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EXPERT OPINION

Advances in pharmacotherapy for the treatment of allergic rhinitis; MP29-02 (a novel formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) fills the gaps

Jean Bousquet[†], Claus Bachert, Jonathan Bernstein, G Walter Canonica, Warner Carr, Ronald Dahl, Pascal Demoly, Philippe Devillier, Peter Hellings, Wytske Fokkens, Ludger Klimek, Phil Lieberman, Eli Meltzer, David Price, Dermot Ryan & Ulrich Wahn

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Introduction: Effective pharmacologic treatment exists for most patients suffering from allergic rhinitis (AR). However, both in clinical trials and in real-life studies, many patients are dissatisfied with treatment. Physicians often use multiple therapies, in an attempt to improve symptom control, often with limited evidence of success. Novel treatment options are needed and must consider unmet medical needs.

Areas covered: This article reviews the clinical data for a new AR treatment. MP29-02 (Dymista®, Meda, Solna, Sweden) contains azelastine hydrochloride (AZE) and fluticasone propionate (FP), in a novel formulation and delivered in an improved device as a single nasal spray. It has shown superior efficacy in AR patients than either commercially available AZE or FP monotherapy for both nasal and ocular symptom relief, regardless of disease severity. MP29-02 also provided more effective and rapid symptom relief than either AZE or FP monotherapy delivered in the MP29-02 formulation and device. However, the effect was less than that observed versus commercial comparators, suggesting the impact of formulation and device on clinical efficacy.

Expert opinion: MP29-02 simplifies AR management, surpassing the efficacy of gold standard treatment, intranasal corticosteroids (INS), for the first time. It is indicated for the treatment of moderate-to-severe seasonal allergic rhinitis and perennial allergic rhinitis when monotherapy with either intranasal antihistamine or INS is NOT considered sufficient. Most patients present with moderate/severe disease, with evidence of current or previous treatment insufficiency. MP29-02 should be the treatment of choice for these patients.

Keywords: allergic rhinitis, ARIA, azelastine, fluticasone, MP29-02, treatment

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Allergic rhinitis (AR) is a global health problem that causes major illness and disability worldwide [1]. It affects social life, school and work [2]. Patients with AR are also more likely to suffer from co-morbidities affecting the upper (e.g., chronic rhinosinusitis) and lower (e.g., asthma) airways [3], a consequence of the one airway one

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Box 1. Drug summary.

Drug name	Dymista, a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system
Phase (for indication under discussion)	Phase III
Indication (specific to discussion)	Relief of symptoms of moderate-to-severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient
Pharmacology description/mechanism of action	Mechanism of action studies currently ongoing
Route of administration	Intranasal spray
Pivotal trials	NCT00660517 [67]; NCT00651118 [69]; NCT00740792 [69]; NCT00883168 [69]

disease or global airway disease concept [2,4,5]. The economic impact of AR is often underestimated, because the indirect costs are substantial [2].

Current treatments for AR provide insufficient control for many patients. Both in clinical trials and in real-life studies, many patients are dissatisfied with treatment [6,7] and experience breakthrough symptoms [8]. Physicians often use multiple therapies, sequentially and/or concomitantly [8-13], in an attempt to achieve quicker and more profound nasal and ocular symptom relief [14,15], despite evidence of failure of this approach in the literature [16,17].

Novel treatment options are needed and must consider unmet medical needs, demonstrating faster and more complete symptom control in direct comparison studies versus currently available first-line AR therapy (e.g., intranasal corticosteroids [INS] or H_1-antihistamines). They should also show superior efficacy in patients regardless of disease severity, and for those patients who present with a particularly bothersome or predominant symptom.

2. Phenotypes of patients with AR

Describing AR in terms of chronicity of symptoms is one method of classification. The classification of AR was revised by Allergic Rhinitis and its Impact on Asthma (ARIA) in 2001 introducing the terms 'intermittent' and 'persistent' [18]. Previously, AR was classified based on the time and type of exposure and symptoms, into seasonal, perennial and occupational [19]. However, this classification is not entirely satisfactory since most patients are polysensitized [20], in certain areas pollens and moulds are perennial allergens [21] whereas house dust mites show seasonal trends [22]. In 2008, the US rhinitis practice parameters [23] proposed the term 'episodic' AR. This term has not been validated, although it might refer to 'intermittent'.

AR can also be classified according to severity or response to treatment. Severity is linked with the disease process, control is the degree to which therapy goals are met and responsiveness is the ease with which control is achieved by therapy. The concepts of severity and control have been largely developed for asthma guidelines [24]. The uniform definition of severe asthma presented to WHO [25] used an approach derived from the National Asthma Education Prevention Programme – Expert Panel Report 3 guidelines [26]. This approach has been used for all allergic diseases including AR [10]. Severity may fluctuate from year to year in relation to allergen exposure and many other factors. Most patients seeking medical care present with moderate-to-severe AR [27-30].

Severe Chronic Upper Airway Disease (SCUAD), proposed by a joint ARIA-Global Allergy and Asthma European Network-World Allergy Organization expert group, defines patients whose symptoms are insufficiently controlled despite adequate (i.e., effective, safe and acceptable) pharmacologic treatment based on guidelines. These patients have an impaired quality of life (QoL), affecting social functioning, sleep and school/work performance [31]. This concept of patient-oriented definition of severity has now been extended to all allergic diseases [32]. Of those who do not present, most have mild disease and self-medicate.

Symptoms of AR include sneezing, rhinorrhea, nasal obstruction and pruritus. In pollen allergic patients, bothersome ocular symptoms, such as redness, itching and tearing, commonly occur in the presence of nasal symptoms. The most bothersome symptoms of allergic rhinoconjunctivitis are ocular ones and are often difficult to control [11,33].

Stratification of patients by phenotypes may help to characterize progression of the disease and response to treatment. Heterogeneity also exists within each dimension of the disease (e.g., eosinophils and asthma severity) [34], across diseases (e.g., eosinophils in asthma) and in relation to co-morbidities [35]. Phenotypes may change over time, possibly driven by allergic, infectious or other triggers.

3. Pharmacologic treatment of AR

There are many treatment options for AR, but there is a lack of coverage of all symptoms by a single medication (**Table 1**). All guidelines agree that INS are the most effective monotherapy for AR [18,23,36,37]. Several INS exist, but the vast majority of head-to-head comparisons did not show a significant difference between any of them, except in timing of administration [38-41]. INS do not, however, fully control patients as shown in clinical trials and real-life studies. INS have some efficacy on ocular symptoms. The mechanisms behind this process are not fully understood but have been observed in multiple clinical development programs. Fluticasone furoate (FF) [42] and mometasone furoate [43] have

Table 1. Treatment options for allergic rhinitis.

Symptom	H_1-AH	Intranasal H_1-AH	INS	Nasal anticholinergic	Decongestant	Mast cell stabilizer	LTRA	INS + oral AH
Nasal congestion	+	+	++	–	+	+/–	+/–	++
Nasal pruritus	+	+	+	–	–	+	+	+
Rhinorrhea	+	+	++	+	–	+	+	++
Sneezing	+	+	++	–	–	+	+	++
Ocular itching	+	++	+	–	–	–	+	+
Ocular watering	+	++	+	–	–	–	+	+
Ocular redness	+	++	+	–	–	–	+	+

Modified from ARIA [2].

AH: Antihistamine; INS: Intranasal corticosteroid; LTRA: Leukotriene receptor antagonist.

consistent ocular effects in seasonal AR (SAR) studies. However, intraocular olopatadine was found to be more effective than intranasal FF in this regard [44]. Oral corticosteroids (short course) are recommended in AR patients with moderate-to-severe nasal and/or ocular symptoms that are not controlled with other treatments [36].

Oral H_1-antihistamines are effective for all forms of AR, but their effect is less pronounced than INS [18,23,36,37,45]. They are primarily used to treat symptoms of the early phase, with less obvious effects noted for congestion relief. The newer second-generation antihistamines (like cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, etc.) have less sedating side effects than the first-generation ones, as they do not cross the blood–brain barrier and should be used in preference [36].

Intranasal H_1-antihistamines represent another treatment option. Although there are different opinions in guidelines [18,23,36,37], azelastine (AZE) is a potent drug [46]. In a large placebo-controlled study in mountain cedar allergic patients, fluticasone propionate (FP) was superior to AZE in alleviating rhinorrhea, but AZE showed comparable efficacy for all other nasal and ocular symptoms [47]. Moreover, more AZE patients exhibited a 50% reduction in reflective total ocular symptom score (rTOSS) by day 14 versus FP, and days faster [47].

Leukotriene receptor antagonists (e.g., montelukast) are effective in the treatment of AR with similar efficacy (at best) to oral H_1-antihistamines [18,23,36,37]. They are well tolerated [48], and recommended for the treatment of SAR and in preschool children with persistent AR [36]. It has not been confirmed whether their addition to other pharmacological treatment could improve disease control. However, they may be useful for use in AR patients with asthma comorbidity [49]. They are not recommended for use in adults with persistent disease due to their limited efficacy and high cost [36]. Anticholinergic agents such as ipratropium bromide are particularly effective in reducing rhinorrhea [50], but they have no effect on the other nasal symptoms associated with AR. Nasal decongestants (e.g., pseudoephedrine) are very effective for nasal congestion relief and have a fast onset of action [51]. However, side effects are common when given orally (e.g., headache, hypertension, insomnia, etc.) with a risk of rhinitis medicamentosa and rebound congestion when given intranasally over a prolonged period of time [52] Intranasal decongestants are recommend in adults with severe nasal obstruction for no longer than 5 days, and preferably shorter than that [36]. Regular use of oral decongestants is not recommended. Mast cell stabilizers (e.g., intranasal cromones) inhibit both the early and late phases of the allergic response, but not as potently as INS or antihistamines and require multi-daily dosing regimen. The need for administration four times daily is likely to reduce patient adherence and reduce efficacy.

The majority of published data confirm that addition of oral therapy to intranasal therapy does not translate into clinical benefit in terms of improved symptom relief. Adding an oral H_1-antihistamine to an INS has been investigated, but no additional efficacy above that achieved with INS monotherapy was apparent [16,53].

Specific immunotherapy (SIT) is the only disease-modifying treatment, but is time-consuming (should be administered over several years) and expensive. Allergen immunotherapy can be administered sublingually (SLIT, with drops or tablets) or subcutaneously (SCIT, with no evidence of superiority of one over the other) [54]. SIT improves the clinical symptoms of AR, with long-lasting persistent effects after discontinuation [55]. It may also prevent new allergen sensitizations [56] and reduce the risk of developing asthma [57]. Potential adverse reactions are still a concern, particularly for SCIT which should only be administered under medical supervision. ARIA acknowledges that local adverse events are relatively frequent (~ 35%) with SLIT and that alternative choices may be equally reasonable depending upon patients' values and preferences [36].

4. Unmet needs in the management of AR

Impairment of QoL is seen in adults and in children with AR [2]. Patients may also suffer from sleep disorders, emotional problems as well as impairment in activities and social functioning. Poorly controlled symptoms of AR may contribute to sleep loss or disturbance [58]. Moreover, H_1-antihistamines

with sedative properties can increase functional disturbances in AR patients.

Another unmet need in AR is that control and severity need to be better delineated. SCUAD has defined uncontrolled AR patients pharmacologically [32], but a common language of AR control does not exist. Measures of AR control include symptom scores, visual analogue scale (VAS) score [13,27], QoL [59] or scores with several items [60,61]. A common control language is needed for AR, to enable effective communication between healthcare providers and patients in order to better manage this disease.

However, insufficiency of current first-line treatment options is perhaps the greatest unmet need in AR. The majority of patients visiting their physician have moderate-to-severe disease, and most of these continue to experience symptoms while treated, even those on multiple therapies [13,62]. It is thought that around 20% of patients with severe persistent rhinitis are not controlled, and some have severe symptoms, particularly due to associated eye symptoms [31]. Novel treatments are needed, which are more effective and faster than current ones.

5. MP29-02

A new treatment option for AR, MP29-02 (Dymista®; Meda, Solna, Sweden) (**Box 1**) has recently been developed, with the aim of overcoming many of the shortcomings observed with current first-line AR treatments as described above. MP29-02 draws on the best from both worlds, incorporating an antihistamine (AZE) and an INS (FP) in a novel intranasal formulation, delivered in a single device. It thus has the potential for broad AR pathologic coverage, and it is also likely that the formulation of MP29-02 is superior to other marketed intranasal sprays (**Figure 1**). The deposition in the nasal cavity with MP29-02 appears to be influenced by several distinct properties including a larger spray volume with MP29-02 (i.e., 137 vs 100 µl; **Figure 1**), a finer droplet size distribution and lower viscosity compared with marketed FP comparator products. These formulation characteristics may contribute to spray pattern improvements, including superior dispersion, larger spray pattern diameter and larger total area covered as compared with a marketed FP product [63]. These formulation and device characteristics may be associated with pharmacokinetic (PK) differences and improved efficacy.

5.1 Pharmacokinetics

Two PK studies were conducted to determine whether there were any drug–drug interactions between the active components of MP29-02, and to evaluate the bioavailability of these components versus commercially available formulations of AZE and FP [63]. Both studies had a randomized, 3-period, 6-sequence 3-treatment crossover design and were conducted in healthy subjects after a single dose (2 sprays/nostril twice a day).

No interactions of AZE and FP were found in the MP29-02 formulation. AZE bioavailability was similar for the MP29-02 formulation and marketed AZE (Astelin®). However, FP bioavailability differed between the marketed and MP29-02-FP-mono formulations. Maximum and total FP exposure was higher for the MP29-02-FP-mono compared with marketed FP indicating a difference due to formulation (**Table 2**). This unique PK profile of the FP component within the MP29-02 formulation suggests that MP29-02 is more than just two molecules in the same device [63]. FP levels were generally very low with all investigational products and unlikely to suggest clinically meaningful differences concerning systemic safety.

5.2 Efficacy and safety in SAR

While there is no shortage of comparisons of active AR treatments to placebo in the literature (as such studies are required for registration), there is a paucity of direct comparisons of active treatments. This deficit represents a serious gap in our knowledge on the comparative efficacy of various AR treatments. The situation should be rectified with head-to-head studies of good design and with efficacy assessed using both traditional (to facilitate cross-study comparison) and more clinically relevant end points.

5.2.1 Head-to-head comparisons with commercially available single components

Many clinical trials of seasonal allergic rhinoconjunctivitis use the mountain cedar (*Juniperus ashei*) season as a model. Thirty-seven clinical trials during 18 pollen seasons were analyzed [64]: 1 trial evaluated onset of allergy, 8 trials evaluated immunotherapy and 28 trials were pharmacotherapy studies. Mountain cedar allergy was found to present a dependable and durable model of allergic rhinoconjunctivitis. Although mountain cedar allergy, like other Cupressaceae, may have some specific patterns [65], the analysis of these trials indicates that results obtained in mountain cedar studies can be extended to other pollen allergens.

A study in patients with mountain cedar allergy (TRIAL REGISTRATION: MP4001 clinicaltrials.gov Identifier: NCT00660517) compared MP29-02 with commercially available AZE nasal spray and FP nasal spray, two first-line AR therapies. This pivotal randomized trial had a 14-day, multicenter, double-blind design [66].

After a 7-day placebo lead-in, 610 patients, ≥ 12 years old, with moderate-to-severe nasal symptoms were randomized to treatment with nasal sprays of: i) commercially available AZE (137 µg/spray), ii) commercially available FP (50 µg/spray), iii) MP29-02 (137 µg/50 µg per spray) or iv) placebo. All treatments were given as one spray per nostril twice daily [66].

The primary efficacy variable was the change from baseline in reflective total nasal symptom score (rTNSS; range, 0 – 24) over the treatment period, consisting of nasal congestion, runny nose, itchy nose and sneezing measured in the morning and the evening. Secondary efficacy variables were: i) 12-h reflective individual nasal symptom scores; ii) onset of action; iii) 12-h rTOSS, including itchy eyes, watery eyes and red

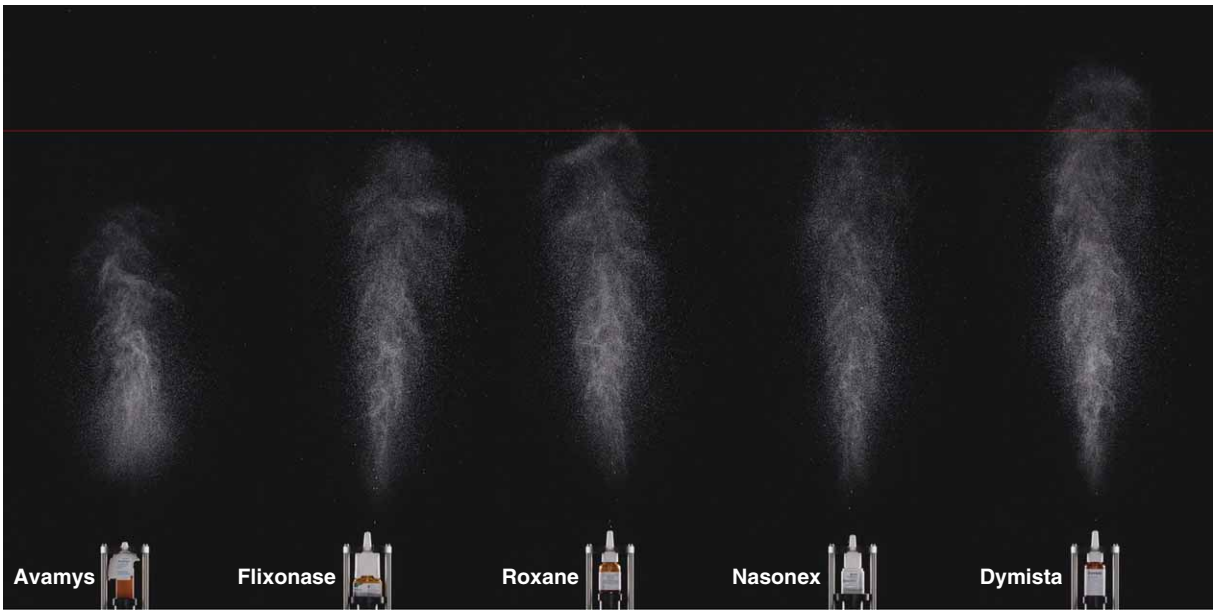

Figure 1. Spray plume comparison of MP29-02 and marketed intranasal corticosteroid formulations. From left to right: fluticasone furoate (Avamys, GSK), fluticasone propionate (Flixonase, GSK), fluticasone propionate (Roxane Laboratories), mometasone furoate (Nasonex, SP), MP29-02 (Dymista, Meda).

Table 2. Pharmacokinetic parameters following single-dose administration of MP29-02, MP29-02-FP (mono) and marketed FP in healthy volunteers (n = 19).

Parameter (PP)	MP29-02 (n = 19)	MP29-02-FP mono* (n = 19)	FP BI‡ (n = 19)
AUC (0 – t_{last}) (pg/ml h)	70.1 ± 36.5	74.0 ± 40.4	41.5 ± 19.5
T_{max} (h)	0.98 ± 0.50	0.99 ± 0.49	1.13 ± 0.59
C_{max} (pg/ml)	10.3 ± 3.9	11.7 ± 5.9	6.7 ± 3.2
$t_{1/2}$ (h)§	13.6 ± 7.5	14.6 ± 5.6	20.6 ± 21.9
CL/F (l/h)§	2534.7 ± 1313.3	2512.3 ± 1097.3	3935.4 ± 1997.4

Data are presented as mean ± standard deviation.

*MP29-02 formulation without azelastine.

‡Boehringer-Ingelheim/Roaxane laboratories.

§n = 16.

Data taken from [63].

AUC (0 – t_{last}): Area under the curve from 0 to last time point; C_{max}: Maximum plasma concentration; CL/F: Clearance; FP: Fluticasone propionate; $t_{1/2}$: Half-life; T_{max}: Time to maximum plasma concentration; PP: Per protocol.

eyes and iv) the Rhinoconjunctivitis QoL Questionnaire (RQLQ) overall score [59]. *Post hoc* analyses were further carried out in the same study [67], in line with European Medicines Agency (EMA) suggestions to consider responder analysis [68].

All three active groups were statistically superior ($p \leq 0.02$) to placebo, and MP29-02 was statistically superior to both active comparators in providing overall nasal symptom relief [66,67]. From a baseline rTNSS of 18.08 – 18.68, MP29-02 reduced the rTNSS by an average of –5.31 versus –3.84 for FP ($p = 0.0031$), –3.25 for AZE ($p < 0.0001$) and –2.20 for placebo ($p < 0.0001$), a relative difference of 47 and 66% to FP and AZE, respectively [67]. MP29-02's effect was observed rapidly from the first day of treatment and sustained for the study duration. A uniform reduction in each of the four individual symptoms of the rTNSS contributed to MP29-02's superior effect. For example, MP29-02-provided significantly greater relief from nasal congestion (–1.24), the most bothersome nasal symptom reported by AR patients, compared with FP (–0.86; $p = 0.0034$), AZE (–0.75; $p = 0.0001$) and placebo (–0.54; $p < 0.0001$), with a relative difference of 54% to FP and 70% to AZE [67]. The improved nasal symptom relief over AZE and FP afforded

by MP29-02 occurred irrespective of severity or patients' predominant symptom [67].

Patients treated with MP29-02 also experienced greater relief from their overall ocular symptoms with a relative improvement of 58% to FP and 35% to AZE. A reduction in each of the individual ocular symptoms contributed to this effect [67]. This was particularly evident for ocular itching, the symptom which has the greatest negative impact on patient QoL [11]; with MP29-02 reducing this symptom score by –1.23 compared with –0.70 for FP ($p = 0.0001$), –0.88 for AZE ($p = 0.0127$) and –0.44 for placebo ($p < 0.0001$), equating to a relative difference of 67 and 44% to FP and AZE, respectively [67]. When considering both nasal and ocular symptoms together, bearing in mind that patients frequently present with symptoms from both origins, MP29-02 patients experienced significantly greater relief (–8.74) than those on FP (–6.05; $p = 0.0013$) or AZE (–5.83; $p = 0.0004$), with a relative difference of 52 and 56%, respectively, making MP29-02 twice as effective as either first-line therapy in providing relief from the entire rhinitis symptom complex (**Figure 2A**) [67]. MP29-02 was effective days before AZE or FP (**Figure 2B**).

By day 14, all active treatments produced a statistically significant ($p < 0.001$) improvement from baseline, both for the overall RQLQ score and each of the individual RQLQ domain scores. However, a clinically meaningful change (i.e., 0.5 units) compared with placebo was only achieved in the MP29-02 group [66].

This study shows that MP29-02 nasal spray provided statistically significant improvement in the rTNSS, rTOSS and the entire rhinitis symptom complex (rT7SS), and at least additive clinical benefit compared with either FP or AZE alone in patients with moderate-to-severe SAR.

5.2.2 *Head-to-head comparisons with single components in the same formulation*

Three studies investigated the efficacy of intranasal MP29-02-with AZE and FP using the same formulation and device [69]. Three thousand three hundred and ninety-eight patients (≥ 12 years old) with moderate-to-severe SAR were enrolled into three multi-center, randomized, double-blind, placebo- and active-controlled, parallel-group trials (MP4002 [NCT00651118], MP4004 [NCT00740792] and MP4006 [NCT00883168]). Each trial was conducted for 14 days during different allergy seasons (spring, autumn, spring/summer). The primary efficacy variable was the sum of the morning and evening change from baseline in rTNSS (range, 0 – 24) over the treatment period. Other outcomes for the meta-analysis included efficacy according to disease severity. The design and inclusion criteria of the three studies were comparable, so they were analyzed in a meta-analysis [69].

MP29-02 reduced the mean rTNSS from baseline (–5.7 [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]; $p < 0.001$), with a relative difference of 30% to FP and 39% to AZE [69] (**Figure 3**). This benefit was observed from the first day of assessment, with uniform improvement noted in each individual nasal symptom, even in those patients with the most severe disease. Patients treated with MP29-02 also experienced superior relief from their ocular symptoms than those treated with FP alone [69].

These studies showed that MP29-02 provided superior symptomatic relief to FP and AZE in patients with moderate-to-severe AR, even when the effect of formulation and device had been eliminated; providing sound evidence for a purely pharmacological benefit over either monotherapy. The data suggest that FP and AZE have at least additive effects in AR in keeping with the additive effects of inhaled formoterol and budesonide in the lower airway [70], including the very fast non-genomic effects of corticosteroids [71].

5.2.3 *Short-term safety*

Safety in all four SAR studies was excellent (**Table 3**). The incidence of all treatment-related adverse events (TRAE) was low in all active treatment groups, with a similar incidence to placebo in many instances. Dysgeusia was most commonly reported in the MP29-02 (2.1 – 7.2%) and AZE groups (2.0 – 7.2%), and headache the most frequently reported TRAE in the FP groups (1.3 – 3.9%) [61,65]. The vast majority of all TRAES were mild and transitory in nature.

5.2.4 *Safety (and efficacy) in chronic rhinitis*

In another study (MP4000), the long-term safety of MP29-02-was evaluated in 12- to 80-year-old patients (n = 612) with chronic rhinitis (e.g., perennial AR [PAR; n = 424] or non-AR [n = 188]) [72]. In this randomized, open-label, active-controlled, parallel-group study, patients were treated in a 2:1 ratio with either MP29-02 (n = 404 patients; one spray per nostril twice daily) or FP (n = 207 patients; two sprays per nostril once daily). Safety and tolerability assessments were conducted at regular intervals during the 1-year study.

Efficacy was assessed as secondary end point in this safety study by change from baseline in the 12-h PM rTNSS score assessed over the 52-week treatment period at 4-weekly intervals, and *post hoc* by time to response analysis and assessment of symptom-free days. Furthermore, clinical investigations were performed after 1, 3, 6, 9 and 12 months [72].

The results showed that the efficacy of MP29-02 was sustained over the 1-year duration of the study. MP29-02-treated patients with chronic rhinitis (including the PAR subpopulation) experienced greater relief from their nasal symptoms than those patients treated with the marketed FP comparator, with benefit observed from day 1 and consistent statistical significance achieved up to and including week 28 [72]. Treatment difference was sustained for 52 weeks, representing on average a 75% reduction in symptom score in the MP29-02-group. Moreover, more chronic rhinitis patients treated with MP29-02 (7 out of 10 patients) first achieved complete symptom relief (i.e., 100% rTNSS reduction from baseline) in the first month, and achieved this response a median of

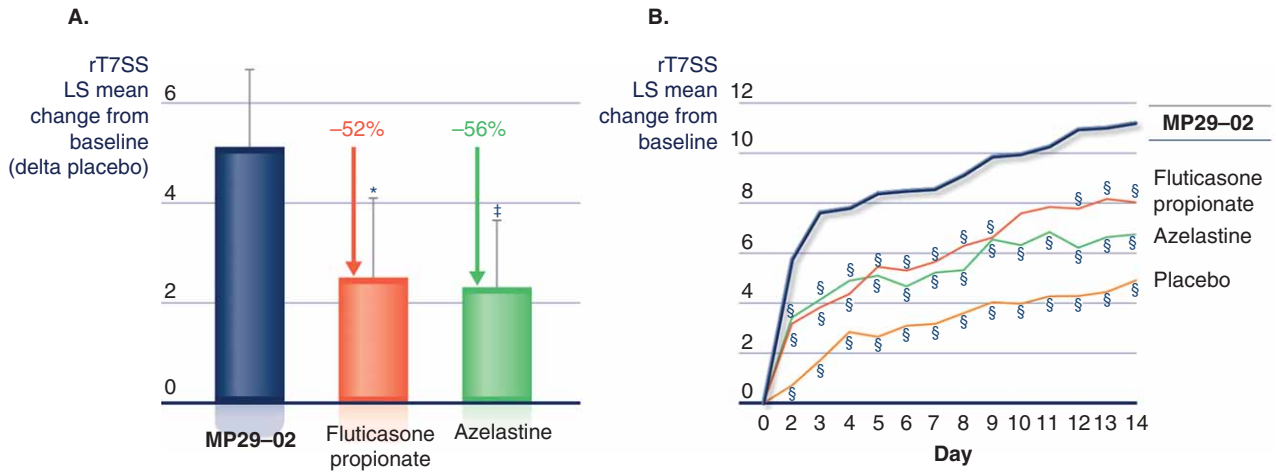

Figure 2. Effect of MP29-02, fluticasone propionate (FP) and azelastine (AZE) on reflective total of 7 symptom score (rT7SS [nasal congestion, itching, rhinorrhea, sneezing, ocular itching, watering and redness]; AM & PM) **(A)** over the entire 14-day period and **(B)** by treatment day. MP29-02 provides twice the symptom relief of FP or AZE. Superiority is noted from the first day of assessment and sustained for 14 days. Study MP4001: MP29-02 n = 153; AZE: n = 152; FP: n = 151; PLA: n = 151. **(A)** The precision of these estimates is indicated by the upper bounds of the respective 95% confidence intervals. *p = 0.0013 vs MP29-02; ‡p = 0.0004 vs MP29-02. **(B)** §p ≤ 0.0336 vs MP29-02.

A. Data taken from [67].

B. Reprinted with permission from [67].

9 days earlier than those patients treated with the marketed FP comparator (8 days earlier in PAR subpopulation) (**Figure 4A and B**) [68]. In addition, chronic rhinitis patients taking MP29-02 experienced approximately 1 month more symptom-free days (25.9 more days [or 8.4% more days; p = 0.0005]) than those on FP treatment, with a similar pattern noted in the PAR subpopulation (23.9 more symptom-free days than FP; 7.3% more; p = 0.0122) [72].

MP29-02 was well-tolerated long-term. The proportion of subjects with a treatment-emergent or treatment-related adverse event was similarly low for both treatment groups, and most of the events were mild in nature. The most common TRAEs were headache in 4.3% of patients taking FP (1.0% with MP29-02), dysgeusia in 2.5% of patients taking MP29-02 (0.5% with FP) and epistaxis in 1.2% of patients treated with MP29-02 (0.5% with FP) [73]. There was no evidence for an accumulation of adverse events over time, or any occurrence of late adverse reactions. There were no clinically relevant nasal examination findings, in particular no evidence of nasal ulceration or perforations in either group. Ocular examinations were also unremarkable. No appreciable changes in laboratory values were observed during the study, and there were no significant changes from baseline in fasting serum cortisol levels in either treatment group (**Table 4**).

The results demonstrated that MP29-02 has an excellent safety profile with no safety concerns which would preclude its long-term use. They further confirmed its broad therapeutic spectrum and its consistent superiority over an INS.

5.3 Clinical relevance

It is unclear what constitutes a clinically meaningful response for AR outcomes. Ideally, a clinical trial should be able to demonstrate not only a statistically significant improvement in the primary efficacy end point, but also that QoL is improved, and the magnitude of the effect is clinically relevant. A proposed approach to address this question is a responder analysis, in which a continuous primary efficacy measure is dichotomized into 'responders' and 'non-responders' [74]. This responder approach is also described in regulatory guidance documents, endorsing the responder analysis as an alternative approach to assess clinical relevance [68,75], and to define a level of response not achievable with available first-line therapy. The EMA proposes that a 50% response compared with baseline is a meaningful clinical difference [68].

The objective of the *post hoc* analysis of the MP4001 study was to compare the efficacy of MP29-02 with commercially available FP, AZE and placebo in SAR patients, using novel efficacy measures which are clinically relevant according to EMA [68]. A responder sensitivity analysis was used to define a level of response not achievable with available first-line therapy. The parameters assessed in these *post hoc* analyses were defined *a priori* by an independent expert panel, without having access to the data.

More MP29-02 patients achieved a ≥ 30, ≥ 50, ≥ 60, ≥ 75 and ≥ 90% rTNSS reduction, days faster than either AZE or FP (**Table 5**) [67]. One in two MP29-02 patients achieved a halving of their nasal symptom burden (**Table 5**, **Figure 5A**),

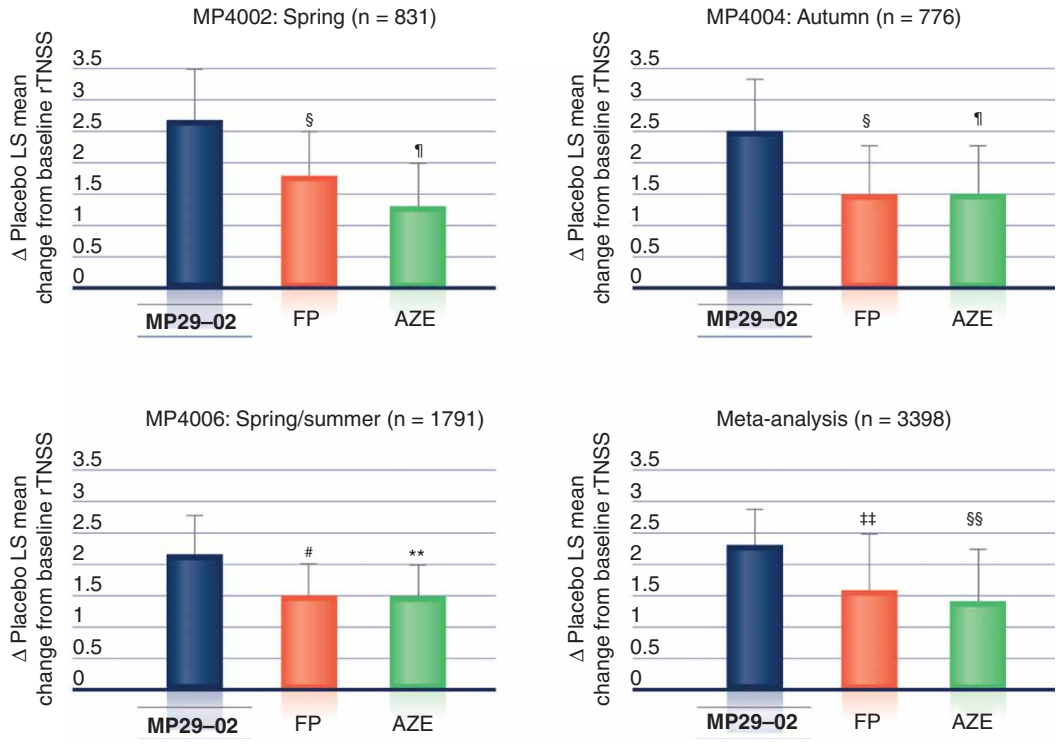

Figure 3. Effect of MP29-02, fluticasone propionate (FP) and azelastine (AZE) on overall reflective total nasal symptom score (rTNSS; AM + PM) in patients with moderate-to-severe seasonal allergic rhinitis. Data are presented as LS mean change from baseline derived by ANCOVA minus placebo. The precision of these estimates are indicated by the upper bounds of the respective 95% confidence intervals. Study MP4002: n = 831, *p = 0.034 vs FP; ‡p = 0.001 vs AZE; Study MP4004: n = 776, §p = 0.038 vs FP; ¶p = 0.032 vs AZE; Study MP4006: n = 1791, #p = 0.029 vs FP; **p = 0.016 vs AZE; Meta-analysis: n = 3398, ‡‡p < 0.001 vs FP; §§p < 0.001 vs AZE.

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and one in three MP29-02-patients achieved a ≥ 60% rTNSS reduction; neither FP nor AZE were effective at this threshold (**Table 5**). One in six MP29-02-patients achieved complete/near-to-complete response (i.e., ≤ 1 point remaining in each score of the rTNSS or mild or less for each symptom) and achieved this response many days faster than AZE- or FP-treated patients [67].

This responder sensitivity analysis shows the significant advantage of MP29-02 over the most effective medication class currently available to treat AR (i.e., INS) and also shows the responder criterion at which INS cease to benefit patients over the placebo response (i.e., ≥ 60% rTNSS reduction from baseline) (**Table 5**).

5.4 Contribution of formulation and device to clinical efficacy

Each of the four MP29-02 SAR studies had essentially identical study design and was carried out in patients with moderate-to-severe disease. The only major difference between them was that in study MP4001 [66,67], MP29-02 was compared with commercially available AZE (Astelin, Meda) and FP nasal sprays (Roxane Laboratories), whereas in the other studies MP29-02 was compared with formulation- and device-matched AZE and FP (i.e., re-formulated, non-commercially available comparators) [69]. This was done at the request of the FDA to observe the pure pharmacological differences between active groups, without the contribution of formulation and device. The extent to which MP29-02's formulation and device contribute to its clinical efficacy may be seen in two ways. First, by comparison of the efficacy results obtained in study MP4001 [67] with the other three SAR studies [69], and second by an assessment of the PK properties of FP contained within MP29-02 and marketed FP [63].

Results from the PK assessment showed that the maximum and total FP exposure was higher when FP was delivered within the MP29-02 formulation and using the MP29-02-device, than as a commercially available FP nasal spray formulation (**Table 2**) [63]. As summarized previously, this unique PK fingerprint for FP contained within MP29-02 is likely due to differences in how it is constituted (formulation) and how it is delivered (device). MP29-02's novel formulation includes a larger spray volume (**Figure 1**), difference in droplet size distribution and lower viscosity [63], which lead to wider

Table 3. Summary of the most common treatment-related adverse events following continuous use of MP29-02, FP, AZE or PLA for 14 days in moderate-to-severe seasonal allergic rhinitis patients.

	MP29-02 (n = 153)	FP (n = 153)	AZE (n = 152)	PLA (n = 151)
Study MP4001				
Dysgeusia, n (%)	11 (7.2)	0 (0.0)	3 (2.0)	0 (0.0)
Epistaxis, n (%)	6 (3.9)	6 (3.9)	4 (2.6)	5 (3.3)
Headache, n (%)	4 (2.6)	6 (3.9)	2 (1.3)	2 (1.3)
	MP29-02 (n = 207)	**FP (n = 207)**	**AZE (n = 208)**	**PLA (n = 210)**
Study MP4002				
Dysgeusia, n (%)	5 (2.4)	2 (1.0)	7 (3.4)	1 (0.5)
Epistaxis, n (%)	2 (1.0)	5 (2.4)	4 (1.9)	2 (1.0)
Headache, n (%)	1 (0.5)	5 (2.4)	1 (0.5)	3 (1.4)
	MP29-02 (n = 195)	**FP (n = 189)**	**AZE (n = 194)**	**PLA (n = 200)**
Study MP4004				
Dysgeusia, n (%)	4 (2.1)	1 (0.5)	14 (7.2)	1 (0.5)
Epistaxis, n (%)	3 (1.5)	3 (1.6)	3 (1.6)	5 (2.5)
Headache, n (%)	5 (2.6)	4 (2.1)	4 (2.1)	1 (0.5)
	MP29-02 (n = 451)	**FP (n = 450)**	**AZE (n = 449)**	**PLA (n = 451)**
Study MP4006				
Dysgeusia, n (%)	21 (4.7)	1 (0.2)	23 (5.1)	0 (0.0)
Epistaxis, n (%)	8 (1.8)	5 (1.1)	5 (1.1)	8 (1.8)
Headache, n (%)	6 (1.3)	6 (1.3)	9 (2.0)	2 (0.4)

Data taken from [67,69].

AZE: Azelastine; FP: Fluticasone propionate; PLA: Placebo.

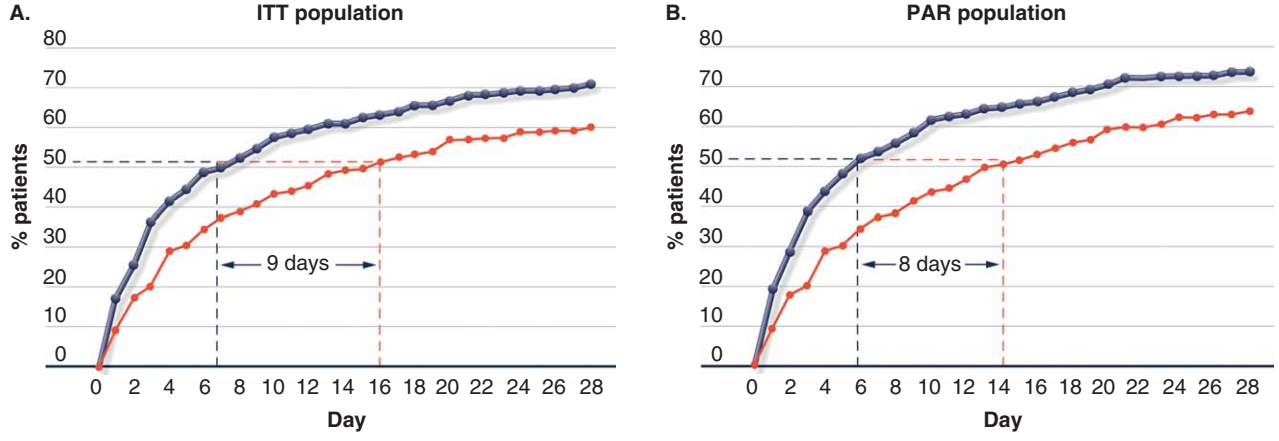

Figure 4. Time response curves showing the % of chronic rhinitis patients first exhibiting 100% improvement in PM rTNSS over the first 28 days following treatment with MP29-02 (blue) or fluticasone propionate (FP; orange) nasal spray in the (**A**) ITT and (**B**) PAR subpopulation. On median patients treated with MP29-02 reached response 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 = 0.0024; PAR: MP29-02 vs FP: p = 0.0063.

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dispersion, larger spray pattern diameter and larger total area covered compared with the marketed FP comparator (data on file, MedaPharma, Bad Homburg, Germany).

The impact of MP29-02's formulation/device on clinical efficacy is suggested from the larger treatment differences observed between MP29-02 and commercially available FP

Table 4. Serum cortisol levels following 6 and 12 months continuous use of MP29-02 or FP in patients with chronic rhinitis (i.e., perennial or non-allergic AR).

Fasting serum cortisol	MP29-02 mean ± SD (n)	FP mean ± SD (n)
Baseline value for 6-month assessment	12.21 ± 4.20 (154)	12.53 ± 4.65 (78)
6 months	11.89 ± 4.55 (154)	11.61 ± 4.62 (78)
Change from baseline to 6 months	–0.31 ± 5.14 (154)	–0.92 ± 5.32 (78)
Baseline value for 12 months/ET assessment	12.19 ± 4.21 (137)	12.52 ± 4.53 (73)
12 months/ET	12.11 ± 4.87 (137)	11.48 ± 4.65 (73)
Change from baseline to 12 months/ET	–0.08 ± 5.53 (137)	–1.04 ± 4.96 (73)

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ET: End of trial; FP: Fluticasone propionate; SD: Standard deviation.

Table 5. Responder analysis with variable levels of response on the rTNSS following 14-day treatment with MP29-02, AZE, FP or PLA in patients with moderate-to-severe SAR.

Response criteria[†]	MP29-02	AZE	FP	PLA
≥ *30% reduction in rTNSS*				
% patients at day 14	71.2[‡]	65.5	61.1	47.2
Days advantage of MP29-02		≤ 5* (p = 0.1)[‡]	≤ 7* (p = 0.02)[‡]	≤ 10 (p < 0.001)
≥ *50 reduction in rTNSS*				
% patients at day 14	49.1[‡]	37.4	38.2	28.3
Days advantage of MP29-02		≤ 6 (p = 0.02)	≤ 6* (p = 0.03)[‡]	≤ 10 (p < 0.001)
≥ *60% reduction in rTNSS*				
% patients at day 14	35.6[‡]	26.0	25.1	20.9
Days advantage of MP29-02		≤ 8 (p = 0.04)	≤ 7 (p = 0.05)	≤ 10 (p = 0.003)
≥ *75% reduction in rTNSS*				
% patients at day 14	25.5[‡]	16.4	17.7	12.9
Days advantage of MP29-02		≤ 8 (p = 0.02)	≤ 7 (p = 0.09)	≤ 9 (p = 0.003)
≥ *90% reduction in rTNSS*				
% patients at day 14	14.5[‡]	3.5	5.4	6.0
Days advantage of MP29-02		≤ 8 (p = 0.001)	≤ 6 (p = 0.01)	≤ 9 (p = 0.01)

*p-values refer to significance versus MP29-02.

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

[‡]Represents significance versus placebo.

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AZE: Azelastine; FP: Fluticasone propionate; PLA: Placebo; rTNSS: Reflective total nasal symptom score.

(i.e., study MP4001) [66,67] than between MP29-02 and re-formulated FP (i.e., studies MP4002/MP4004/MP4006) [69], since in the latter scenario the effect of formulation and device have been eliminated. This greater treatment effect versus a commercial FP occurred for each efficacy parameter assessed, including change from baseline in rTNSS, rTOSS and each of the individual nasal and ocular symptoms [66,67,69]. The ≥ 50% responder analysis proved to be a sensitive tool for measuring the formulation effect (**Figure 5**). **Figure 5A** shows the comparison of MP29-02 with commercially available comparators. Here the AZE and FP lines are virtually identical. More MP29-02 patients achieved a 50% response and did so up to 6 days faster than either AZE or FP [67]. **Figure 5B** shows the comparison of MP29-02 to re-formulated comparators [69]. In this instance, the AZE and FP lines clearly differentiate highlighting the fact that this FP, which is the FP contained within MP29-02, has a different clinical efficacy profile to marketed FP. In this instance, the time advantage of MP29-02 over re-formulated FP (i.e.,- ≤ 3 days) was half of that observed versus the time advantage over commercial FP (i.e., ≤ 6 days) [69].

The importance of associating an inhaled corticosteroid and a long-acting β2-agonist in a single device and the influence of formulation on clinical effect has also been shown in asthma [76-79] and recently by Salapatek *et al*. in AR [80]. In the AR study, solubilization of the INS component of an INS/intranasal antihistamine product (vs the INS in suspension) led to improved clinical benefits, including a faster onset of action [80].

Taken together, these results confirm MP29-02 as a new product for AR. The FP contained within MP29-02 is not commercially available. It has a distinct PK and clinical

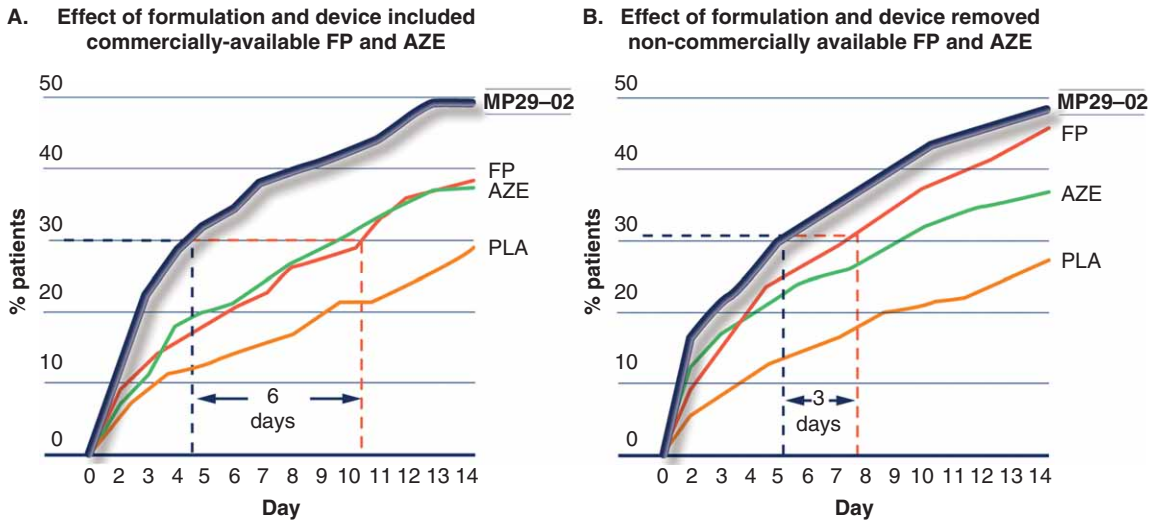

Figure 5. Time response curves showing the % of patients exhibiting 50% improvement in rTNSS by treatment day. (A) MP29-02 compared with commercially available FP and AZE; **(B)** MP29-02 compared with device- and formulation-matched non-commercially available FP and AZE.

A. Reprinted with permission from [67].

B. Reprinted with permission from [69].

AZE: Azelastine; FP: Fluticasone propionate.

efficacy profile, different to marketed comparators. MP29-02's novel formulation/device contributes to its clinical efficacy.

6. Conclusion

Many patients suffer from moderate-to-severe uncontrolled AR despite optimal treatment according to guidelines. Novel treatment options are needed. MP29-02, a novel intranasal formulation of AZE and FP in an advanced delivery system is safe and effective in patients with moderate-to-severe AR. MP29-02 provides faster and more complete symptom control than first-line therapies. It affords better symptom relief than an INS irrespective of severity, response criteria or patient type. MP29-02 represents a first-line therapy in patients with moderate-to-severe AR.

7. Expert opinion

AR is increasing in prevalence in many areas around the globe. It is becoming increasingly challenging to treat for a variety of reasons, including changing severity, sensitivity and phenotype presentations (e.g., mixed disease and SCUAD). Increased disease complexity has been accompanied by increased treatment regimen complexity, with high multiple therapy usage reported in surveys conducted in Europe [8,9,11-13]. Although the addition of oral antihistamines and leukotriene receptor antagonists is a logical response to INS therapy insufficiency or failure, theoretically broadening pathologic and symptomatic coverage, this practice is not recommended by ARIA due to a lack of evidence. The vast majority of published literature on this subject has confirmed no additional benefit of adding onto INS monotherapy [16,17]. For many patients, this means that their AR symptoms remain uncontrolled despite guideline-directed or multiple therapy treatment. Paradoxically, patient expectation from their AR treatment remains high [81], with patients cycling through various treatments and combination permutations in a vain effort to achieve better and faster nasal and ocular symptom relief [14]. Clearly, a new and more effective AR treatment is needed which meets patient expectations. MP29-02 is the first advance in the symptomatic management of AR since the introduction of INS. It is the first entry into a new class of AR medications (WHO code ATC R01AD58) and the first time that the efficacy of INS has been exceeded. MP29-02 should simplify the way we manage our AR patients. Socioeconomic benefits are expected including a positive impact on asthma and associated costs, reduced multiple therapy usage and reduced GP visits, but these remain to be determined. In tandem with improving AR treatment strategies, there is also a need to standardize our concept of rhinitis control (in line with asthma) and to introduce a common control language for use by healthcare providers and patients alike. ARIA in collaboration with MACVIA-LR (an EU reference site on active and healthy aging) has proposed a simple VAS to fulfill both functions: i) VAS score cutoffs to determine level of control and ii) VAS score measured over time to monitor symptom severity and effectiveness of treatment. This VAS will be incorporated into an app called *Allergy Diary* for AR patients, with companion apps introduced for both physicians and

pharmacists. In concert with more effective treatment options, the overall aim of *Allergy Diary* is to close the communication loop between physicians who prescribe pharmacists who dispense and recommend and patients who live with AR symptoms and treatment consequences.

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