The journey from unmet need in allergic rhinitis to rationale for, and clinical development of, a new treatment option, MP29-02

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Practice points

- Currently considered first-line allergic rhinitis (AR) therapy provides insufficient symptom relief for many AR patients.
- MP29-02 (Dymista®, Meda AB, Solna, Sweden) is a new intranasal AR therapy, consisting of azelastine hydrochloride (AZE) and fluticasone propionate (FP) in a novel and patented formulation and advanced device.
- It is indicated for the symptomatic relief of moderate/severe seasonal AR and perennial AR in patients 12 years and older where monotherapy with either intranasal antihistamine or intranasal corticosteroid is not considered sufficient.
- MP29-02 is twice as effective as FP and AZE for the relief of nasal and ocular symptoms in seasonal AR patients and provides more complete symptom control days faster.
- Its novel formulation and improved device contribute to this superiority.
- Superiority of MP29-02 over FP was confirmed in patients with chronic rhinitis (i.e., perennial AR or non-AR) and is sustained for 1 year.
- MP29-02 is well tolerated both short and long term.
- MP29-02 should be considered first-line therapy for all moderate/severe AR patients in consultation with their clinicians, since current first-line therapy may be considered inadequate for the majority of them.

The aim of allergic rhinitis treatment is to control symptoms, but currently considered first-line therapy provides suboptimal symptom relief for many patients. MP29-02 is a new treatment for allergic rhinitis, developed to fill this unmet need. Moderate/severe seasonal allergic rhinitis patients treated with MP29-02 experienced twice the nasal and ocular symptom relief as those treated with azelastine or fluticasone propionate. The effect was consistent across seasons, symptoms and by severity. MP29-02 delivered substantial and complete response in more patients and many days faster than fluticasone propionate or azelastine. Its efficacy advantage over fluticasone propionate extended beyond 14 days, up to 1 year, in chronic rhinitis patients. MP29-02 was well tolerated, both short and long term, and may change the way allergic rhinitis is managed, for the better.

Keywords: allergic rhinitis • azelastine • Dymista® • fluticasone propionate • MP29-02

Background

Unmet need in allergic rhinitis: inadequacy of current therapy

Allergic rhinitis (AR) is a debilitating allergic condition affecting the upper airways, with over 600 million sufferers worldwide, a figure that is both underestimated and increasing [1]. Over 80 years have passed since the discovery of antihistamines, and 50 years since the first use of intranasal steroids (INSs), but both physician and patient surveys show no substantial improvement in patients' quality of life or symptom burden [2,3], highlighting an unmet need in the treat-

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ment and control of this prevalent and chronic disease. When uncontrolled, AR becomes the dominant factor in patients' lives, affecting social life, school, sleep, work and even mental health [4]. Despite this, it is often overlooked as a disease of significant importance. AR also has a significant economic burden. A Swedish study estimated the annual national cost of AR to be €2.7 billion in terms of lost productivity alone, primarily due to absenteeism [5].

Aim of treatment

The aim of any treatment is adequate control of symptoms [1]. However, the concept of control in AR is very much in its infancy compared with other chronic diseases, such as asthma. Although tools for assessing control of AR do exist [6,7], there is no single definition of 'disease control,' as the variables and thresholds necessary to define relief differ between tools [8].

While the reflective total nasal symptom score (rTNSS), comprising nasal symptom scores for congestion, itch, rhinorrhea and sneezing, is currently the gold standard parameter when assessing and comparing efficacy in clinical trials, control cut-offs have yet to be validated. Barnes and colleagues have suggested a minimal clinically important difference of 0.55 in the rTNSS [9]. Others have defined control as ≤1 point remaining in each of the four nasal symptom scores of the rTNSS [10,11]. The visual analog scale is a simple, quantitative tool, which has been used mainly in AR trials to assess severity [12,13], and more recently to assess clinically relevant difference (i.e., change of 23 mm) [14]. Both of these approaches will enable an assessment of disease control.

Allergic rhinitis landscape is challenging

In contrast to the almost static picture that has been seen (until recently) on the AR treatment front, the AR landscape is undergoing some changes. The majority of patients present to their doctor with moderate/severe disease [15–17] and most have persistent disease [18]. This may be due, in part, to the fact that most patients are polysensitized [4,19], making allergen avoidance particularly challenging and an almost redundant step in AR management. Current therapy provides insufficient symptom relief for many moderate/severe patients [17,20,21].

New phenotypes of AR have been defined. For example, it is estimated that 50–70% of patients suffer from mixed rhinitis, which is a combination of nonallergic AR and AR [22]. Treatment-resistant phenotypes, such as severe chronic upper airway disease have also recently been described [23]. These factors (and many others) confound AR treatment, making AR a disease that is difficult to control.

How is allergic rhinitis currently managed?

The majority of AR patients attending primary or specialist care are undergoing treatment [17,24]. Patients with mild disease primarily use oral antihistamines (OAH). Intranasal antihistamines (IAH) tend to be used for those patients with more bothersome symptoms, while INSs are recommended as first-line for those with moderate/severe persistent disease [1,25]. Expectation from treatment is high [26], but most patients are dissatisfied with their AR treatment [27]. Furthermore, multiple therapy usage is common in AR ranging from 43.3 to 74.4% [15,16,24,28,29], and although this seems a logical response to single treatment failure, the majority of published data assert that the use of multiple therapies does not yield the additive effect that would be expected [30–33].

Pathologic gaps with current treatment

The reasons why patients continue to experience symptoms are manifold and complex, and include deficits in AR pathologic coverage. No AR medication class covers all AR pathologic pathways, optimally relieving all symptoms associated with this disease. These gaps in treatment are as much a function of the limited symptomatic coverage by the individual therapies themselves as the multiple disease processes that they serve to inhibit.

OAH antagonize the H_1 histamine receptor on neurons, smooth muscle cells and the vascular endothelium. Their mode-of-action is to relieve the histamine-mediated symptoms of the acute phase. Where OAH fail to be optimally effective is in controlling nasal congestion, which is, most likely, a consequence of it being modulated by multiple mediators. Oral antihistamines are recommended in preference to IAH in the guidelines [25]. However, this recommendation is based on patients' preference and another treatment choice is reasonable (e.g., in the case of somnolence). Published studies have shown that intranasally administered antihistamines are more effective than OAH [34,35], particularly for ocular symptom relief, most likely due to a broader mode-of-action, including antihistamine, antileukotriene, anti-inflammatory and mast cell-stabilizing effects, as well as localized delivery to the nasal mucosa [36,37].

INSs are currently recommended as first-line therapy for the symptomatic treatment of AR [1,25,38]. Their mode-of-action is broad, mitigating late-phase cellular infiltration, and relieving all of the nasal (and some of the ocular) symptoms of AR. INSs have some shortcomings, in that they do not prevent mast cell degranulation or possess antihistamine, or antileukotriene activity. INSs are more effective than OAH in achieving nasal symptom relief [33], and more effective than

IAH in relieving rhinorrhea and nasal congestion, but not ocular symptoms [39]. Accordingly, it is clear that, until recently, use of one single medication class cannot provide optimal relief from the array of AR symptoms.

Introducing MP29-02 (Dymista®)

MP29-02 (Dymista®; Meda AB, Solna, Sweden) is a new class of treatment for AR, developed to fill the unmet medical need in AR. It consists of azelastine hydrochloride (AZE) and fluticasone propionate (FP); two potent drugs from different medication classes with complementary effects), as well as a novel and patented formulation and an advanced device (vs currently marketed steroid sprays) [40]. MP29-02, therefore, has antihistaminic, mast cell-stabilizing, antileukotriene and anti-inflammatory properties, comprising all the pharmacological principles foreseen in the Allergic Rhinitis and its Impact on Asthma treatment algorithm in a single puff [1,41]. It has been described as the drug of choice for AR [10,11] and a real advancement in the treatment of this chronic disease [42]. The evidence to support these statements is reviewed here.

Proof of concept

A proof-of-concept study investigated the concomitant use of AZE and FP, one after the other, versus monotherapy with either agent [43]. One hundred and fifty one patients with moderate/severe seasonal AR (SAR) were randomized in a double-dummy design to AZE (two sprays/nostril two-times a day [b.i.d.])+ placebo (two sprays/nostril once a day [q.d.]), FP (two sprays/nostril q.d.) + placebo (two sprays/nostril b.i.d.) or AZE (two sprays/nostril b.i.d.) + FP (two sprays/nostril q.d.) for 2 weeks. Change from baseline in 12-h rTNSS (AM [morning] + PM [evening]) was assessed primarily. All three groups demonstrated improvement from baseline TNSS after 2 weeks ($p < 0.001$). The FP + AZE group improved 37.9%, the FP group improved 27.1% and the AZE group improved 24.8%. AZE + FP was more effective ($p < 0.05$) than either monotherapy in reducing rTNSS, as well as the individual nasal symptoms of itch and congestion, and it was well tolerated [43].

However, this study, while proving that AZE and FP made good AR therapeutic partners, had several limitations [43]. Administration of FP q.d., but AZE b.i.d. and incorporation of a 15–30-min interval between doses is complicated. This sequential administration, different dosing schedules and significant time-lag between intranasal applications would have a significant negative compliance effect in a real-life setting. Coadministration of AZE and FP leads to increased run-off [44], which would also be problematic in the monotherapy arms due to application of placebo nasal spray. The absence of a placebo arm, which would need to consist of placebo two sprays/nostril AM + PM plus two sprays/nostril AM (effectively amounting to nasal rinsing) makes cross comparison with other studies difficult and assessment of treatment effect impossible.

Why was MP29-02 created?

Having established proof of the superior efficacy of intranasal AZE plus FP versus the monoproducts, MP29-02 was created to improve compliance; maximize convenience for patients; simplify dosing; reduce the volume sprayed up the nose; improve drug deposition within the nasal mucosa; and to optimize retention by reducing run-off (posteriorly and anteriorly). Secondly, as other AR treatments were providing suboptimal pathologic and symptomatic coverage [15,17,20], a need for a more effective treatment option was apparent. Finally, considering the well-known link between AR and asthma [1], and the contribution of formulation and device to the efficacy of topically administered medications in the latter [45–47], it was considered likely that formulating two potent AR treatments in a novel and patented formulation, in an improved device and delivered as a single spray would provide efficacy exceeding that of the two active principles.

Review of the clinical evidence

The clinical evidence for MP29-02 comes from a large clinical development program [10,11,48–50]. Its efficacy has been assessed and compared with current first-line therapies in four 14-day SAR trials [10,11] and one 52-week trial including 612 patients with chronic rhinitis (i.e., perennial AR [n = 424] or nonallergic AR [n = 188]) [49,50].

Meta-analysis

Acknowledging the importance of formulation and device on the efficacy of topically administered medications, three of the SAR studies (MP4002 [NCT00651118], MP4004 [NCT00740792] and MP4006 [NCT00883168]), compared MP29-02 to AZE and FP monotherapy made up in the MP29-02 formulation and delivered using the MP29-02 device [11]. In total, 3398 patients were randomized in an equal ratio into these three 14-day, double-blind, placebo-controlled trials to MP29-02, AZE, FP or placebo. All treatments were administered as one spray/nostril b.i.d. The total daily doses of AZE and FP were 548 and 200 µg, respectively. The US FDA requested this comparison to negate the effect of formulation and device and, in doing so, to establish the true pharmacological difference between MP29-02 and the aforementioned first-line therapies. All studies had the same active

comparators (i.e., noncommercially available AZE and FP in the same formulation and device as MP29-02), the same study design, similar inclusion/exclusion criteria and the same end points, and so the data were presented both for the individual studies and pooled as a meta-analysis [11].

Patients included in these studies were 12 years of age or older, had a minimum 2-year history of SAR, significant current clinical rhinitis symptomatology and a positive skin prick test to relevant pollen. Additionally, all patients had moderate/severe SAR defined by a rTNSS of at least eight out of 12 with a congestion score of 2 or 3 during screening. Subjects were excluded if they had any nasal condition or disease, 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.

In all studies, MP29-02 provided significantly superior overall nasal symptom relief than either AZE or FP (Figure 1) [11]. The meta-analysis found that over a 14-day period, MP29-02 reduced mean rTNSS from baseline (-5.7 [standard deviation (SD): 5.3]), significantly more than FP (-5.1 [SD: 4.9], $p < 0.001$), AZE (-4.4 [SD: 4.8], $p < 0.001$) or placebo (-3.0 [SD: 4.2], $p < 0.001$) [11]. The authors calculated the effects beyond first-line therapy with change from baseline (Δ placebo) given as -2.3 for MP29-02, -1.6 for FP and -1.4 for AZE, a relative difference of 30% versus FP and 39% versus AZE (Figure 1). Onset of action was rapid at 30 min. This clinical superiority was observed for each individual nasal symptom, from the first day of assessment, was sustained over the course of the study and was apparent regardless of severity [11]. More patients treated with MP29-02 achieved a 50% reduction from baseline in rTNSS and complete/near-to-complete symptom control (i.e., ≤1 point remaining in each nasal symptom score of the rTNSS) and days faster than either monotherapy [11]. MP29-02 also reduced patients' overall ocular symptom burden, reducing the mean reflective total ocular symptom score (rTOSS, comprising itching, redness and watering) from baseline by -3.2 points (SD: 4.0), significantly more than FP (-2.8 [SD: 3.6]; $p = 0.003$) or placebo (-1.8 [SD: 3.4]; $p < 0.001$) [11].

MP29-02 versus marketed comparators

Nasal symptoms

The treatment difference of MP29-02 versus marketed comparators was greater than seen in the meta-analysis, most likely due to the contribution of MP29-02's formulation and device to its efficacy [10,11]. In this study (MP4001 [NCT00660517]), 610 patients were randomized to treatment with MP29-02, a commercially-available FP or AZE nasal spray, or placebo. Dose and dosing frequency were the same as for the other SAR trials. Patient's baseline rTNSS scores ranged from 18.08 to 18.84. MP29-02-treated patients reported a least square mean reduction of 5.31 points compared with reductions of 3.84, 3.25 and 2.20 for patients treated with FP ($p = 0.0031$), AZE ($p < 0.0001$) and placebo ($p < 0.0001$), respectively, giving effects beyond first-line therapy (Δ placebo) of -3.11 for MP29-02, -1.64 for FP and -1.05 for AZE, a relative difference of 47% versus FP and 66% versus AZE (Figure 2A). The superiority of MP29-02 over AZE and FP was noted from first day of assessment and sustained for 14 days (Figure 2B). MP29-02 was significantly superior to both FP and AZE in alleviating patients' overall nasal symptoms regardless of symptom severity (Figure 3), and each of the nasal symptoms of congestion (54% to FP [$p = 0.0034$]; 70% to AZE [$p = 0.0001$]), nasal itch (44% to FP [$p = 0.0240$], 56% to AZE [$p = 0.0033$]), rhinorrhea (32% to FP [$p = 0.0678$]; 65% to AZE [$p < 0.0001$]) and sneezing (49% to FP [$p = 0.0009$]; 61% to AZE [$p < 0.0001$]) [10].

Ocular symptoms

As the presence of ocular symptoms was not a prerequisite for entry to this study, rTOSS (change from baseline) was assessed *post-hoc* in those patients with a baseline rTOSS of ≥8. MP29-02 delivered significant relief from ocular symptoms in this group (baseline range: 13.22–13.77), reducing rTOSS by -3.89 points versus -2.47, -2.96 and -1.65 in the FP ($p = 0.0012$), AZE ($p = 0.0456$) and placebo groups ($p < 0.0001$), respectively [10], a relative difference of 63% to FP and 42% to AZE (Figure 3). Relief from all ocular symptoms contributed to this superiority, with a relative difference to FP and AZE of 67% ($p = 0.0001$) and 44% ($p = 0.0127$), respectively for the most bothersome symptom of ocular itching [10].

Rhinitis symptom complex

In order to assess these data in arguably a more clinically relevant way, the authors conducted several other *post-hoc* analyses [10]. These *post-hoc* analyses were defined *a priori* by an independent panel of experts without having access to the data. Change from baseline in the reflective total of 7 symptom scores (rT7SS) was analyzed to assess efficacy in providing relief from the entire symptom complex (i.e., both nasal and ocular symptoms) as it is rare that AR patients only present with one or the other. The rT7SS incorporates nasal congestion, itching, rhinorrhea and sneezing as well as ocular itching, redness and watering in a single score. Baseline rT7SS scores ranged from 29.88 to 31.15.

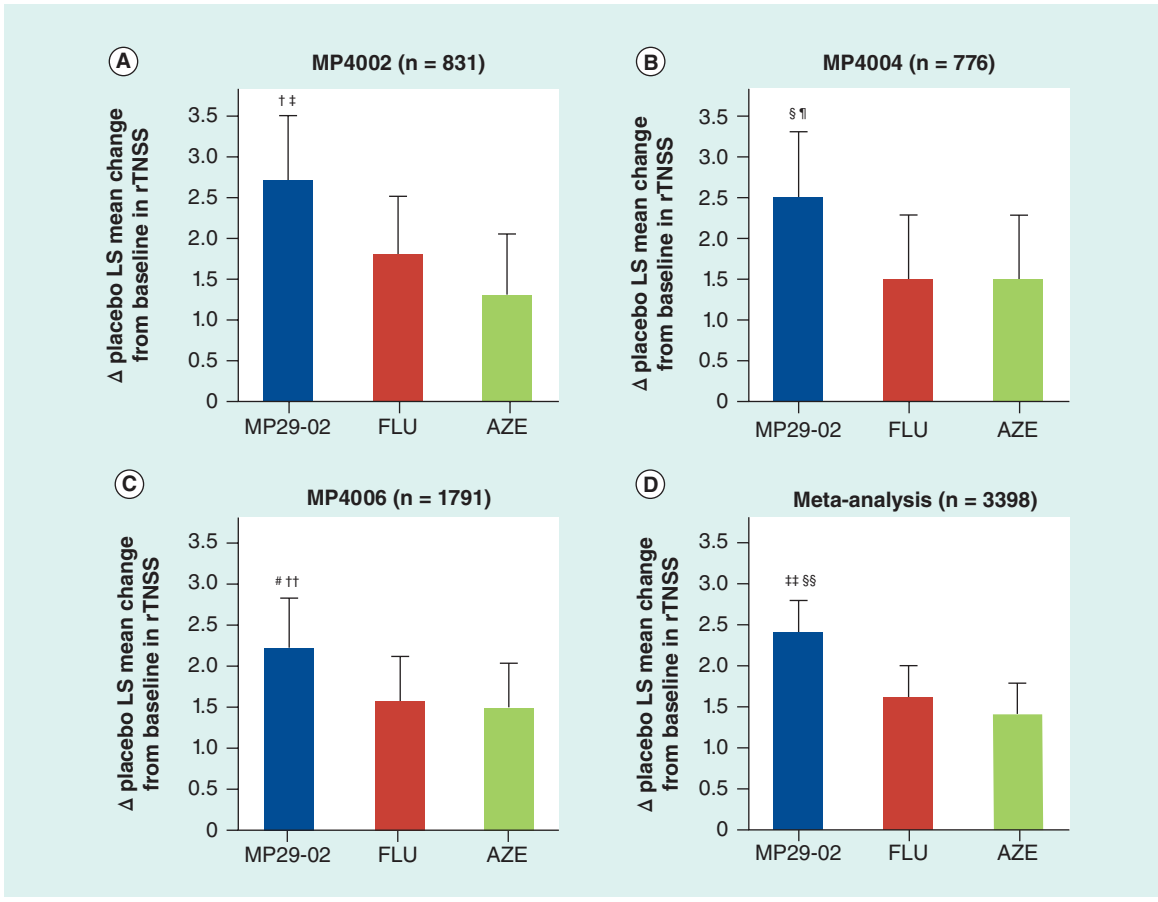

Figure 1. Effect of MP29-02, fluticasone propionate and azelastine on overall reflective total nasal symptom score (morning plus evening) in patients with moderate/severe seasonal allergic rhinitis. Data are presented as LS mean change from baseline derived by means of Analysis of Covariance (ANCOVA) minus placebo. The precision of these estimates is indicted by the upper bounds of the respective 95% CIs. **(A)** Study MP4002: n = 831. **(B)** Study MP4004: n = 776. **(C)** Study MP4006: n = 1791. **(D)** Meta-analysis: n = 3393.
†p = 0.034 vs FP.
‡p = 0.001 vs AZE.
§p = 0.038 vs FP.
¶p = 0.032 vs AZE.
#p = 0.029 vs FP.
††p = 0.016 vs AZE.
‡‡p < 0.001 vs FP.
§§p < 0.001 vs AZE.
AZE: Azelastine; FP: Fluticasone propionate (FLU); LS: Least squares.
Reproduced with permission from [11].

MP29-02 was twice as effective as either FP or AZE in relieving both nasal and ocular symptoms with patients reporting a 8.74-point reduction in rT7SS compared with -6.05, -5.83 and -3.55 for FP (p = 0.0013), AZE (p = 0.0004) and placebo (p < 0.0001), respectively, a relative difference of 52% to FP and 56% to AZE (Figure 4) [10].

Responder sensitivity analyses

Responder analyses were also carried out *post-hoc*, with response cut-offs defined from 30 to 90% rTNSS reduction from baseline [10]. Following 14 days of treatment, 49.1% of MP29-02 patients (one in two) first experienced a 50% reduction in their nasal symptoms compared with 38.2, 37.4 and 28.3% of FP, AZE and placebo patients, respectively. More importantly, this substantial improvement occurred days faster for those patients treated with MP29-02, up to 6 days faster than FP (p = 0.0284) and AZE (p = 0.0223) and up to 10 days ahead of placebo (p < 0.0001) (Figure 5A) [10].

The responder sensitivity analysis defined a level of response not achievable with available first-line therapy, a response ceiling. For the ≥60% rTNSS reduction or higher, only MP29-02 could be statistically differenti-

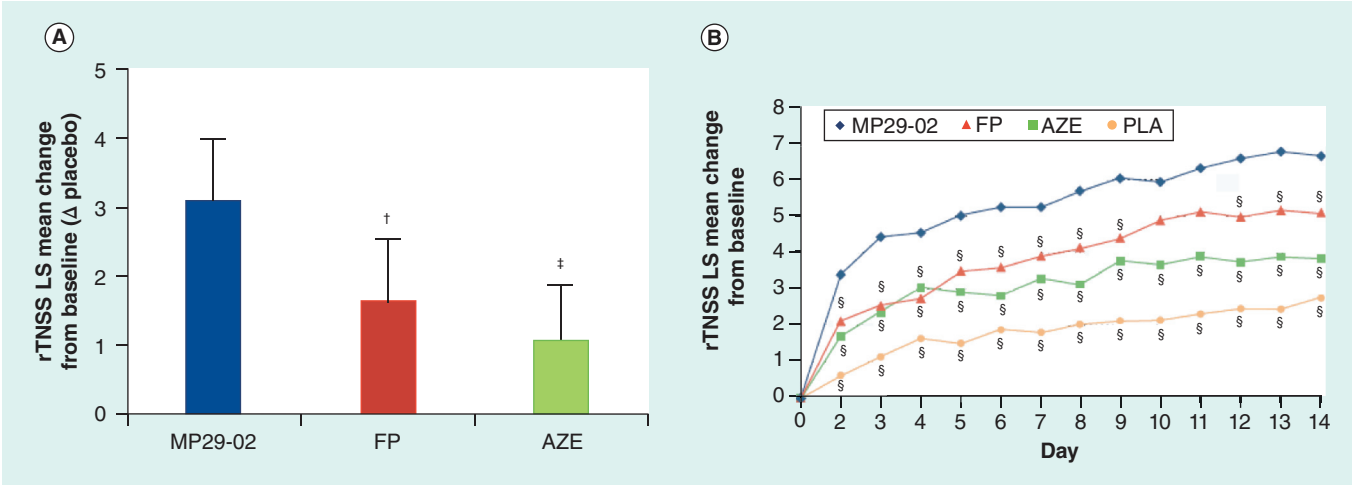

Figure 2. Effect of MP29-02, fluticasone propionate and azelastine hydrochloride on reflective total nasal symptom score (AM + PM). (A) Change from baseline in rTNSS over the entire 14-day period. The precision of these estimates is indicated by the upper bounds of the respective 95% CIs. MP29-02: n = 153; AZE: n = 152; FP: n = 151. **(B)** Change from baseline in rTNSS by treatment day. MP29-02: n = 153; AZE: n = 152; FP: n = 151, PLA: n = 151.
†p = 0.0031 vs MP29-02.
‡p < 0.0001 vs MP29-02.
§p ≤ 0.04 vs MP29-02.
AZE: Azelastine; FP: Fluticasone propionate; LS: Least squares; PLA: Placebo; rTNSS: Reflective total nasal symptom score.
Reproduced with permission from [10]; Meltzer E, Ratner P, Bachert C *et al.* Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int. Arch. Allergy Immunol.* 161(4), 369–377 (2013); S. Karger AG, Basel, Germany.

ated from placebo. One in three MP29-02 patients (35.6%) achieved this response, and did so up to 7 and 8 days faster than FP (p = 0.0496) and AZE (p = 0.0404), respectively. FP and AZE could not be statistically differentiated from placebo for this or higher responses, which may explain why moderate/severe AR patients still complain of bothersome symptoms despite Allergic Rhinitis and its Impact on Asthma-guided treatment [1,23]. More MP29-02 patients (one in six) also achieved complete/near-to-complete symptom relief versus first-line monotherapy and days faster (Figure 5B). Neither FP nor AZE differentiated from placebo in this regard [10].

Predominant symptom

Patients were also characterized by predominant symptoms based on their maximum individual symptom scores at baseline [10]. This was considered a clinically relevant analysis since patients frequently present with a predominant or particularly bothersome symptom. Taking nasal congestion as an example, nasal congestion-predominant patients treated with MP29-02 experienced a 5.64-point reduction in their rTNSS compared with -3.93 for FP (p = 0.0093) and -3.28 for AZE (p < 0.0001), a relative difference of 57 and 79%, respectively (Figure 6A). Similarly, nasal congestion-predominant patients treated with MP29-02 experienced a 1.41-point reduction in their nasal congestion score, significantly more than either FP (-0.90; p = 0.00018) or AZE (-0.83; p = 0.0001), corresponding to a relative difference of 71% to FP and 81% to AZE (Figure 6B) [10].

Long-term efficacy

An open-label, randomized, parallel-group study of MP29-02 versus marketed FP nasal spray was carried out in chronic rhinitis patients [49,50]. The primary aim was to assess long-term safety, but efficacy was assessed secondarily. The study consisted of 612 patients aged 12–80 years with perennial AR (n = 424) or nonallergic AR (n = 188). After a 7-day screening period, these patients were randomized to either MP29-02 (one spray/nostril b.i.d.) or FP nasal spray (two sprays/nostril q.d.) for 52 weeks. Efficacy was assessed using change from baseline in PM rTNSS [49]. Although the open-label design of this study was not ideal for efficacy assessment, it was quite pragmatic, closely mimicking real-world behavior, including minimal clinic visits. Notwithstanding the limitations of study design, patients receiving MP29-02 showed a rapid and significant reduction in PM rTNSS compared with FP from day 1 with treatment difference sustained for up to 52 weeks [49]. Currently, MP29-02 is indicated for the symptomatic relief of moderate-to-severe SAR and perennial AR in patients 12 years and older where monotherapy with either IAH or INS is not considered sufficient [40].

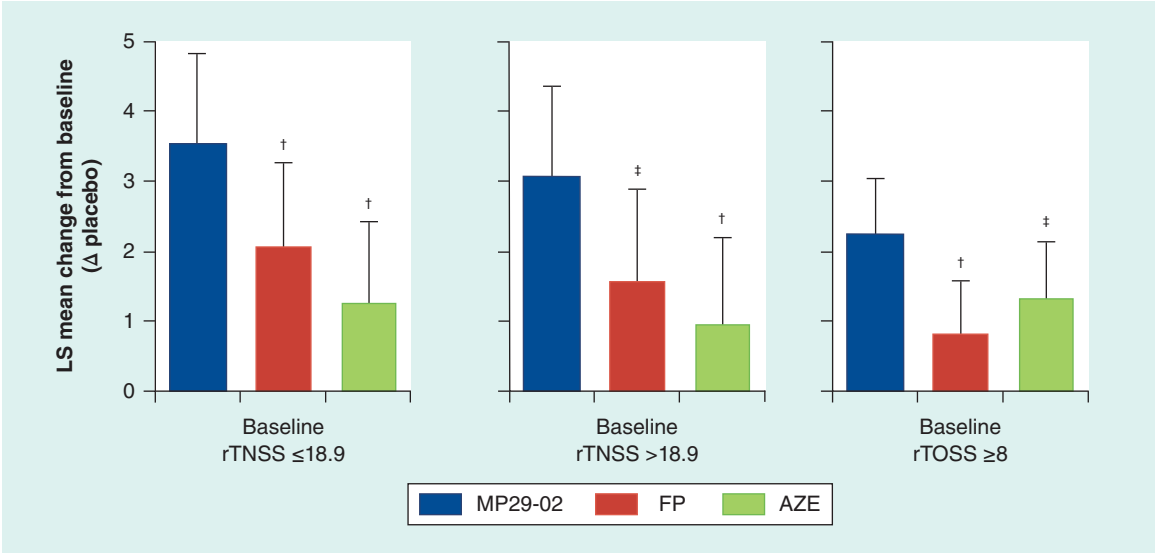

Figure 3. Effect of MP29-02, fluticasone propionate and azelastine on reflective total nasal symptom score and reflective total ocular symptom score over the entire 14-day treatment period according to symptom severity at baseline. The precision of these estimates is indicated by the upper bounds of the respective CIs. rTNSS ≤18.9: MP29-02: n = 76, FP: n = 87, AZE: n = 84; rTNSS >18.9: MP29-02: n = 77, FP: n = 64, AZE: n = 68; rTOSS ≥8: MP29-02: n = 128, FP: n = 125, AZE: n = 118.
†p ≤ 0.0188 vs MP29-02.
‡p ≤ 0.0456 vs MP29-02.
AZE: Azelastine; FP: Fluticasone propionate; LS: Least squares; rTNSS: Reflective total nasal symptom score; rTOSS: Reflective total ocular symptom score.
Reproduced with permission from [10]; Meltzer E, Ratner P, Bachert C *et al*. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int. Arch. Allergy Immunol.* 161(4), 369–377 (2013); S. Karger AG, Basel, Germany.

Place in therapy

Patient selection/therapeutic indication

Most patients attending their doctor have moderate/severe AR [15–17], the vast majority of patients are treated or have previously been treated [24] and most remain symptomatic on treatment (even those on multiple therapies) [17,20]. These patients should be prescribed MP29-02. As clinicians, we should consider the benefits of obtaining AR symptom control reliably and quickly with MP29-02, rather than risk a graded series of monotherapy treatment failures and return visits for step up. MP29-02 should improve patient compliance. It comprises two different drug classes with complementary effects, benefiting from antihistamine, mast cell-stabilizing, antileukotriene and anti-inflammatory properties. It is made up in a novel formulation and delivered using an improved device and in a single spray. All of these properties ensure that MP29-02 antagonizes both the early- and late-phase allergic response, providing rapid symptom relief and a sustained effect, and also that it is convenient to use. MP29-02 has been unequivocally and safely proven to exceed the efficacy of an INS regardless of season, symptom, severity or patient type [10,11,49] and has also demonstrated superior efficacy over IAH and INS in treating ocular symptoms [10,11], which are the most detrimental to patient's quality of life [17,51,52]. Given this evidence, MP29-02 should be considered first-line therapy for all moderate/severe AR patients in consultation with their clinicians, since current first-line therapy may be considered inadequate for the majority of them.

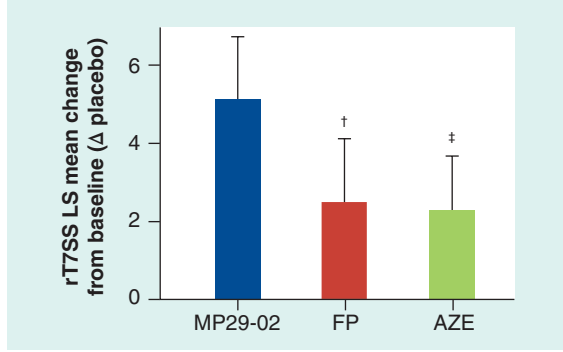

Figure 4. Effect of MP29-02, fluticasone propionate and azelastine on reflective total of seven symptom scores (AM + PM) change from baseline over the entire 14-day period. The precision of these estimates is indicated by the upper bounds of the respective 95% CIs. MP29-02: n = 153; AZE: n = 152; FP: n = 151.
†p = 0.0013 vs MP29-02.
‡p = 0.0004 vs MP29-02.
AZE: Azelastine; FP: Fluticasone propionate; LS: Least squares; rT7SS: Reflective total of 7 symptom scores.
Data taken from Supplementary Table 6 [10].

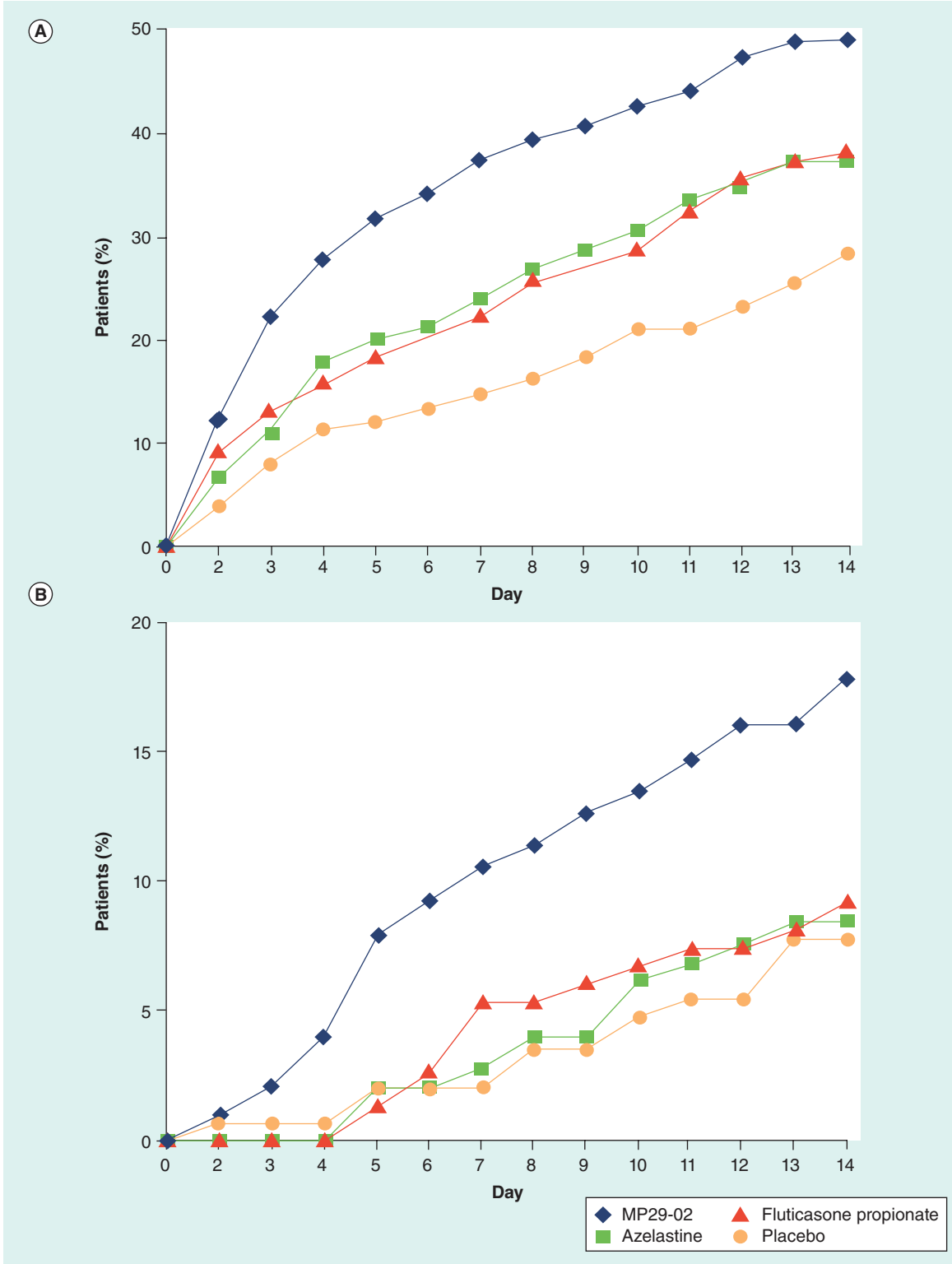

Figure 5. Time to response curves following treatment for 14 days with MP29-02 (blue), fluticasone propionate (red), azelastine (green) and placebo (yellow). **(A)** 50% response; **(B)** reflective total nasal symptom score ≤1 point remaining for each nasal symptom.
Reproduced with permission from [10]; Meltzer E, Ratner P, Bachert C *et al*. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int. Arch. Allergy Immunol.* 161(4), 369–377 (2013); S. Karger AG, Basel, Germany.

Dosing/administration/formulation

MP29-02 should be administered as one spray/nostril twice daily, in the morning and evening (approximately 12 h apart). The total daily dose of AZE and FP is 548 and 200 µg, respectively [40]. As with all topical medication, how it is formulated and delivered have important consequences for clinical efficacy [45–47]. In this regard, MP29-02 shows relevant advantages over existing intranasal therapies. The difference in efficacy results between studies where the effect of formulation and device has been eliminated (i.e., MP4002, MP4004 and MP4006) [11] and those where it has not (i.e., MP4001 and MP4000) [10,49] point to a contribution of formulation and device to MP29-02's superiority over currently considered first-line therapy. MP29-02 is delivered in a wider spray angle, has a larger volume/spray, with a smaller droplet size and a lower viscosity compared with the most commonly prescribed INS sprays [53]. A pharmacokinetic analysis further distinguished MP29-02 as a treatment class of its own by proving that FP within MP29-02 has a different pharmacokinetic profile than other commercial FP formulations [53]; FP was noted to have increased bioavailability in MP29-02 compared with a commercial FP formulation, which the authors hypothesized was due to increased nasal distribution and/or increased contact area for absorption. Increased concentrations of FP delivered within MP29-02 were in the pg range so would have no negative impact on safety.

Tolerability/adverse events

AZE and FP both individually are well tolerated [54–56]. The results of MP29-02's clinical development program proved that these drugs together (in concert with MP29-02's formulation and device) make good therapeutic partners and that MP29-02 is equally well tolerated for both short-term, episodic treatment of SAR [10,11] and long-term treatment of chronic rhinitis [50]. Incidence of treatment-related adverse events for the active groups was low in all studies, in many cases not exceeding placebo, and the vast majority were classed as 'mild' and were transitory. Dysgeusia (2.1–7.2%), headache (0.5–2.6%) and epistaxis (1.0–3.9%) were the most commonly reported treatment-related adverse events for MP29-02 [10–11,50] and are in line with those previously reported in studies of AZE and FP monotherapy. There is no evidence for hypothalamic pituitary adrenal axis suppression [50]. In fact, the plasma FP concentrations measured following a single dose of MP29-02 were at least eight-times lower than those required to suppress hypothalamic pituitary adrenal axis function [57–59] and are not considered clinically meaningful [60].

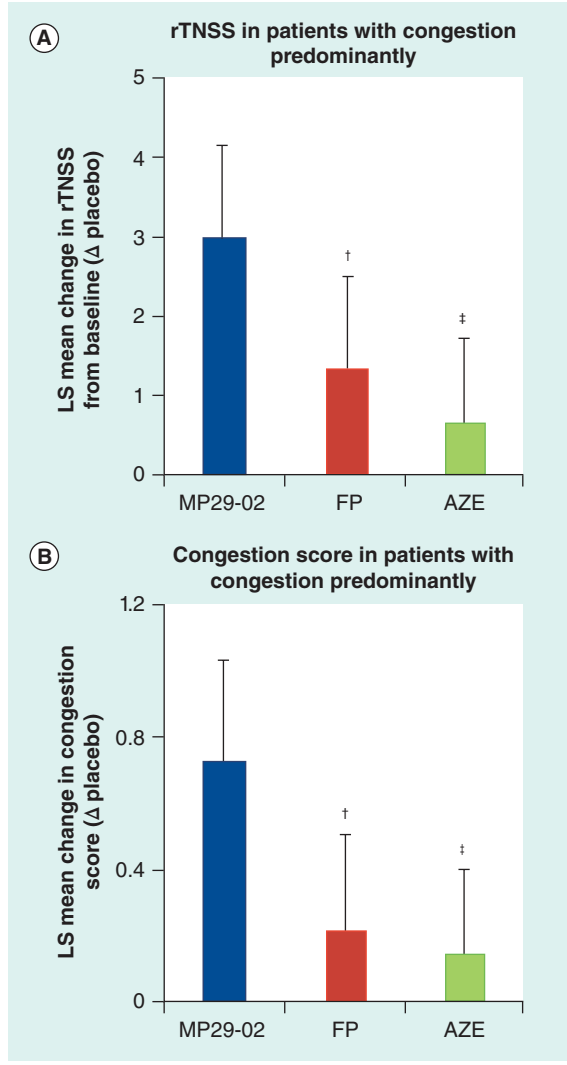

Figure 6. Effect of MP29-02, fluticasone propionate or azelastine over the entire 14-day treatment period in nasal congestion-predominant patients. (A) Effect of MP29-02, FP or AZE over the entire 14-day treatment on rTNSS. **(B)** Effect of MP29-02, FP or AZE over the entire 14-day treatment on nasal congestion score in those patients with nasal congestion predominantly at baseline. The precision of these estimates is indicated by the upper bounds of the respective 95% CIs.
MP29-02: n = 98, FP: n = 84, AZE: n = 93.
†$p \leq 0.0093$ vs MP29-02.
‡$p \leq 0.0001$ vs MP29-02.
AZE: Azelastine; FP: Fluticasone propionate; LS: Least squares; rTNSS: Reflective total nasal symptom score.
Reproduced with permission from [10]; Meltzer E, Ratner P, Bachert C *et al.* Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int. Arch. Allergy Immunol.* 161(4), 369–377 (2013); S. Karger AG, Basel, Germany.

Conclusion

The results of MP29-02's large clinical development program confirm it as a major advancement in the treatment of AR. MP29-02 should change the lives

of AR patients for the better, providing superior, more rapid and more complete relief from their symptoms than previously experienced. Incorporation of an INS and an IAH in a novel formulation and delivered in single spray contribute to MP29-02's broad symptom coverage and rapid effect, which should improve compliance and eliminate the need for additional therapies. M29-02 represents a new class of AR treatment and should simplify AR management.

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