

EXPERT  
REVIEWS

# MP29-02 for the treatment of seasonal allergic rhinitis: a review of clinical pharmacology, efficacy and safety

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This review presents the pharmacology, clinical efficacy and safety of MP29-02 (Dymista®), a unique product for the treatment of allergic rhinitis. Allergic rhinitis is often thought of more as a nuisance than a meaningful medical condition, and the health impact of allergic rhinitis can easily be underestimated. As a result, allergic rhinitis can be undertreated, expectations for relief may not be met, and patients may be left dissatisfied and non-compliant with their medications. MP29-02 is the only currently available allergic rhinitis medication to provide potent early-phase histamine-receptor blocking and long-term anti-inflammatory effects in a single intranasal formulation and delivery system that represents an advance in the therapy of allergic rhinitis, in particular for patients with moderate-to-severe disease.

**KEYWORDS:** allergic rhinitis • azelastine hydrochloride • clinical trials • fluticasone propionate • intranasal • randomized

Allergic rhinitis is a global health problem. As many as 500 million people worldwide are affected by allergic rhinitis [1] and the prevalence in the USA is now estimated at 60–90 million individuals or nearly 30% of the population [2]. For reasons that are not fully understood, the worldwide prevalence of allergic rhinitis continues to increase at a steady rate [3]. The direct healthcare cost of allergic rhinitis in the USA is estimated at approximately US\$7 billion annually [1], with frequently associated co-morbidities such as asthma and sinusitis that can add substantially to the financial burden of the disease [4]. Indirect costs, for example, lost school, lost productivity, etc. may be as high as US\$9.7 billion annually [5].

Despite available therapies, studies continue to identify an unmet need for treatments that provide rapid and sustained relief of allergic rhinitis symptoms [101] and for interventions that improve the overall quality of life for these patients [6]. According to the current US Guidelines, intranasal corticosteroids are

considered the most effective single-class of treatments for this condition and are recommended for use in patients with mild, mild-to-moderate and moderate-to-severe disease [1]. Until the approval of MP29-02, no single treatment to date has been identified as superior in efficacy to intranasal corticosteroids [7]. As a class, intranasal antihistamines are also considered first-line therapy in the USA [1].

In the MP29-02 clinical program, this unique intranasal product was compared directly in head-to-head clinical studies with two active therapies (fluticasone propionate, the most widely prescribed intranasal steroid, and azelastine hydrochloride, the most widely prescribed intranasal antihistamine). The clinical program included the commercially available comparators (in one study), and reformulated comparators in three studies. Both commercially available drugs are recommended as first-line by the Guidelines of the US Joint Task Force (US JTF) on Practice Parameters for Allergy and Immunology [1]. These parameters were developed by the

American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma and Immunology and the Joint Council of Allergy Asthma and Immunology with the goal of improving the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of allergic rhinitis. At this time, no recommendations for the use of MP29-02 are included in either the US JTF [1] or Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines [8], since MP29-02 was not commercially available when the guidance documents were updated in 2008 and 2010, respectively.

In randomized, active- and placebo-controlled clinical trials, MP29-02 demonstrated a consistent and reproducible statistical superiority to both commercially available and re-formulated azelastine and fluticasone propionate for improving nasal symptoms of allergic rhinitis while maintaining a favorable safety profile [9]. The design of these clinical trials is consistent with the criteria needed for positioning in the guidance documents with strong recommendations based on results of randomized controlled trials.

### Overview of the market

Both industry- and professional-sponsored surveys consistently identify the need for allergic rhinitis medications that can provide rapid and more complete relief than currently available therapies [10,101,102]. Between 2006 and 2010, there were four entries into the allergic rhinitis market; however, the physician- and patient-surveys still indicate that no substantial improvement in patient quality of life has been gained. Since 2011, there have been three new nasal spray products introduced into the US market: two intranasal corticosteroids (Zetonna [ciclesonide] and Qnasal [beclomethasone]), both administered in devices with a hydrofluoroalkane propellant, and MP29-02 in an aqueous suspension.

### Introduction to the drug

MP29-02 is the only currently available agent in the class of intranasal therapies for allergic rhinitis to provide H<sub>1</sub>-receptor antagonism and anti-inflammatory effects, thereby providing inhibitory effects on both the early- and late-phase allergic reaction in a single product. The complementary pharmacology of MP29-02 may contribute to the efficacy that was seen when compared with the recognized effective active controls in the MP29-02 clinical studies. In the USA, MP29-02 is indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief. In the EU, MP29-02 is indicated for SAR and perennial allergic rhinitis.

### Chemistry

MP29-02 is a novel intranasal product comprising a unique formulation and delivery system of azelastine hydrochloride and fluticasone propionate in a stable, structured suspension. The azelastine hydrochloride ingredient is as a white, crystalline

powder with high affinity for the histamine H<sub>1</sub> receptor. Fluticasone propionate is a synthetic corticosteroid that has high affinity for the glucocorticoid receptor with multiple anti-inflammatory effects.

MP29-02 is formulated as an aqueous structured suspension administered as a fine mist. A single spray delivers 137 µg (0.1%) of azelastine HCl and 50 µg (0.037%) of fluticasone propionate to the nasal cavity. MP29-02 has a spray volume of 137 µl/spray and the metered spray device allows for a consistent and reproducible delivery of medication. The formulation is isotonic and has a pH of 6. MP29-02 contains glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol (2.5 mg/g), edetate disodium, benzalkonium chloride (0.1 mg/g), polysorbate 80 and purified water as excipients.

### Pharmacokinetics & metabolism

#### Absorption

After a single dose of two sprays per nostril, the mean ( $\pm$  standard deviation) peak plasma level ( $C_{\max}$ ) was  $194.5 \pm 74.4$  pg/ml for azelastine and  $10.3 \pm 3.9$  pg/ml for commercially available fluticasone propionate. The median time to peak exposure ( $t_{\max}$ ) after a single dose was 30 min for azelastine and 1.0 h for fluticasone. The systemic bioavailability of fluticasone from MP29-02-nasal spray was 4 pg/ml higher than with fluticasone propionate alone ( $6.7 \pm 3.2$  pg/ml). Due to the low intranasal bioavailability (<2%), the pharmacokinetics of fluticasone propionate are based on oral administration which showed low bioavailability.

#### Metabolism

Azelastine hydrochloride is metabolized by the P450 enzyme system to desmethylazelastine, an active metabolite. Fluticasone propionate is metabolized to an inactive metabolite (a 17 $\beta$ -carboxylic acid derivative), via the CYP3A4 enzymatic pathway.

### Clinical efficacy

#### MP29-02 clinical trials program (Phase III studies)

The MP29-02 clinical development program was one of the largest drug development programs conducted to date in the field of allergy and immunology (TABLE 1). The clinical studies were carried out according to the guidelines and recommendations of both the US FDA and EMA [103,104]. All efforts were made to ensure the safety of the patients in these studies. Independent Review Board (IRB) approval of the protocols was obtained for all study sites, and, all patients (or guardians) signed a written informed consent form before being treated with any medication. All serious adverse events during the study were followed for a reasonable time until confirmation of a resolution of the event could be obtained.

Following positive results of a small pilot study [11], four key MP29-02 efficacy and safety studies were conducted in which more than 4000 patients 12 years of age and older with moderate-to-severe SAR were enrolled for a 2-week study period (TABLE 1). The design of the four 2-week efficacy and safety studies was similar. All treatments were administered 1 spray per

**Table 1. Overview of MP29-02 studies.**

| Study number | Season conducted        | Sites (n) | Randomized (n) | Comparators                                              |
|--------------|-------------------------|-----------|----------------|----------------------------------------------------------|
| MP-4001      | 2007/2008 Texas Cedar   | 7         | 610            | Commercial Astelin and generic fluticasone               |
| MP-4002      | 2008 spring             | 44        | 832            | Azelastine and fluticasone formulated in MP29-02 vehicle |
| MP-4004      | 2008 fall               | 41        | 779            |                                                          |
| MP-4006      | 2009 spring and fall    | 49        | 1801           |                                                          |
| MP-4000      | 2009–2010 (PAR and VMR) | 37        | 612            | Generic fluticasone                                      |

nostril twice daily and the total daily doses of fluticasone and azelastine were 200 and 548 µg, respectively. The notable distinction was that in the three US registration studies, MP29-02 was compared with a non-commercially available formulation of fluticasone and azelastine, which were reformulated and prepared in the same vehicle and delivery device as MP29-02 to eliminate any confounding effects due to formulation or delivery system [9]. However, in the fourth trial, conducted during Texas Mountain Cedar season [12], MP29-02 was compared with commercially available azelastine (Astelin) and a generic version of fluticasone propionate. The Texas Cedar study was conducted in a specific geographic area of southwest Texas, with a climate suitable to a cedar bush (*Juniperus ashei*) which releases pollen that is highly allergenic. The MP29-02 registration studies represent the first clinical trials to show superior efficacy to both an intranasal antihistamine and an intranasal steroid in a head-to-head study design. In addition, a long-term safety study was conducted in India in which 612 patients with perennial allergic rhinitis or non-allergic vasomotor rhinitis were treated for 1 year with MP29-02 or a generic fluticasone [13].

#### Studies in seasonal allergic rhinitis

In these SAR studies, efficacy was determined by analyzing the change from baseline in a patient-reported measure of symptom severity: the 12-h reflective total nasal symptom score (TNSS) consisting of nasal congestion, rhinorrhea, sneezing and nasal itching. The TNSS is the preferred efficacy variable recognized by the US FDA as evidence of efficacy for allergic rhinitis drugs [103]. To report this efficacy outcome, the patients recorded their nasal symptom scores in diaries twice daily, in the morning and again in the evening each day of the 2-week study. The symptoms were scored on a 4-point scale, with 0 being symptom free; 1: mild symptoms; 2: moderate symptoms and 3: severe symptoms, so that 24 was the maximum daily score.

Other evaluations of efficacy included: i) the change from baseline in the total ocular symptom score (TOSS, made up of watery eyes, itchy eyes and red eyes); ii) time to onset of the drug's action, defined as the first timepoint at which MP29-02 was statistically superior to placebo for change from baseline in TNSS and maintained that superiority during a 4-h assessment period; iii) analysis of the individual nasal symptom scores and iv) an evaluation of the patients' health-related quality of life using the Rhinoconjunctivitis Quality of Life Questionnaire

(RQLQ) consisting of seven domains including: sleep, eye symptoms, nose symptoms, non-nose/eye symptoms, emotional function, daily activities and practical problems [14]. In the 1-year safety and tolerability study, efficacy was evaluated as a secondary end point by the TNSS and RQLQ score.

#### MP29-02 versus commercial comparators (study MP 4001)

##### Primary efficacy end point (TNSS)

In this study [12], all active treatments significantly ( $p < 0.05$ ) improved the TNSS compared with placebo. MP29-02 reduced the TNSS by 5.31 points from a baseline score of 18.64 (TABLE 2). This reduction in symptom severity was statistically significant ( $p < 0.01$ ) compared with both active monotherapies. Improvements in the TNSS with fluticasone, azelastine and placebo were 3.84, 3.25 and 2.20 from baseline scores of 18.12, 17.87 and 18.49, respectively. When the placebo effect, which is consistently high in studies of intranasal therapies for allergic rhinitis and likely derives from beneficial effects of saline irrigation [15,16] is removed from the treatment differences, the improvement in the TNSS with MP29-02 was 90% greater relative to fluticasone (FIGURE 1).

##### Additional efficacy evaluations

MP29-02 significantly ( $p \leq 0.024$ ) improved the individual symptoms of nasal congestion, itchy nose and sneezing compared with azelastine, fluticasone and placebo. Runny nose was significantly ( $p < 0.001$ ) improved compared with azelastine and placebo but not fluticasone. The change from baseline in the RQLQ score met the specified criterion for a clinically important change (0.5 units) in the MP29-02 group compared with placebo but fluticasone and azelastine did not [17]. MP29-02 significantly ( $p < 0.001$ ) improved the TOSS compared with fluticasone and placebo but not azelastine. MP29-02 significantly ( $p < 0.05$ ) improved all individual ocular symptoms compared with azelastine, fluticasone and placebo with the exception of watery eyes when compared with azelastine.

#### MP29-02 versus reformulated comparators (studies MP 4002, MP 4004, MP 4006)

Studies MP 4002 (spring), 4004 (fall) and 4006 (spring and fall) were large multicenter trials conducted during the spring and fall allergy seasons in the USA [9]. All comparators were reformulated in the same vehicle and delivery system as MP29-02 in order to eliminate potential formulation and delivery effects. Sites were

**Table 2. Change from baseline in total nasal symptom score in the intent-to-treat population<sup>†</sup>.**

| Study/treatment      | Patients analyzed (n) | Mean baseline TNSS (SD) <sup>‡</sup> | Change from baseline (SD) | Treatment difference | p-value <sup>§</sup> |
|----------------------|-----------------------|--------------------------------------|---------------------------|----------------------|----------------------|
| <i>Study MP 4001</i> |                       |                                      |                           |                      |                      |
| MP29-02              | 153                   | 18.6 (3.1)                           | −5.3 (5.1)                |                      |                      |
| Fluticasone          | 151                   | 18.1 (3.5)                           | −3.8 (4.8)                | MP29-02-FP           | 0.003                |
| Astelin              | 152                   | 17.9 (3.7)                           | −3.3 (4.2)                | MP29-02-AZE          | <0.001               |
| Placebo              | 150                   | 18.5 (3.5)                           | −2.2 (4.2)                | MP29-02-PLA          | <0.001               |
| <i>Study MP 4002</i> |                       |                                      |                           |                      |                      |
| MP29-02              | 207                   | 18.3 (3.0)                           | −5.6 (5.2)                |                      |                      |
| Fluticasone          | 207                   | 18.2 (3.2)                           | −4.7 (4.7)                | MP29-02-FP           | 0.034                |
| Azelastine           | 208                   | 18.3 (3.5)                           | −4.2 (4.6)                | MP29-02-AZE          | 0.001                |
| Placebo              | 209                   | 18.6 (3.2)                           | −2.9 (3.9)                | MP29-02-PLA          | <0.001               |
| <i>Study MP 4004</i> |                       |                                      |                           |                      |                      |
| MP29-02              | 193                   | 18.3 (3.3)                           | −5.5 (5.2)                |                      |                      |
| Fluticasone          | 188                   | 18.6 (2.9)                           | −4.6 (5.1)                | MP29-02-FP           | 0.038                |
| Azelastine           | 193                   | 18.5 (3.1)                           | −4.5 (4.6)                | MP29-02-AZE          | 0.032                |
| Placebo              | 199                   | 18.2 (3.1)                           | −3.0 (3.9)                | MP29-02-PLA          | <0.001               |
| <i>Study MP 4006</i> |                       |                                      |                           |                      |                      |
| MP29-02              | 448                   | 19.3 (2.4)                           | −5.5 (5.2)                |                      |                      |
| Fluticasone          | 450                   | 19.4 (2.4)                           | −4.9 (4.7)                | MP29-02-FP           | 0.029                |
| Azelastine           | 443                   | 19.5 (2.5)                           | −4.8 (4.8)                | MP29-02-AZE          | 0.016                |
| Placebo              | 448                   | 19.4 (2.4)                           | −3.4 (4.3)                | MP29-02-PLA          | <0.001               |

<sup>†</sup>Total number of patients with available data.

<sup>‡</sup>Least-square mean obtained from analysis of variance (ANOVA) model for Baseline or analysis of covariance (ANCOVA) model for Overall.

<sup>§</sup>p-value for between treatment group comparison, for Baseline, was based on an ANOVA model containing treatment group and site as fixed effects. For Overall, the p-value was based on a repeated measures ANCOVA model containing study day as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate and unspecified, heterogeneous covariance structure.

SD: Standard deviation; TNSS: Total nasal symptom score.

distributed so that all major geographic regions and the prevalent pollens within those regions would be represented.

#### Study MP 4002

##### Primary efficacy end point (TNSS)

In this study, the improvement in TNSS was statistically significant for all active treatment groups (MP29-02, azelastine and fluticasone) compared with placebo ( $p < 0.001$ ). The improvement in the TNSS of 5.61 points from a baseline of 18.27 was statistically significant compared with both fluticasone (4.71 from baseline 18.22;  $p = 0.034$ ) and azelastine (4.23; from baseline 18.26;  $p = 0.001$ ). The improvement in the TNSS with MP29-02 was 50% greater relative to fluticasone (FIGURE 1).

##### Additional efficacy evaluations

MP29-02 significantly ( $p \leq 0.015$ ) improved all individual symptoms of the TNSS compared with placebo and azelastine and significantly improved runny nose compared with fluticasone ( $p = 0.043$ ). Based on a 4-h in-office assessment of the TNSS at

15- and 30-min intervals over a 4-h period after the patients' first dose of medication, MP29-02 had an onset of action within 45 min compared with placebo. Patients treated with MP29-02 had statistical improvement in the RQLQ score compared with placebo ( $p < 0.001$ ) and azelastine ( $p = 0.029$ ). The improvement in the RQLQ score met the criterion of a clinically important difference of 0.5 units in the RQLQ score compared with placebo. MP29-02 significantly ( $p < 0.001$ ) improved the TOSS compared with placebo; there were numerical differences favoring MP29-02 but there were no statistical differences between MP29-02 and the reformulated monotherapy active controls.

#### Study MP 4004

##### Primary efficacy end point (TNSS)

As in study MP 4002, the improvement in the TNSS was statistically significant for all active treatment groups (MP29-02, azelastine and fluticasone) versus placebo ( $p < 0.001$ ). The improvement in the TNSS from baseline in the MP29-02 group

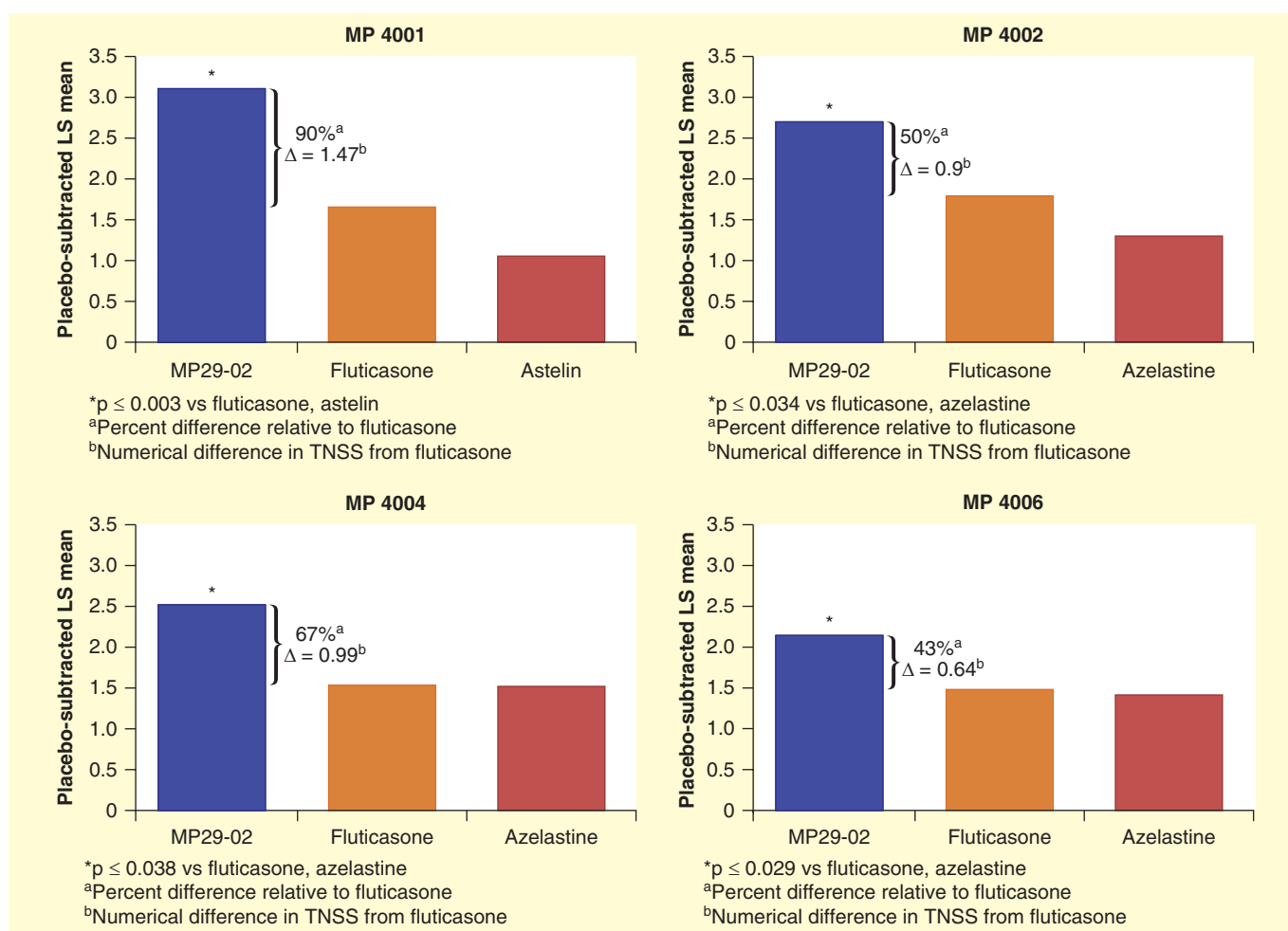


**Figure 1. Placebo-subtracted mean improvement from baseline in the patient-reported 12-h total nasal symptom score comparing MP29-02 with the active monotherapy controls (fluticasone propionate and azelastine).**

LS mean: Least-squares mean; TNSS: Total nasal symptom score.

(5.54 points from a baseline of 18.28) was also statistically significant compared with fluticasone (4.55 from a baseline of 18.64;  $p = 0.038$ ) and azelastine (4.54 from a baseline of 18.54;  $p = 0.032$ ) [18]. The improvement in the TNSS with MP29-02 was 67% greater relative to fluticasone (FIGURE 1).

#### Additional efficacy evaluations

MP29-02 significantly improved all individual symptoms of the TNSS compared with placebo ( $p < 0.001$ ) with significantly greater improvement in nasal congestion ( $p = 0.022$ ) and sneezing ( $p = 0.046$ ) compared with fluticasone. Based on the same 4-h in-office assessment as in MP 4002, MP29-02 had a rapid onset of action within 30 min compared with placebo. Patients treated with MP29-02 had statistical ( $p < 0.001$ ) and clinical ( $>0.5$  units) improvement in the RQLQ score compared with placebo. MP29-02-significantly ( $p < 0.001$ ) improved the TOSS compared with placebo ( $p < 0.001$ ) and fluticasone ( $p = 0.009$ ) and was numerically better than azelastine but the difference was not statistically significant.

#### Study MP 4006

Study MP 4006 was a large multicenter study conducted during both the spring and fall allergy seasons. The results for all primary and secondary efficacy assessments in this study were similar to the results of studies MP 4002 and MP 4004 (FIGURE 1). MP29-02 significantly ( $p \leq 0.029$ ) improved the TNSS compared with both active controls and placebo, significantly ( $p < 0.001$ ) improved all individual symptoms compared with placebo, and demonstrated an onset of action within 30 min. The RQLQ score was statistically ( $p < 0.001$ ) and clinically ( $>0.5$  units) improved compared with placebo, and TOSS was significantly ( $p < 0.001$ ) improved compared with placebo.

#### Safety & tolerability

##### Two-week studies (MP 4001, 4002, 4004 & 4006)

A total of 3411 patients were evaluated for safety and tolerability in the 2-week studies (4002, 4004 and 4006) using the reformulated comparators, and more than 95% of the patients completed the full duration of the study period. In all of the

**Table 3. Most frequently reported adverse events in 2-week efficacy and safety trials<sup>†</sup>.**

| AE        | MP29-02 (n = 853) | Azelastine (n = 851) | Fluticasone (n = 846) | Placebo (n = 861) |
|-----------|-------------------|----------------------|-----------------------|-------------------|
| Dysgeusia | 4%                | 5%                   | 1%                    | 1%                |
| Headache  | 2%                | 2%                   | 2%                    | 1%                |
| Epistaxis | 2%                | 2%                   | 2%                    | 2%                |

<sup>†</sup>Includes three studies with reformulated comparators.

AE: Adverse event.

studies, the incidence and types of adverse events were similar across the active treatment groups (TABLE 3). The majority of all adverse events were considered mild in severity and to be unrelated to treatment. The most frequently reported adverse events with MP29-02 were dysgeusia (4%), headache (2%) and epistaxis (2%). The adverse event profile in study MP 4001, using commercially available comparators, was similar to the profile seen with the studies using reformulated comparators.

The reasons that the patients dropped out of the studies varied widely among the participants; however, there were no dropouts due to serious or unexpected adverse events. One patient in the MP29-02 group, two patients in the fluticasone group and one patient in the placebo group discontinued treatment due to a mild or moderate mucosal erosion; one patient in the placebo group discontinued due to a nasal septal ulceration. There were no mucosal ulcerations or septal perforations in any of the active treatment groups.

#### Long-term safety (MP 4000)

A randomized, open-label, 1-year safety study was conducted to evaluate the potential for adverse events over time, the effects of the intranasal formulation on nasal and ocular parameters and any changes in laboratory values including serum cortisol levels [13]. The study included 612 patients randomized in a 2:1 ratio to treatment with MP29-02 or generic fluticasone. MP29-02 was administered 1 spray per nostril twice daily and fluticasone was administered 2 sprays per nostril once daily. Adverse event reports indicated that the proportion of patients with any type of adverse event was similar for both groups and there was no evidence of an accumulation of adverse events over time or any evidence of late-occurring adverse reactions. The overall rate of adverse events that were considered by the investigators to be related to treatment was 9.4% with MP29-02 and 11.1% with fluticasone. The most frequently occurring adverse event considered related to treatment was dysgeusia (2.5%) with MP29-02 and headache (4.3%) with fluticasone. Less than 3% of the patients in each treatment group discontinued the study due to an adverse event. The completion rate among the patients over the 1-year study period was approximately 75% in each treatment group.

The most frequently reported nasal examination findings during the study were mucosal edema, nasal discharge and mucosal erythema, all consistent with a diagnosis of chronic rhinitis. During the study, the incidence and type of nasal examination findings was similar in the two treatment groups.

In both groups, there were fewer adverse nasal examination findings as the study progressed through 12 months of treatment and importantly, no nasal mucosal ulcerations or septal perforations were observed in either group.

The incidence of abnormal ocular findings on ophthalmologic examination was also low for both groups. There was evidence of a posterior subcapsular cataract in three patients in the MP29-02-group at month 6, all of which were considered unlikely related to study drug. All three patients were discontinued from the study as specified by the protocol. One patient in the MP29-02-group had evidence of moderate glaucoma at month 6 and was discontinued from the study and one patient had a mild subcapsular cataract at month 12, both of which were considered possibly related to study medication. Three patients in the fluticasone group had posterior subcapsular cataracts at the 12-month ophthalmologic examination, two of these were later found to be present at screening (the patients having been randomized in error) and the third was considered unrelated to study medication. The incidence of cataract in this study did not exceed the expected rate over a 1-year period in the general population [19].

There were no unexpected findings on clinical laboratory assessments and there were no dropouts from the studies due to any laboratory abnormality. The mean hematology, chemistry and urinalysis values obtained at months 6 and 12 or upon any early discontinuation from the study were comparable with the values determined at screening and were similar between the two treatment groups. Mean fasting serum cortisol levels were similar between treatment groups at baseline, month 6 and month 12. There was also no appreciable reduction in serum cortisol from baseline following continuous treatment over the 1-year study with either MP29-02 ( $-0.08 \pm 5.5 \mu\text{g/dl}$ ) or fluticasone ( $-1.04 \pm 5.0 \mu\text{g/dl}$ ).

#### Conclusions

One of the notable findings in these studies was that MP29-02, as a single product, improved nasal symptoms of SAR to a substantially greater degree than two active comparators. This significant improvement is noteworthy because there are few direct comparative clinical trials in this therapeutic category. Onset of action with MP29-02 was as early as 30 min. MP29-02 also provided clinically important improvement in the overall RQLQ score and significantly improved the overall TOSS when compared with placebo.

There was no substantial difference in the incidence or types of adverse events with MP29-02 compared with fluticasone or

azelastine alone. The percentage of patients who discontinued the study due to an adverse event was similar in the active treatment groups. In the long-term safety study, the incidence of adverse findings on nasal examinations was greatest at the beginning of the study and lower at the end of the 1-year study period. Overall, there were no safety findings that would preclude the clinical usefulness of MP29-02 in patients with SAR.

### Expert commentary

The typical allergic reaction to allergens begins with an early-phase reaction that takes place within minutes after exposure to pollen. This early phase is characterized by symptoms that are mostly caused by histamine [20]. In many patients, the early phase is followed by a late-phase reaction that is triggered by chemical mediators that are released during the early phase [19]. These late-phase mediators recruit inflammatory cells and other chemical mediators that cause inflammation in the nasal passages and worsening of allergy symptoms. MP29-02 is the only currently available agent in the class of intranasal therapies for allergic rhinitis that provides inhibitory effects on histamine and other mediators of both the early- and late-phase allergic reaction in a single spray administered twice daily. The complementary pharmacology of MP29-02 may contribute to the additive efficacy that was seen when compared with the highly effective active controls in the MP29-02 clinical studies.

MP29-02 improved all individual symptoms of the TNSS and, in a meta-analysis of the three studies using reformulated comparators [9], MP29-02 was significantly better than fluticasone for improving nasal congestion, which is generally accepted as the most troublesome symptom for allergic rhinitis patients [101]. The benefits of intranasal administration of medications for the treatment of allergic rhinitis are well recognized [21,22]. Intranasal treatment of allergic rhinitis has been shown to be superior to any commonly used oral medications [1]. Intranasal administration provides increased concentrations of medication at the site of inflammation, which is accompanied by a significant reduction in the inflammatory mediators [23]. Intranasal administration also minimizes the potential for drug/drug interactions [20], although patients should be cautioned about drinking excessively or using drugs that affect the central nervous system when using MP29-02 [24].

At this time, MP29-02 is approved in the USA for the treatment of SAR in patients 12 years of age and older. MP29-02 is also approved in the European Union for SAR and perennial allergic rhinitis [25]. There are no recommendations for the use of MP29-02 in the current US or International guidance documents for treatment and management of allergic rhinitis. However, based on the most recent US guideline criteria [1], the efficacy and safety data for MP29-02 appear to be consistent with a recommendation for first-line use in patients with mild or moderate disease as well as in patients

with more severe rhinitis. MP29-02, as a single spray administered twice daily, provided greater clinical efficacy than the monotherapy comparators in these studies. In addition, there are no studies that compare MP29-02 with the individual agents used separately.

### Five-year view

Oral H<sub>1</sub> antagonists remain the mainstay for the treatment of allergic rhinitis although they are not as effective as the intranasal therapies for most patients. There does not appear to be significant interest in future development of second-generation antihistamines at this time. Several possibilities exist for the development of products that include a corticosteroid component. The US FDA is currently giving consideration to making one of the older generic intranasal steroids an over-the-counter product. Allergen immunotherapy is an option for patients with severe allergies who do not respond well to symptomatic treatment. Allergen extracts can be administered subcutaneously or orally (sublingual immunotherapy (SLIT)) to induce sustained tolerance to the allergen. SLIT is currently available in Europe but still under investigation in the USA. Depending on the rate of progress through the regulatory approval process, it could be 3–5 years before SLIT is an FDA-approved therapy in the USA. Recombinant DNA technology has delivered the prospect of a new generation of preparations for allergen-specific immunotherapy. Recombinant preparations include only allergens or allergen derivatives (removing unrelated allergens and other irrelevant proteins) and allowing greater standardization, product consistency and uniform concentration of the active pharmaceutical ingredients.

### Information resources

The two guidance documents (the US JTF Practice Parameters and the ARIA Guidelines) for allergic rhinitis referenced in this review contain the most up-to-date evidence-based information for the treatment and management of allergic rhinitis. Websites for the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology are also both excellent resources for information.

### Financial & competing interests disclosure

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## Key issues

- Allergic rhinitis is a global health problem. As many as 500 million people worldwide are affected by allergic rhinitis and its prevalence in the USA is now estimated at 60–90 million individuals or nearly 30% of the population.
- Despite available therapies, studies continue to identify an unmet need for treatments that provide adequate relief of allergic rhinitis symptoms and for interventions that improve health-related quality of life for these patients.
- In the MP29-02 direct comparative clinical trials, MP29-02 demonstrated statistical superiority to both reformulated and commercially available azelastine and fluticasone propionate for improving nasal symptoms of allergic rhinitis.
- In all of the studies, the incidence and types of adverse events were similar across the active treatment groups. MP29-02, as a single spray administered twice daily, provided greater clinical efficacy than the monotherapy comparators in these studies.

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