [EudraCT number: 2011-001368-23] comparing the efficacy of MP29-02 to intranasal FP in patients with persistent rhinitis (ie, chronic AR or NAR). It was conducted in accordance with Good Clinical Practice [18], the Declaration of Helsinki, and applicable regulatory requirements during 2008 and 2009 at 37 investigational sites in India. The sites covered a wide geographical area in India and included hospitals, specialist centers, and private facilities.

Inclusion Criteria

Individuals (12-80 years old) with an established 1-year history of chronic rhinitis due to either perennial allergies or NAR were randomized. Those with a seasonal allergic component were included, provided that they had significant symptoms persisting outside the allergy season. The diagnosis of rhinitis was confirmed by medical history, physical examination, presence of at least 3 symptoms (rhinorrhea, sneezing, nasal obstruction, or itching), skin prick testing, and/or allergen-specific immunoglobulin E (RAST). Patients were required to have documented proof of the presence of nasal symptoms on at least 2 days during the 7-day screening period.

Exclusion Criteria

Patients with evidence of nasal ulceration (grade 3), septal perforation (grade 4), plasma cortisol levels of 5 mcg/dL or less, other nasal diseases or structural abnormalities, nasal or sinus surgery within 1 year of screening, asthma (other than mild, intermittent), significant pulmonary disease or arrhythmia, glaucoma, or cataract were excluded. The use of the following treatments was not permitted during the study: antihistamines other than the test treatment, oral and intranasal anticholinergic agents, topical decongestants, intranasal corticosteroids (other than the test treatment), inhaled or systemic corticosteroids, omalizumab, leukotriene inhibitors, nasal saline, any intranasal medication, and anti-coagulants.

Planned Interventions and Timing

The study comprised a 7-day screening period and a 52-week treatment period with 6 outpatient study visits at randomization (Day 1), and then at months 1, 3, 6, 9 and 12 (Figure 1). Phone contact was made with patients at months 2, 4, 5, 7, 8, 10, and 11. On Day 1 eligible patients were randomized in a 2:1 ratio to 52 weeks' treatment with either (i) MP29-02 nasal spray (a novel intranasal formulation of AZE [137 µg] and FP [50 µg]; 1 spray per nostril in the morning and evening separated by approximately 12 hours; total daily dose of 548 µg and 200 µg, respectively) or (ii) FP (commercially available generic fluticasone, Boehringer Ingelheim/Roxane Laboratories, Columbus, OH; 50 µg) nasal spray (2 sprays/nostril in the morning; total daily dose of 200 µg). Patients recorded nasal symptom scores and each dose (number of sprays) of study medication in a special diary every day.

Safety

A full report of the safety results are intended for a separate publication.

Efficacy Variables

Efficacy was assessed secondarily by change from

baseline in a 12-hour period, assessed by PM rTNSS (sum of individual nasal symptoms of congestion, itching, rhinorrhea, and sneezing) according to previous studies [14-16] and as recommended by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [19,20] over the 52-week treatment period at 4-week intervals. Patients recorded their nasal symptoms on a 4-point scale once daily prior to the PM dose of MP29-02 or approximately 12 hours after the AM dose of FP on each study day.

Sample Size, Randomization, Blinding, and Concordance

Sample Size

The sample size was based on ICH guideline E1A, which stipulates treatment of at least 300 individuals for 6 months and 100 for 1 year. Based on an estimated attrition rate of 25% at 6 months, and of 50% by 12 months, 400 individuals in the MP29-02 group were considered sufficient.

Randomization and Blinding

At enrolment patients were assigned a unique identification number. Eligible patients were randomly assigned to open-label study treatment using central randomization via an interactive voice response system.

Concordance

Individuals recorded each dose of study drug in their diary. At each visit, study site staff documented that the study drug was returned and reviewed the diary. Bottles were also weighed at each visit.

Statistical Analyses

All efficacy analyses were performed using the ITT population, consisting of all randomized individuals with at least 1 postbaseline efficacy observation. Efficacy was assessed by PM rTNSS at each clinic visit. Averages over 4-week intervals of changes from baseline (=mean over

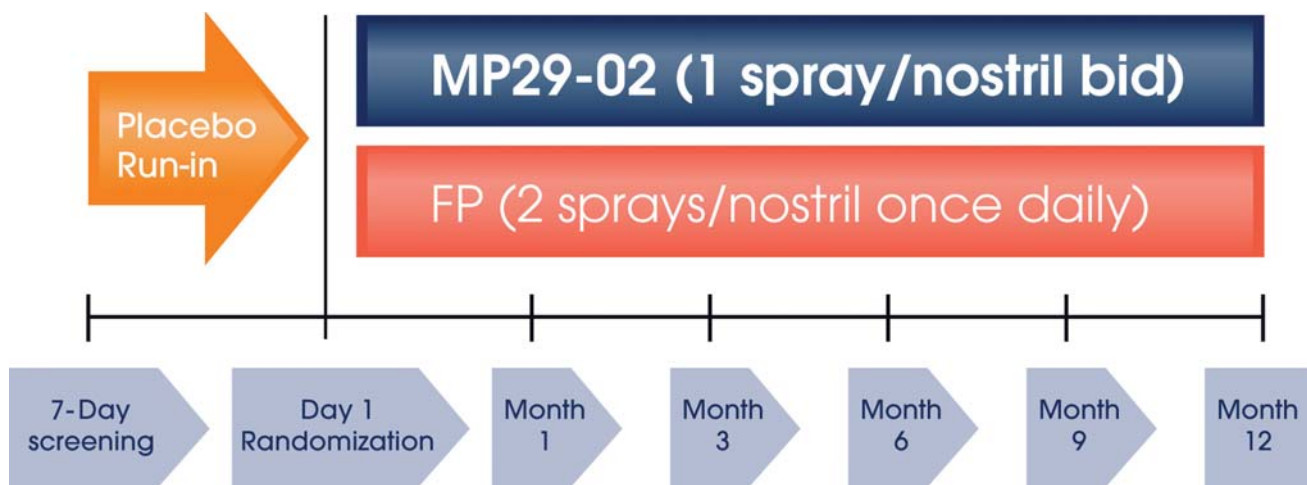


Figure 1. Study design. FP indicates fluticasone propionate; MP29-02, novel intranasal formulation of azelastine hydrochloride and FP.

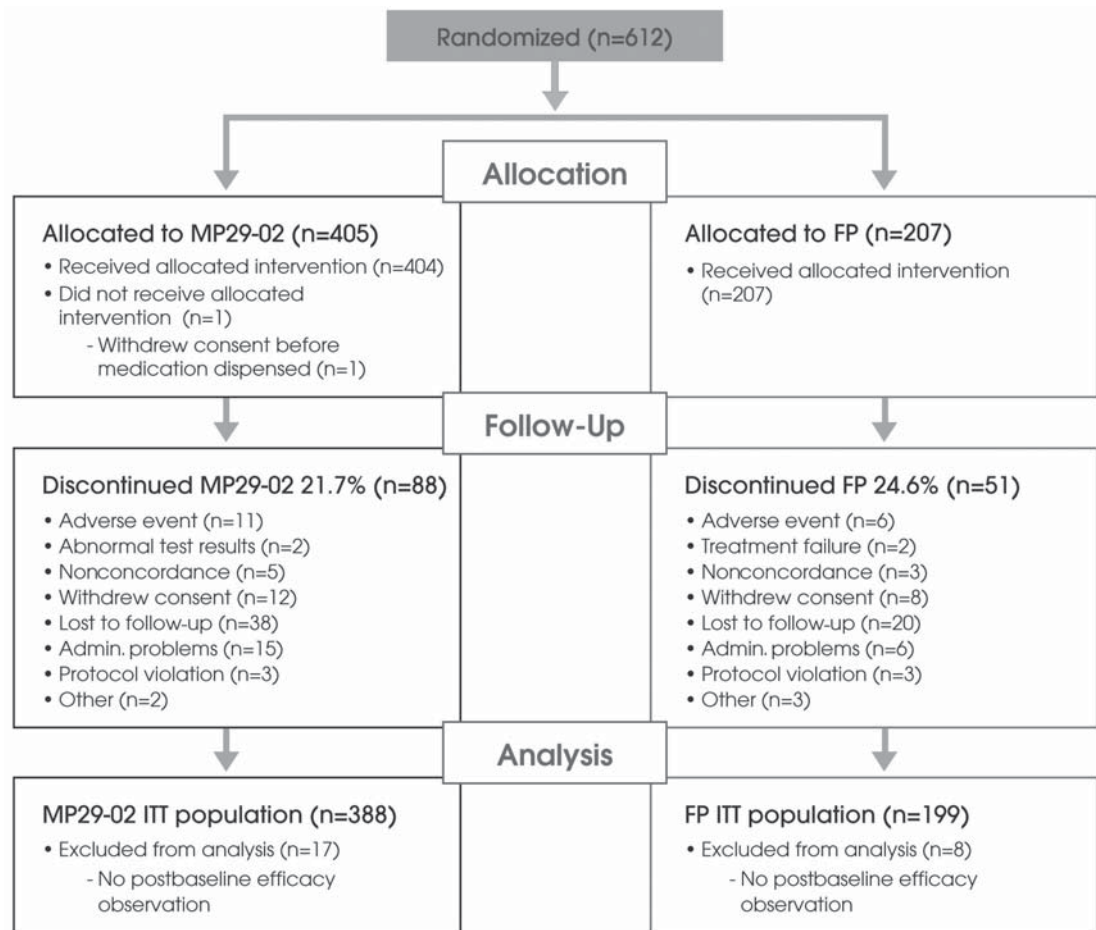


Figure 2. CONSORT flow diagram. Admin indicates administration; FP, fluticasone propionate; MP29-02, novel intranasal formulation of azelastine hydrochloride and FP.

7-day screening period) were analyzed descriptively. Those 4-week averages and the proportion of symptom-free days over the 52-week study period were analyzed posthoc by baseline-adjusted analysis of covariance (ANCOVA) for treatment differences between MP29-02 and FP nasal spray. The ANCOVA model included treatment group and site as fixed effects. The variances were allowed to vary between treatment groups (Satterthwaite approximation). Time to first response was analyzed by Kaplan Meier estimates and log rank tests. Change from baseline in PM rTNSS of 100% was used to define response in the total ITT and PAR subpopulations.

Results

Patients

Of the 612 individuals randomized to treatment, 464 (75.8%) completed the 1-year study period, and 139 (22.7%) discontinued the study. Completion rates were similar in both treatment groups (Figure 2). Patients with AR to indoor allergens made up approximately two-thirds of the population (ITT population: MP29-02, n=265 [65.4%]; FP, n=140 [67.6%+]). The most frequent reason for study discontinuation

Table 1. Baseline Characteristics of Study (Safety) Population^a

	MP29-02 (n=404)	FP (n=207)
Age, y	32.8 (11.5)	35.3 (11.5) ^b
12 to <18, No. (%)	28 (6.9)	8 (3.9)
18 to <65, No. (%)	373 (92.3)	196 (94.7)
≥ 65, No. (%)	3 (0.7)	3 (1.4)
Sex		
Male, No. (%)	240 (59.4)	110 (53.1)
Race		
Asian, No. (%)	404 (100.0)	206 (99.5)
Black, No. (%)	0 (0.0%)	1 (0.5)
Height, in	63.8 (3.9)	63.9 (3.9)
Weight, lb	135.9 (29.1)	136.1 (26.8)
PM rTNSS	3.84 (2.49)	3.87 (2.33)
Overall RQLQ score	2.1 (1.1)	2.2 (1.1)
Disease duration, y	5.9 (5.0)	6.3 (6.4)

Abbreviations: FP, fluticasone propionate; MP29-02, novel intranasal formulation of azelastine hydrochloride and FP; rTNSS, reflective total nasal symptom score; RQLQ, Rhinitis Quality of Life Questionnaire.

^aData expressed as mean (SD) unless otherwise indicated.

^bP=.015 vs MP29-02 (based on a 2-way analysis of variance model containing treatment group and site as fixed effects).

was loss to follow-up (Figure 2). Patients were not actively retained after 6 months, as although according to ICH guideline E1A, at least 300 patients are required to receive treatment for 6 months, only 100 patients are required for 12 months. The baseline characteristics of the 2 treatment groups were similar (Table 1).

Safety Outcomes

In general, no serious safety concerns have been noted with the long-term use of MP29-02 [17].

Efficacy Outcomes

PM rTNSS Change From Baseline

Mean (SD) baseline PM rTNSS was 3.84 (2.49) in the MP29-02 group and 3.87 (2.33) in the FP group. Over the first 7 days of treatment, MP29-02 patients experienced greater nasal symptom relief than FP patients, with a 1.55-point reduction in PM rTNSS versus a 0.75-point reduction in the FP group. This superiority of MP29-02 over FP was evident from Day 1 (MP29-02: -1.21 [SE 0.14]; FP: -0.25 [SE 0.18]), with consistent statistical significance maintained for up to 28 weeks (-2.88 vs -2.53; Diff, -0.35; 95% CI, -0.59, -0.11; *P*=.0048) (Figure 3). The difference between the groups was sustained up to 52 weeks (-2.98 vs -2.71; Diff: -0.27; 95% CI: -0.56, 0.02; *P*=.0642; Figure 3), representing a 75% reduction in symptom score in the MP29-02 group.

PM rTNSS Responder Analyses

Figure 4 shows the time to achieve the first 100% reduction in rTNSS. The purpose of this analysis was to show the proportion of patients who first achieved symptom-free status and, by examining horizontal differences on the X-axis, to show the time advantage of MP29-02 over FP in achieving this response. During the first month more patients treated with MP29-02 achieved their first 100% reduction from baseline in PM rTNSS, and they did so earlier than patients treated with FP. In the ITT population, the rapid efficacy of MP29-02 was apparent, as by Day 1 almost twice as many MP29-02-treated patients (17.4%) achieved a 100% reduction in their nasal symptoms compared to those treated with FP (Figure 4A). One in 3 patients treated with MP29-02 achieved their first 100%

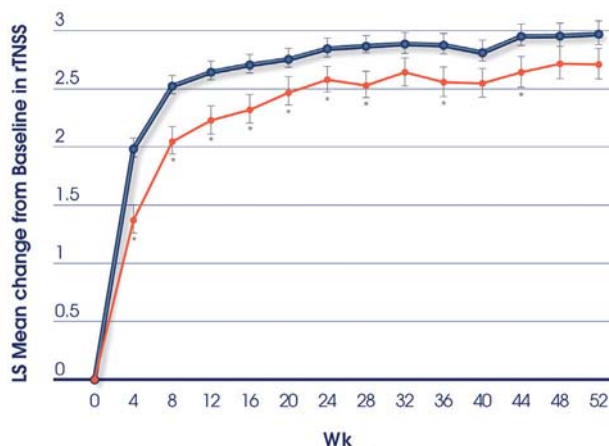


Figure 3. Effect of MP29-02 (n=388; blue) and FP (n=199; orange) nasal spray on the reflective total nasal symptom score (rTNSS) in patients with chronic rhinitis. Data are presented as least squares (LS) mean change from baseline at 4-week intervals, derived by analysis of covariance with the precision of these estimates indicated by the standard error. Baseline PM rTNSS: MP29-02 = 3.84; FP = 3.87. FP indicates fluticasone propionate; MP29-02, novel intranasal formulation of azelastine hydrochloride and FP. * *P*≤.0453 vs MP29-02.

response by Day 3 (Day 6 for FP), and this proportion increased to 1 in every 2 patients by Day 7 (Day 16 for FP). Overall, during the first month 71.1% of patients in the MP29-02 group achieved their first 100% response vs 60.3% of FP patients and they did so a median of 9 days earlier (*P*=.0024; Figure 4A). A similar pattern was observed in the PAR subpopulation. Overall, after 1 month of treatment, 73.4% of MP29-02 PAR patients achieved a 100% reduction in PM rTNSS from baseline vs 63.5% of FP patients, and they did so a median of 8 days faster (*P*=.0063) (Figure 4B).

Symptom-Free Days

In the ITT population MP29-02 patients experienced an average of 173 symptom-free days; this was 26 days, or 8.4%, more days than experienced by those treated with FP over the

Table 2. Days Free of Nasal Symptoms

Population	Days Available ^a		Symptom-Free Days ^a		Difference MP29-02-FP
	MP29-02	FP	MP29-02	FP	
ITT ^b	314.1 (88.2)	304.8 (106.6)	172.8 (114.5)	146.9 (116.6)	25.9 d
PAR ^c	318.2 (87.5)	306.3 (106.3)	173.8 (118.1)	149.9 (117.8)	23.9 d

Abbreviations: FP, fluticasone propionate; ITT, intent to treat; MP29-02: novel intranasal formulation of azelastine hydrochloride and FP; PAR, perennial allergic rhinitis.

^aData expressed as mean (SD).

^bITT: MP29-02, n=388; FP, n=199.

^cPAR: MP29-02, n=265; FP, n=140.

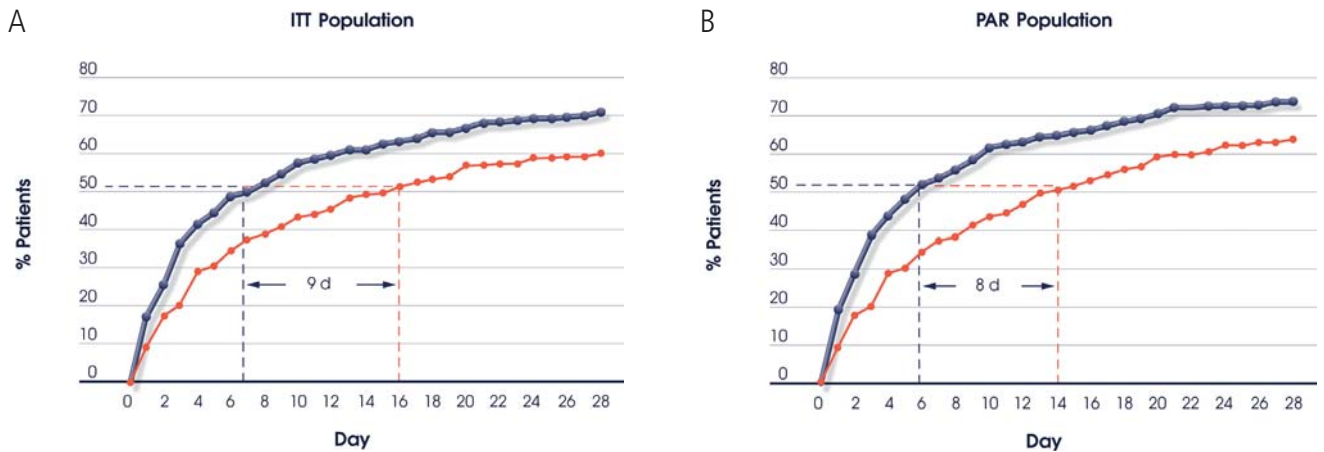


Figure 4. Time response curves showing the percentage of chronic rhinitis patients first exhibiting a 100% improvement in PM rTNSS over the first 28 days following treatment with MP29-02 (blue) or FP (FP; orange) nasal spray in the (A) ITT and (B) PAR subpopulation. Patients treated with MP29-02 achieved a response a median of 9 days earlier than those treated with FP in the ITT population and 8 days earlier than those treated with FP in the PAR population. ITT: MP29-02 vs FP, $P=.0024$; PAR: MP29-02 vs FP, $P=.0063$. FP indicates fluticasone propionate; ITT, intent to treat; MP29-02, novel intranasal formulation of azelastine hydrochloride and FP.

duration of the study ($P=.0005$) (Table 2). This advantage in terms of symptom-free days was also apparent in the PAR subpopulation, with MP29-02 patients experiencing 24 or 7.3% more symptom-free days (Table 2) than those treated with FP ($P=.0122$).

Discussion

In this study, we provide evidence for the first time that MP29-02 is more effective than FP for the treatment of chronic rhinitis, and that this superior efficacy extends to a full year. Although the open-label design of this study could have introduced bias, this design, combined with the 52-week study duration and the fact that patients had minimal clinical visits, makes the trial pragmatic [21] and provides evidence of MP29-02 effectiveness in an everyday clinical context.

As the primary aim of this study was to evaluate the safety and tolerability of MP29-02 with daily, chronic use over a 1-year period, only PM rTNSS was measured and ocular symptoms were not captured, in order to maintain compliance with study procedures. Although MP29-02 showed consecutive superiority over FP in reducing PM rTNSS from baseline up to and including 28 weeks, consistent statistical superiority was subsequently lost. Fluctuation in significance after week 28 might be explained, at least in part, by decreasing sample size. The sample size was based on ICH guideline E1A, which stipulates treatment of at least 300 patients for 6 months and 100 patients for 1 year [18]. So, although discontinuation was relatively low for a 52-week study, patient numbers were permitted to fall at the 6-month mark (according to the guideline), which coincided with loss of consistent statistical significance of MP29-02 over FP after week 28. The generalizability of data is an inherent limitation of this, and all, randomized trials, since inclusion and exclusion criteria

were in line with both FDA and EMA guidelines and of open-label studies. It is, therefore, possible that many patients seen in primary care are not in line with those included in this study [22]. In particular, there may be some patients who present with more severe symptoms than those shown here [23]. However, it should be noted that MP29-02 was effective in alleviating symptoms in SAR patients regardless of severity [15].

The safety of intranasal corticosteroids following continuous use for 1 year has been established in patients with PAR [24-26]. However, in general, their effectiveness has been assessed over a shorter duration and versus placebo [27-32]. Direct head-to-head active comparator studies are scarce. One long-term (12-month), evaluator-blind active comparator trial of mometasone versus beclomethasone dipropionate in children aged 6-11 years showed no difference in efficacy between the 2 drugs [33]. The present study is important, not only because it compared 2 active therapies in chronic rhinitis patients for 52 weeks, but also because the results confirmed the superiority of MP29-02 over an intranasal corticosteroid, which currently represents the gold-standard therapy for PAR.

MP29-02 exhibited consistent statistical superiority over FP for more than 6 months, with clinical benefit apparent from the first day of treatment up to 1 year. On average, symptom scores were reduced by 75% following 52 weeks' treatment with MP29-02. This may have a positive impact on patient quality of life and overall treatment adherence. This study shows that MP29-02 is effective for patients with PAR, an important observation when one considers that between 43% and 47% of AR patients have persistent disease in Europe and the United States [9-11]. MP29-02 has also been shown to be well tolerated, with a similar, low incidence of adverse events reported for both MP29-02 and FP groups after 52 weeks of continuous use [17]. Dysgeusia was more common in the MP29-02 group (2.5%) and headache in the FP group (4.3%) [17]. There was also no appreciable reduction in mean (SD)

fasting AM serum cortisol levels from baseline following 12 months' continuous treatment with either MP29-02 (-0.08 [5.5] mcg/dL) or FP (-1.04 [SD 5.0] mcg/dL). There were no nasal mucosal ulcerations or perforations noted in the MP29-02 group, and ocular examination findings were unremarkable [17].

MP29-02 patients experienced almost 1 month's extra symptom-free days a year, and more of them experienced complete and faster symptom reduction than FP patients (71.1% vs 60.3%). Every second MP29-02 patient achieved 100% symptom reduction by Day 7 but it took FP patients 16 days to achieve the same level of response. These patients will have minimal or no functional impairment, with no productivity loss at work or at school. Therefore, MP29-02 is expected to reduce the socioeconomic costs of AR, which are substantial. In Sweden alone the total costs attributed to AR amount to €2.7 billion a year in terms of lost productivity, with a reduction in lost productivity of just 1 day per individual per year, potentially saving €528 million [34]. The advantage of MP29-02 over FP was also noted in the PAR subpopulation, with an 8-day time advantage in terms of achieving 100% symptom reduction in every second patient in the first month. This is important since the time to achieve complete symptom relief is crucial for AR patients [35] and helps maintain adherence to treatment [36]. More than 70% of AR patients already take multiple therapies in an attempt to achieve symptom control [35], with patients expressing a preference for treatments that can provide them with faster and more complete relief [37].

In summary, to our knowledge this is the largest, long-term head-to-head active comparator trial in patients with chronic rhinitis. MP29-02 was faster and more effective than an established first-line intranasal corticosteroid therapy (intranasal FP) in this chronic population. A substantial and clinically relevant complete response (100% reduction in PM rTNSS) was obtained 9 days earlier during the first 28-day treatment interval and in 7 out of 10 patients. These results were mirrored in PAR patients. MP29-02 has previously been shown in a large meta-analysis of almost 3400 patients to be faster and more effective than intranasal FP or AZE in patients with moderate-to-severe SAR [15]. Taken together, these results confirm MP29-02's large therapeutic spectrum, covering not only SAR but also PAR, with consistent superiority over an intranasal corticosteroid.

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Conflicts of Interest

David Price has consultant arrangements with Almiral, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz, and Teva. He or his research team

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■ **Phil Lieberman**

7205 Wolf River Blvd, Germantown
TN 38138-1777, USA
E-mail: phillieberman@hotmail.com