

MP29-02 a novel intranasal therapy for the treatment of chronic rhinitis: safety data from a 12 month-trial

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Introduction

MP29-02, a novel azelastine/fluticasone propionate (FP) formulation, has recently been shown to be superior to established first-line allergic rhinitis (AR) therapies, intranasal FP and intranasal azelastine (AZE), for the treatment of patients with moderate-to-severe seasonal AR (SAR) in the largest direct head-to-head clinical development program in AR to date.¹ However, not all patients with non-infective rhinitis have SAR. A significant proportion of patients suffer from chronic rhinitis which can have an allergic (i.e. perennial allergic rhinitis [PAR]) or a non-allergic (i.e. vasomotor rhinitis [VMR]) etiology. It has been estimated that of patients with rhinitis of non-infective origin, 71% have AR (either SAR or PAR) and 29% have non-allergic rhinitis,² with most AR patients sensitized to more than one trigger and suffering from persistent and moderate/severe symptoms.³ Unlike SAR patients, who can be treated in short bursts corresponding to the season and patient symptoms, patients with chronic rhinitis require treatment of unlimited duration.

Aim

The aim of this study was to evaluate the safety and tolerability of MP29-02 with long-term use in patients with chronic rhinitis (i.e. PAR and VMR), and to compare its efficacy with intranasal FP in this population.

Methods

- 612 patients (≥ 12 yrs old) with chronic rhinitis (PAR or VMR) were enrolled into this open-label, active-controlled, parallel-group study.
- The study comprised a 7-day screening period, and a 52-week treatment period, with 6 out-patient study visits at randomisation (Day 1), and then at Months 1, 3, 6, 9 and 12.
- After 1-week screening, qualified subjects were randomised in a 2:1 ratio to 52-week's treatment with MP29-02 (1 spray/nostril bd) or FP nasal sprays (2 sprays/nostril od).
- The total daily dose of AZE and FP was 548 mcg and 200 mcg respectively.
- Safety and tolerability assessments were made at months 1, 3, 6, 9, and 12.
 - Safety was assessed by incidence, type, and severity of adverse events.
 - Patients underwent a direct visual nasal examination at each visit which included an assessment of nasal irritation (from none to Grade 4 [septal perforation]), epistaxis (None to severe) and mucosal edema/nasal discharge/mucosal erythema/ mucosal bleeding/mucosal crusting (none to severe).
 - Eye examinations were carried out at Months 6 and 12 and consisted of slit-lamp examination and intraocular pressure measurement. The presence of glaucoma, lens opacity and/or posterior sub-capsular cataracts was also noted.
 - Vital signs were recorded at each visit. Chemistry, haematology and fasting AM plasma cortisol (in a sub-set of patients) concentrations were assessed at Months 6 and 12.
- Efficacy was investigated as a secondary endpoint and was assessed by change from baseline in 12-hour PM reflective total nasal symptom score (rTNSS; sum of the individual nasal symptoms of congestion, itching, rhinorrhea and sneezing) over the 52-week treatment period at 4 weekly intervals.
- Quality of life was assessed (in subjects > 18 yrs old) using the 28-item Rhinitis Quality of Life Questionnaire (RQLQ) at randomization, prior to the first dose and at each clinic visit.

Study subjects (Table 1)

- Of the 612 subjects randomised to treatment, 464 (75.8%) completed the 1-year study period (MP29-02: 77.0%; FP: 73.4%). The main reason for study discontinuation was patients 'lost to follow-up' as common in long-term studies. This is because the International Conference on Harmonization (ICH) guideline E1A requires at least 300 subjects for 6 months but only 100 subjects for 1 year.
- The baseline characteristics of the two treatment groups were similar. Patient baseline rTNSS and overall RQLQ scores were well-matched (Table 1).

Table 1: Subject baseline characteristics (safety population)		
	MP29-02 (n=404)	FP (n=207)
Age, yrs	32.8 (11.5)	35.3 (11.5)
Male, n (%)	240 (59.4%)	110 (53.1%)
Race, n (%)	Asian	206 (99.5%)
PM rTNSS	3.81 (2.49)	3.90 (2.32)
Overall RQLQ score	2.06 (1.05)	2.23 (1.06)
Disease duration, yrs	5.9 (5.0)	6.3 (6.4)

Results expressed as mean (standard deviation) unless otherwise stated.
FP: fluticasone propionate; rTNSS: reflective total nasal symptom score (comprising nasal congestion, itching, rhinorrhea, sneezing; range 0-12); RQLQ: rhinitis quality of life questionnaire.
Safety population was defined as all randomised subjects who received at least one dose of study drug

Adverse events

- The mean duration of exposure was 339.9 days for the MP29-02 group and 329.0 days for the FP group, with a mean of 632.9 and 302.2 total number of doses taken in the MP29-02 and FP groups respectively.
- 38 patients (9.4%) in the MP29-02 group and 23 patients (11.1%) in the FP group experienced a treatment-related AE. None of these events were considered severe.
 - The most common treatment-related AEs were dysgeusia (2.5%) in the MP29-02 group and headache (4.3%) in the FP group (Table 2).
- In both groups <3% of subjects discontinued from the study due to an AE (MP29-02: 2.7%; FP 2.9%).
- 3 patients (0.7%) in the MP29-02 group and 1 FP patient (0.5%) experienced a serious AE during the course of the study. All of these events were considered unlikely related to study medication.

Laboratory results, vital signs and serum cortisol

- There were no clinically-relevant changes from baseline in mean values of hematology, chemistry, quantitative urinalysis parameters or vital signs in either treatment group.
- There was also no appreciable reduction in serum cortisol from baseline following 12 month's continuous treatment with either MP29-02 or FP (Table 3).

Table 2: treatment-related adverse event occurring in >1% of subjects in either group (safety population)

	MP29-02 (n=404)	FP (n=207)
Any event	38 (9.4)	23 (11.1)
Dysgeusia	10 (2.5)	1 (0.5)
Epistaxis	5 (1.2)	1 (0.5)
Headache	4 (1.0)	9 (4.3)
Cough	4 (1.0)	0 (0.0)
Blood cortisol increased	2 (0.5)	1 (0.5)
Weight increased	2 (0.5)	1 (0.5)
Glucose tolerance impaired	2 (0.5)	1 (0.5)
Acne	2 (0.5)	0 (0.0)
Vomiting	2 (0.5)	0 (0.0)
Rhinitis	2 (0.5)	0 (0.0)

Table 3: Fasting serum cortisol (safety population)

Serum cortisol (mcg/dL)	MP29-02	FP
N= 154	N=78	
Baseline for Month 6	12.21 (4.20)	12.53 (4.66)
6-months post-treatment	11.89 (4.55)	11.61 (4.62)
6-months change from baseline	-0.31 (5.14)	-0.92 (5.32)
N=137	N=73	
Baseline for Month 12	12.19 (4.21)	12.52 (4.53)
12-months post-treatment	12.11 (4.87)	11.48 (4.65)
12-month change from baseline	-0.08 (5.53)	-1.04 (4.96)

Results

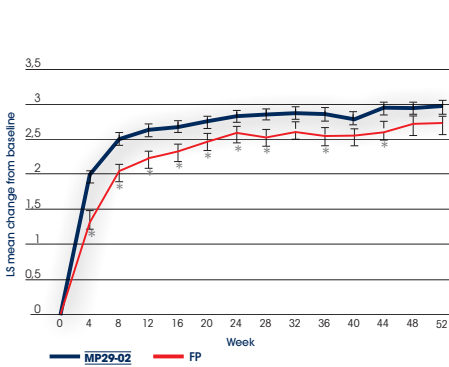
Focused Nasal and Ophthalmologic Examinations

- There were no nasal mucosal ulcerations or perforations noted during this 1-year study.
- The most commonly reported nasal findings were mucosal edema, nasal discharge and mucosal erythema. The incidences and intensity of these focused nasal examination findings were comparable in the two treatment groups, and were reduced following 6 and 12 months treatment with either MP29-02 or FP (Table 4).
- Ocular examination findings were unremarkable and similarly low for both groups.

Efficacy

- Patients treated with MP29-02 experienced significantly greater nasal symptom relief than those treated with FP. Superiority of MP29-02 over FP, in terms of change from baseline in 12h PM rTNSS, was evident from Day 1 (MP29-02: -1.21; FP: -0.25), with consistent significance maintained for up to 28 weeks (p=0.0048). This benefit of MP29-02 over FP was sustained for the remainder of the study, up to 52 weeks (Figure 1), representing an approximate 80% change from baseline in the MP29-02 group. Treatment differences were consistent for the entire observation period although after week 28 p-values did not constantly remain below 5% due to decreasing sample sizes.

Figure 1
Absolute change in reflective Total Nasal Symptom Score (AM + PM) on each treatment day



* p<0.05 vs MP29-02
rTNSS: reflective total nasal symptom score (comprising nasal congestion, itching, rhinorrhea, sneezing; range 0-12); FP: fluticasone propionate
N numbers MP29-02/FP: wk 0 (379/194); wk 4 (372/188); wk 8 (370/187); wk 12 (361/179); wk 16 (358/178); wk 20 (346/166); wk 24 (345/165); wk 28 (347/165); wk 32 (329/158); wk 36 (329/156); wk 40 (325/156); wk 44 (303/153); wk 48 (295/148); wk 52 (295/148)

Table 4: Focused nasal examination – most commonly reported findings (safety population)						
	Pre-dose		Month 6		Month 12	
	MP29-02	FP	MP29-02	FP	MP29-02	FP
Mucosal Oedema n (%)						
Mild	186 (46.0)	103 (49.8)	101 (28.5)	49 (29.0)	48 (14.4)	21 (12.9)
Moderate	130 (32.2)	62 (30.0)	16 (14.5)	9 (5.3)	5 (1.5)	6 (3.7)
Severe	0	4 (1.9)	0	0	0	1 (0.6)
Nasal Discharge n (%)						
Mild	180 (44.6)	91 (44.0)	119 (33.5)	56 (33.1)	53 (15.9)	21 (12.9)
Moderate	166 (41.1)	80 (38.6)	20 (5.6)	13 (7.7)	5 (1.5)	6 (3.7)
Severe	7 (1.7)	5 (2.4)	0	0	0	1 (0.6)
Mucosal Erythema n (%)						
Mild	174 (43.1)	88 (42.5)	105 (29.6)	58 (34.3)	65 (19.5)	28 (17.2)
Moderate	60 (14.9)	32 (15.5)	8 (2.3)	5 (3.0)	4 (1.2)	4 (2.5)
Severe	0	0	1 (0.3)	1 (0.6)	0	1 (0.6)

FP: fluticasone propionate
Safety population was defined as all randomised subjects who received at least one dose of study drug

Conclusions

In conclusion, MP29-02 was safe and effective during this 1-year study in subjects with chronic (perennial and vasomotor) rhinitis. The results are consistent with what has previously been shown in more than 4000 patients with SAR. In summary MP29-02 is safe and effective in all form of rhinitis