

# Long-term, Randomized Safety Study of MP29-02 (a Novel Intranasal Formulation of Azelastine Hydrochloride and Fluticasone Propionate in an Advanced Delivery System) in Subjects With Chronic Rhinitis

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**What is already known about this topic?** Many patients are dissatisfied with current therapy, often comedicated in an attempt to achieve better and faster symptom relief. The efficacy of an intranasal corticosteroid has been significantly exceeded for the first time with MP29-02.

**What does this article add to our knowledge?** MP29-02 also is safe and well tolerated after 1 year of continuous use. There are no safety findings that would limit the long-term use of MP29-02 in the treatment of allergic rhinitis.

**How does this study impact current management guidelines?** MP29-02 should be positioned favorably in the guidelines because, not only is it more effective than an intranasal corticosteroid or an intranasal antihistamine in the treatment of allergic rhinitis, but it also has an excellent safety and tolerability profile.

**BACKGROUND:** MP29-02 is a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate (FP) in an advanced delivery system for the treatment of seasonal allergic rhinitis.

**OBJECTIVE:** The objective of this study was to evaluate the long-term safety of MP29-02 in subjects with chronic allergic (perennial) or nonallergic (vasomotor) rhinitis.

**METHODS:** This was a 1-year, randomized, open-label, active-controlled, parallel-group study in subjects with chronic allergic or nonallergic rhinitis. A total of 612 subjects were randomized in a 2:1 ratio to (1) MP29-02, one spray per nostril twice daily (total daily doses of azelastine hydrochloride and FP were 548 mcg and 200 mcg, respectively); or (2) FP, 2 sprays per nostril once daily (total daily dose 200 mcg).

Safety and tolerability assessments were made at months 1, 3, 6, 9, and 12.

**RESULTS:** The incidence of treatment-related adverse events was low with both MP29-02 (9.4%) and FP (11.1%), with no evidence of late-occurring adverse events. Nasal examinations showed no evidence of nasal mucosal ulcerations or septal perforations with MP29-02, and the overall incidence of adverse findings was reduced as the study progressed. There were no unusual or unexpected ocular examination findings and no clinically important laboratory findings or clinically important differences between groups in fasting AM serum cortisol levels after 12 months of treatment.

**CONCLUSIONS:** MP29-02 was well tolerated. There were no safety findings that would preclude the long-term use of

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Conflicts of interest: W. E. Berger has received honoraria, consulted for, and received research support from MEDA and Alcon; has consulted for and received speaker fees from Sunovion and TEVA; has received speaker fees from AstraZeneca; and has received speaker fees and served as an adviser for Allergan. S. Shah has consulted and received research grants from MEDA and given lectures for TEVA, Alcon, and AstraZeneca. P. Lieberman is an adviser for the Allergy Foundation of America and Baxter and has given lectures for MEDA, Genentech, Ista, and TEVA. J. Hadley has consulted and served as an adviser for MEDA, Merck, and TEVA. D. Price has received consultancy and speaker fees from Merck, Mundipharma, Novartis, Medapharma, Kyorin, and TEVA; has received consultancy fees from GlaxoSmithKline, Almirall, and Chiese; has received

consultancy fees and grants from Pfizer and AstraZeneca; has received consultancy fees and grants from Boehringer Ingelheim; has received speaker fees and grants from Aerocrine; has received grants from the UK National Health Service, Nycomed, and Medapharma; is director of research in Real Life LTD; is a guideline group member for Allergic Rhinitis and its Impact on Asthma and European Position Paper on Rhinosinusitis and Nasal Polyps; and has shares in AKL Ltd. U. Munzel is an employee of Medapharma. S. Bhatia has received research grants and consulted for MEDA.

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*Abbreviations used*

|                                              |
|----------------------------------------------|
| AE- Adverse event                            |
| AR- Allergic rhinitis                        |
| AZ- Azelastine hydrochloride                 |
| ET- Early termination                        |
| FP- Fluticasone propionate                   |
| PAR- Perennial allergic rhinitis             |
| RQLQ- Rhinitis Quality of Life Questionnaire |
| rTNSS- Reflective Total Nasal Symptom Score  |
| SAE- Serious adverse event                   |
| SAR- Seasonal allergic rhinitis              |
| TEAE- Treatment-emergent adverse event       |
| TRAE- Treatment-related adverse event        |
| VMR- Vasomotor rhinitis                      |

**MP29-02 in the treatment of allergic rhinitis.** © 2014  
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**Key words:** Clinical trial; Allergic rhinitis; Chronic rhinitis;  
 Azelastine; Fluticasone; Hypothalamic-pituitary-adrenal axis;  
 Perennial allergic rhinitis; Vasomotor rhinitis

MP29-02 (Dymista; Meda Pharmaceuticals, Somerset, NJ) incorporates the effects of both azelastine hydrochloride (AZ) and fluticasone propionate (FP) in an advanced delivery system, benefiting from improved formulation and device characteristics. In clinical trials, it has demonstrated greater efficacy than 2 established first-line allergic rhinitis (AR) monotherapies, intranasal FP and intranasal AZ, in subjects with moderate-to-severe seasonal AR (SAR).<sup>1-4</sup> This body of evidence was gathered in 4 randomized, double-blind, placebo- and active-controlled clinical studies that included more than 4000 subjects.<sup>1-4</sup>

The first of these studies was a randomized, double-blind, placebo controlled and active controlled trial in 610 subjects with allergy to Texas Mountain cedar pollen.<sup>1,2</sup> The study compared MP29-02 with 2 commercially available first-line active comparators (Astelin Nasal Spray [Meda Pharmaceuticals] and a generic FP nasal spray) during a 14-day study period. The results showed that MP29-02 was statistically superior to both AZ and FP for relief of nasal symptoms associated with SAR. There was no increase in the incidence of nasal irritation or epistaxis with MP29-02 when compared with FP, AZ, or placebo.<sup>1,2</sup>

The 3 subsequent studies included 3398 subjects with moderate-to-severe SAR in which MP29-02 and the monotherapy comparators were administered in the same delivery device and the same vehicle. The results of these studies have been summarized and reported as a meta-analysis.<sup>3</sup> These studies compared MP29-02, AZ, FP, and placebo during spring and fall allergy seasons at multiple investigational sites throughout the major geographic regions of the United States. In each study, MP29-02 reduced the mean reflective total nasal symptom score from baseline by a significantly greater margin than FP, AZ, or placebo, with all individual nasal symptoms contributing to the overall clinical effect. Clinical benefit was observed during the first day of assessment and was sustained over the 14-day treatment period. The safety of the monotherapy components is well established, and, in these trials, the overall incidence of adverse events (AEs) was not substantially different between the active treatment groups. A full report of one of these studies is published

separately.<sup>4</sup> MP29-02 was well tolerated during the 2-week studies. However, not all patients with SAR have intermittent symptomatic episodes in response to seasonal triggers. Many patients experience persistent symptoms of SAR, in particular, in areas of the southern tier of the United States where pollen may be present year round. Therefore, the primary objective of this study was to evaluate the long-term safety of MP29-02 in subjects with chronic allergic (perennial AR) or nonallergic vasomotor rhinitis.

## METHODS

This study (EudraCT no. 2011-001368-23) was conducted in accordance with Good Clinical Practice,<sup>5</sup> the Declaration of Helsinki, and applicable regulatory requirements. Before implementing the study, the study protocol, the proposed informed consent form, and other information to subjects was approved by a properly constituted institutional review board or independent ethics committee for each investigational site. After independent ethics committee approval, written informed consent was obtained from all the subjects or legal guardians (subject <18 years old).

## Study population

**Inclusion criteria.** Male and female subjects 12 to 80 years of age with an established history ( $\geq 1$  year) of chronic rhinitis due to perennial allergies or nonallergic triggers were eligible for the study. Subjects with a seasonal allergic component were included, provided that they had significant symptoms outside the allergy seasons. The chronic rhinitis population was chosen for this study due to the extended (1 year) duration of treatment required to fully evaluate safety parameters. The diagnosis of rhinitis, whether allergic or nonallergic, was made on the basis of a thorough evaluation. This evaluation included medical history, physical examination, rhinitis symptoms, and skin testing, or validated in vitro tests for allergen-specific Ig E. All the subjects were symptomatic at study entry, with nasal symptoms of rhinitis for at least 2 days during the screening period. Subjects who received subcutaneous immunotherapy (antigen desensitization) were on a stable maintenance regimen for at least 30 days before the first study visit. All the subjects provided written informed consent or pediatric assent, and, for all minors, written informed consent was obtained from a parent or legal guardian. The subjects agreed to comply with study requirements, including daily use of medication for a 1-year period, even if symptoms were not bothersome. All the subjects were in general good health and free of any disease or concomitant treatment that could have interfered with the interpretation of the study results.

**Exclusion criteria.** Subjects were excluded from the study if, on nasal examination, they had any nasal ulceration (grade 3) or nasal septal perforation (grade 4); recent nasal or sinus surgery; chronic sinusitis; recent acute sinusitis; nasal disease(s), such as rhinitis medicamentosa, clinically significant nasal polyposis, or nasal structural abnormalities. Women who were pregnant or nursing and women of childbearing potential who were not using an acceptable method of contraception were not permitted to enroll. Subjects also were excluded if they had a history of asthma (with the exception of mild intermittent asthma), significant pulmonary disease, posterior subcapsular cataracts or glaucoma, clinically significant arrhythmia or prolonged corrected QT interval, a history of drug or alcohol abuse within the past 2 years, or a hypersensitivity to AZ or FP. Recent use of any

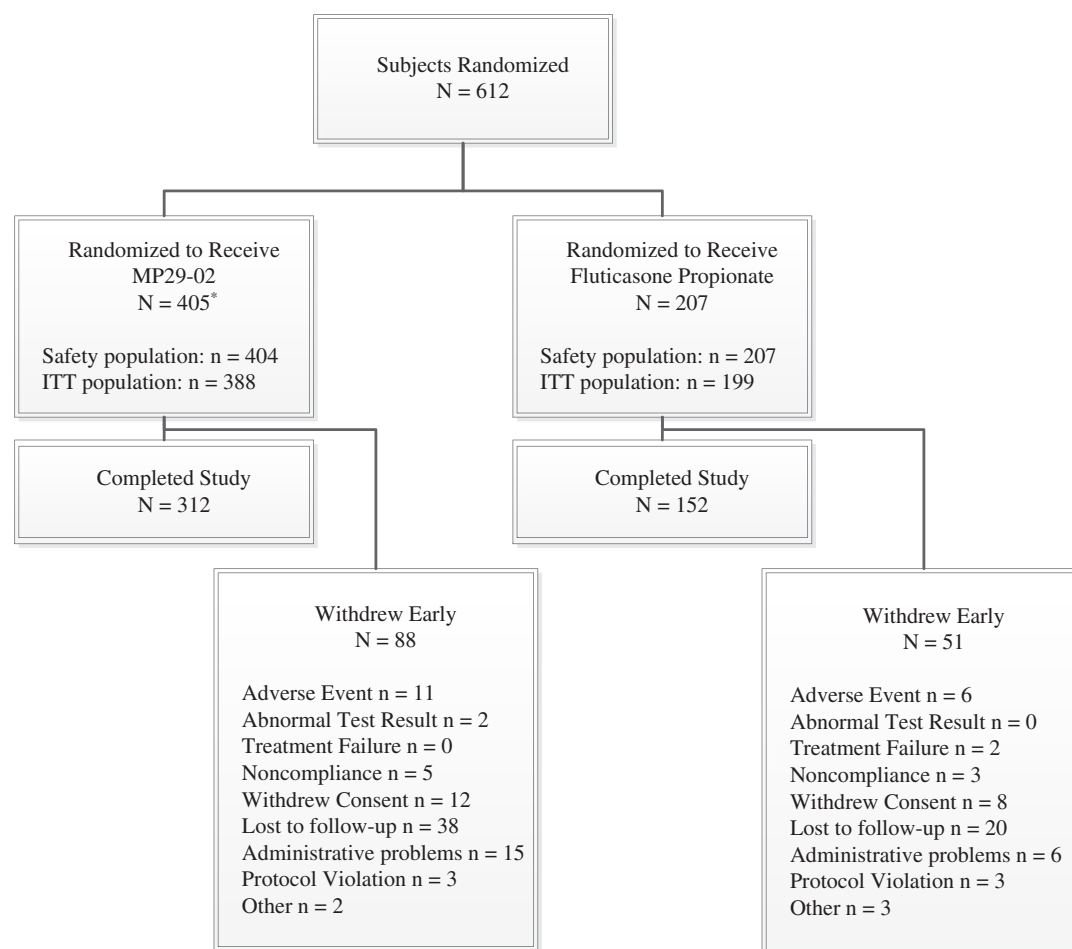


**FIGURE 1.** Subject disposition. \*One subject withdrew after randomization and before study medication was dispensed.

investigational drug, systemic corticosteroids or omalizumab, inhaled corticosteroids or combination inhaled corticosteroids and/or long-acting  $\beta$ -agonists (within 30 days), or sublingual immunotherapy (within 6 months) was not permitted.

### Study design

This was a randomized, open-label, active-controlled, parallel-group, safety and tolerability study in subjects with chronic allergic (perennial) and nonallergic (vasomotor) rhinitis, conducted at 37 investigational sites in India during 2008 and 2009. After an initial screening visit, subjects who met the study entry criteria received a diary to verify the presence of nasal symptoms (rhinorrhea, sneezing, itchy nose, and nasal congestion) due to rhinitis. The subjects then returned to the clinic in 7 days to determine if they met randomization criteria (nasal symptoms of rhinitis noted in the diary on at least 2 days during the screening period). Qualified subjects were randomized in a 2:1 ratio to receive MP29-02 or FP during the 12-month open-label treatment period. At enrollment, the subjects were assigned a unique identification number that consisted of 2 parts: the study-site number (assigned by Meda or its designee) and the subject screening number (assigned in ascending order by each study site sequentially beginning with 001). An interactive voice response system was used to sequentially assign the next available randomization number from a central randomization schedule.

MP29-02 nasal spray was administered at a dosage of 1 spray per nostril twice daily (AM and PM); each metered spray delivered 137 mcg of AZ and 50 mcg of FP per actuation, for a total daily dose of 548 mcg and 200 mcg for AZ and FP, respectively. FP nasal spray (commercially available generic fluticasone; Boehringer Ingelheim/Roxane Laboratories, Columbus, Ohio) was administered at a dosage of 2 sprays per nostril once daily (AM), each metered spray 50 mcg, for a total daily dose of 200 mcg. Baseline evaluations were performed, with additional outpatient evaluations at months 1, 3, 6, 9, and 12.

**Safety variables.** Safety was assessed by incidence, type, and severity of AEs coded by using the Medical Dictionary for Regulatory Affairs.<sup>6</sup> The severity of AEs was defined as (1) mild, the subject may be aware of the signs and symptoms, but these did not cause more than minimal discomfort and were considered not clinically significant; (2) moderate, the subject has discomfort that interferes with usual activities and is considered of some clinical significance; and (3) severe, the subject is unable to work normally or to carry out usual daily activities or the event is of definite clinical significance. The relationship of an AE to study medication was assessed by the investigator as (1) unlikely related, there was a remote possibility that study medication may have been the cause of or contributed to the event; (2) possibly related, a direct cause-and-effect relationship may exist

**TABLE I.** Demographic and baseline characteristics (safety population)

|                                     | MP29-02 (N = 404) | FP (N = 207)     |
|-------------------------------------|-------------------|------------------|
| Age (y), mean $\pm$ SD              | 32.8 $\pm$ 11.5   | 35.3 $\pm$ 11.5* |
| Age, no. (%)                        |                   |                  |
| 12 $\leq$ 18 y                      | 28 (6.9)          | 8 (3.9)          |
| 18 < 65 y                           | 373 (92.3)        | 196 (94.7)       |
| $\geq$ 65 y                         | 3 (0.7)           | 3 (1.4)          |
| Male subjects, no. (%)              | 240 (59.4)        | 110 (53.1)       |
| Race, no. (%)                       |                   |                  |
| Asian                               | 404 (100)         | 206 (99.5)       |
| Black                               | 0 (0.0)           | 1 (0.5)          |
| PM rTNSS, mean $\pm$ SD             | 3.81 $\pm$ 2.49   | 3.90 $\pm$ 2.32  |
| Overall RQLQ score, mean $\pm$ SD   | 2.06 $\pm$ .05    | 2.23 $\pm$ 1.06  |
| Disease duration (y), mean $\pm$ SD | 5.9 $\pm$ 5.0     | 6.3 $\pm$ 6.4*   |
| Rhinitis diagnosis, no. (%)         |                   |                  |
| PAR                                 | 279 (69.1)        | 145 (70.0)       |
| VMR                                 | 125 (30.9)        | 62 (30.0)        |

rTNSS, Reflective Total Nasal Symptom Score; RQLQ, Rhinitis Quality of Life Questionnaire; VMR, vasomotor rhinitis; PAR, perennial AR.

\* $P < .05$ .

(probability considered less than 50%); (3) probably related, a direct cause-and-effect relationship has not been demonstrated but is likely (probability considered more than 50%).

The subjects underwent a direct visual nasal examination at each visit that included an assessment of nasal irritation by using the following grading scale: 0, no irritation; 1A, focal irritation; 1B, superficial mucosal erosion; 2, moderate mucosal erosion; 3, ulceration; 4, septal perforation. Epistaxis, mucosal edema, nasal discharge, mucosal erythema, mucosal bleeding, and mucosal crusting were graded on a 4-point scale (none to severe). Any new finding or any clinically significant findings or worsening of a previously identified condition either reported on a nasal examination or by the patient were considered AEs.

Eye examinations were conducted by ophthalmologists at months 6 and 12, and included a slit-lamp examination and intraocular pressure measurement. The investigators, study coordinators, and ophthalmologists were trained at a prestudy investigator meeting to ensure an appropriate degree of consistency in the evaluations. The presence of glaucoma, lens opacity, and/or posterior subcapsular cataracts was noted. Laboratory assessments included hematology, serum chemistries, and urinalysis at baseline and months 6 and 12. Vital signs (oral body temperature, sitting systolic and diastolic blood pressure, and respiration rate) were recorded at each visit. Telephone contact was maintained with the subjects at months 2, 4, 5, 7, 8, 10, and 11.

Fasting AM plasma cortisol concentrations were measured for 154 subjects treated with MP29-02 and 78 treated with FP. The subjects in this substudy had fasting morning (between 8 AM and 9 AM) plasma cortisol levels measured at baseline and at the month 6 and month 12 or early termination visits; the subjects with a fasting morning plasma cortisol level that was less than or equal to 5 mcg/dL (or 150 nmol/L) at baseline were excluded from the substudy.

### Statistical analysis

The sample size for the study was based on the International Conference on Harmonization Guideline E1: "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening

**TABLE II.** Overview of AEs (safety population)

|                                                      | MP29-02 (N = 404) | FP (N = 207) |
|------------------------------------------------------|-------------------|--------------|
| No. of AEs reported                                  |                   |              |
| All TEAEs*                                           | 653               | 313          |
| All TRAEs†                                           | 61                | 46           |
| Subjects with AE, no. (%)                            |                   |              |
| All TEAEs                                            | 188 (46.5)        | 92 (44.4)    |
| Mild                                                 | 136 (33.7)        | 67 (32.4)    |
| Moderate                                             | 47 (11.6)         | 25 (12.1)    |
| Severe                                               | 5 (1.2)           | 0 (0.0)      |
| All TRAEs                                            | 38 (9.4)          | 23 (11.1)    |
| Mild                                                 | 29 (7.2)          | 16 (7.7)     |
| Moderate                                             | 9 (2.2)           | 7 (3.4)      |
| Severe                                               | 0 (0.0)           | 0 (0.0)      |
| Subjects with SAE, no. (%)                           | 3 (0.7)           | 1 (0.5)      |
| Subjects with AE leading to discontinuation, no. (%) | 11 (2.7)          | 6 (2.9)      |
| Deaths, no. (%)                                      | 0 (0.0)           | 0 (0.0)      |

TEAE, Treatment-emergent adverse event; TRAE, treatment-related adverse event.

\*A TEAE is an AE with an onset date on or after the first dose of study drug (MP29-02 or FP), or an AE that is worsened (increased in severity or frequency) after taking the study drug.

†A TRAE is an AE considered probably or definitely related to the study drug by an investigator.

**TABLE III.** TRAEs occurring in more than 1 subject in either group (safety population)\*

|                            | Subjects, no. (%) |              |
|----------------------------|-------------------|--------------|
| TRAE                       | 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)      |

\*A TRAE is an AE considered probably or definitely related to the study drug by an investigator.

Conditions," which requires treatment of at least 300 subjects for 6 months and 100 subjects for 1 year.<sup>7</sup> Based on an estimated attrition rate of 25% at the 6-month time point and 50% by the 1-year time point, it was determined that 400 subjects in the MP29-02 group would be an appropriate sample size to ensure an adequate safety database.

All subjects who received at least one dose of study medication were included in the safety analyses. A descriptive comparison of the safety and tolerability assessments, including AEs and focused nasal examination findings, was made between MP29-02 and the FP nasal spray. Vital signs were examined for abnormal values and the change from baseline, with clinically important abnormalities being noted. Laboratory values, including hematology, chemistries, urinalysis, and fasting AM plasma cortisol levels were

**TABLE IV.** Nasal examination findings (safety population)

| Parameter          | MP29-02, no. (%)       |                      |                          | FP, no. (%)            |                      |                          |
|--------------------|------------------------|----------------------|--------------------------|------------------------|----------------------|--------------------------|
|                    | Screening<br>(N = 404) | Month 6<br>(N = 355) | Month 12/ET<br>(N = 334) | Screening<br>(N = 207) | Month 6<br>(N = 169) | Month 12/ET<br>(N = 163) |
| Epistaxis          |                        |                      |                          |                        |                      |                          |
| None               | 395 (97.8)             | 354 (99.7)           | 331 (99.1)               | 203 (98.1)             | 168 (99.4)           | 161 (98.8)               |
| Mild               | 9 (2.2)                | 1 (0.3)              | 3 (0.9)                  | 4 (1.9)                | 1 (0.6)              | 2 (1.2)                  |
| Moderate           | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  |
|                    | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  |
| Nasal irritation   |                        |                      |                          |                        |                      |                          |
| None               | 245 (60.6)             | 293 (82.5)           | 294 (88.0)               | 130 (62.8)             | 133 (78.7)           | 140 (85.9)               |
| Grade 1A           | 130 (32.2)             | 51 (14.4)            | 31 (9.3)                 | 66 (31.9)              | 32 (18.9)            | 20 (12.3)                |
| Grade 1B           | 24 (5.9)               | 10 (2.8)             | 9 (2.7)                  | 10 (4.8)               | 3 (1.8)              | 3 (1.8)                  |
| Grade 2            | 5 (1.2)                | 1 (0.3)              | 0 (0.0)                  | 1 (0.5)                | 1 (0.6)              | 0 (0.0)                  |
| Grade 3            | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  |
| Grade 4            | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  |
| Mucosal edema      |                        |                      |                          |                        |                      |                          |
| None               | 81 (20.0)              | 238 (67.0)           | 238 (84.1)               | 43 (20.8)              | 111 (65.7)           | 135 (82.8)               |
| Mild               | 196 (48.5)             | 101 (28.5)           | 48 (14.4)                | 103 (49.8)             | 49 (29.0)            | 21 (12.9)                |
| Moderate           | 125 (30.9)             | 16 (4.5)             | 5 (1.5)                  | 57 (27.5)              | 9 (5.3)              | 6 (3.7)                  |
| Severe             | 2 (0.5)                | 0 (0.0)              | 0 (0.0)                  | 4 (1.9)                | 0 (0.0)              | 1 (0.6)                  |
| Nasal discharge    |                        |                      |                          |                        |                      |                          |
| None               | 49 (12.1)              | 216 (60.8)           | 276 (82.6)               | 27 (13.0)              | 100 (59.2)           | 135 (82.8)               |
| Mild               | 185 (45.8)             | 119 (33.5)           | 53 (15.9)                | 93 (44.9)              | 56 (33.1)            | 21 (12.9)                |
| Moderate           | 163 (40.3)             | 20 (5.6)             | 5 (1.5)                  | 81 (39.1)              | 13 (7.7)             | 6 (3.7)                  |
| Severe             | 7 (1.7)                | 0 (0.0)              | 0 (0.0)                  | 6 (2.9)                | 0 (0.0)              | 1 (0.6)                  |
| Mucosal erythema   |                        |                      |                          |                        |                      |                          |
| None               | 171 (42.3)             | 241 (67.9)           | 265 (79.3)               | 85 (41.1)              | 105 (62.1)           | 130 (79.8)               |
| Mild               | 172 (42.6)             | 105 (29.6)           | 65 (19.5)                | 87 (42.0)              | 58 (34.3)            | 28 (17.2)                |
| Moderate           | 59 (14.6)              | 8 (2.3)              | 4 (1.2)                  | 34 (16.4)              | 5 (3.0)              | 4 (2.5)                  |
| Severe             | 2 (0.5)                | 1 (0.3)              | 0 (0.0)                  | 1 (0.5)                | 1 (0.6)              | 1 (0.6)                  |
| Mucosal bleeding   |                        |                      |                          |                        |                      |                          |
| None               | 398 (98.5)             | 353 (99.4)           | 331 (99.1)               | 202 (97.6)             | 168 (99.4)           | 162 (99.4)               |
| Mild               | 4 (1.0)                | 1 (0.3)              | 3 (0.9)                  | 4 (1.9)                | 0 (0.0)              | 1 (0.6)                  |
| Moderate           | 1 (0.2)                | 0 (0.0)              | 0 (0.0)                  | 0 (0.0)                | 0 (0.0)              | 0 (0.0)                  |
| Severe             | 1 (0.2)                | 1 (0.3)              | 0 (0.0)                  | 1 (0.5)                | 1 (0.6)              | 0 (0.0)                  |
| Crusting of mucosa |                        |                      |                          |                        |                      |                          |
| None               | 344 (85.1)             | 332 (93.5)           | 316 (94.6)               | 173 (83.6)             | 159 (94.1)           | 156 (95.7)               |
| Mild               | 44 (10.9)              | 17 (4.8)             | 15 (4.5)                 | 23 (11.1)              | 7 (4.1)              | 4 (2.5)                  |
| Moderate           | 15 (3.7)               | 5 (1.4)              | 3 (0.9)                  | 10 (4.8)               | 2 (1.2)              | 2 (1.2)                  |
| Severe             | 1 (0.2)                | 1 (0.3)              | 0 (0.0)                  | 1 (0.5)                | 1 (0.6)              | 1 (0.6)                  |

ET, Early termination.

summarized by means (SDs). Inferential statistical methods for the safety end points were not planned because necessary adjustments for multiplicity together with small numbers of subjects in several outcome categories and that the expected small effect sizes would lead to insensitive methodology.

## RESULTS

### Subject disposition and demographics: subjects

Of the 612 subjects randomized to treatment, 464 subjects (75.8%) completed the 1-year study period. Completion rates were similar in both treatment groups (Figure 1). The main reason for study discontinuation of subjects was lost to follow-up. Fewer than 3% of the subjects in either treatment group were discontinued from the study due to AEs. The 2 treatment groups were comparable with regard to demographic and baseline clinical

characteristics (Table I). The majority of subjects were male (57.3%) and Asian (99.8%), ranging in age from 12 to 73 years of age, with a mean age of 33.7 years. The baseline reflective total nasal symptom score was similar in both treatment groups (3.81 in the MP29-02 group and 3.90 in the FP group). The subjects were also well matched for quality-of-life impairment, with baseline rhinitis quality-of-life questionnaire overall scores in the total subject population of 2.06 in the MP29-02 group and 2.23 in the FP group. Most subjects (69.4%) had a diagnosis of perennial AR (Table I).

### Safety

**Exposure.** The mean duration of exposure was 339.9 days for the MP29-02 group and 329.0 days for the FP group. The mean number of doses taken was 632.9 and 302.2 in the MP29-02 and FP groups, respectively. Based on patient diary card entries,

TABLE V. Eye examination findings

| Variable                                                | Subjects, no. (%)    |                 |
|---------------------------------------------------------|----------------------|-----------------|
|                                                         | MP29-02<br>(N = 404) | FP<br>(N = 207) |
| Evidence of glaucoma at screening                       | 0 (0.0)              | 0 (0.0)         |
| Evidence of glaucoma at 6 mo                            | 1 (0.2)              | 0               |
| Evidence of glaucoma at 12 mo/ET                        | 0 (0.0)              | 0 (0.0)         |
| Evidence of posterior subcapsular cataract at screening | 0                    | 2 (1.0)*        |
| Evidence of posterior subcapsular cataract at 6 mo      | 3 (0.7)              | 0 (0.0)         |
| Evidence of posterior subcapsular cataract at 12 mo/ET  | 1 (0.2)              | 3 (1.4)         |

ET, Early termination.

\*Subjects with cataracts noted at screening were randomized in error.

the percentage of subjects with  $\geq 75\%$  compliance was 85.1% in the MP29-02 group and 81.6% in the fluticasone group.

**AEs.** The proportion of subjects with a treatment-emergent AE was similar for both treatment groups (Table II), with no evidence for an accumulation of AEs over time or any occurrence of late adverse reactions. The numbers of patients who experienced treatment-related AEs were low with both MP29-02 (9.4%) and FP (11.1%). The most common TRAEs were dysgeusia (2.5%) in the MP29-02 group and headache (4.3%) in the FP group (Table III). None of these events were considered severe. Fewer than 3% of the subjects in each treatment group were discontinued from the study due to an AE. AEs that led to discontinuation in the MP29-02 group included 3 subjects with decreased cortisol at month 6 (all cases were considered by the investigator as unlikely related to treatment); 3 subjects with evidence of cataract at 6 months, considered unlikely related to treatment; 2 subjects with acne, considered possibly or probably related; and single subjects due to asthma, abdominal pain, vomiting, a visual field defect, and a posterior subcapsular lens opacity. There was one discontinuation in the FP group due to a subject with cataract at month 6 who was lost to follow-up. All other events that resulted in discontinuation in the FP group also were in single subjects and included dermatitis, bitter taste, dry mouth, eye pain, itching, skin rash, and increased levels of creatine phosphokinase. Three subjects treated with MP29-02 experienced a serious AE (SAE), which included Dengue fever, pyrexia, and appendicitis compared with one subject in the FP group (gastroenteritis and dehydration). All of these SAEs were considered unlikely related to treatment. No subject discontinued the study due to an SAE, and all SAEs resolved completely during the study. There were no deaths reported during the study.

**Nasal and ocular examinations.** As shown in Table IV, the subjects in both treatment groups had generally similar nasal examination findings over the course of treatment, with most parameters showing few changes from baseline. 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 2 treatment groups and were reduced after 6 and 12 months of treatment with either MP29-02 or FP (Table IV). There were no findings of moderate or severe epistaxis or grade 3 or 4 nasal

TABLE VI. Serum cortisol levels (subgroup of safety population)

| Fasting serum cortisol<br>(mcg/dL)        | MP29-02, mean $\pm$ SD<br>(no. of subjects) | FP, mean $\pm$ SD<br>(no. of subjects) |
|-------------------------------------------|---------------------------------------------|----------------------------------------|
| Baseline value for<br>6-mo assessment     | 12.21 $\pm$ 4.20 (154)                      | 12.53 $\pm$ 4.65 (78)                  |
| 6 mo                                      | 11.89 $\pm$ 4.55 (154)                      | 11.61 $\pm$ 4.62 (78)                  |
| Change from baseline<br>to 6 mo           | -0.31 $\pm$ 5.14 (154)                      | -0.92 $\pm$ 5.32 (78)                  |
| Baseline value for<br>12-mo/ET assessment | 12.19 $\pm$ 4.21 (137)                      | 12.52 $\pm$ 4.53 (73)                  |
| 12 mo/ET                                  | 12.11 $\pm$ 4.87 (137)                      | 11.48 $\pm$ 4.65 (73)                  |
| Change from baseline to<br>12 mo/ET       | -0.08 $\pm$ 5.53 (137)                      | -1.04 $\pm$ 4.96 (73)                  |

ET, Early termination.

irritation. One subject in each group had a grade 2 nasal irritation at month 6. No nasal mucosal ulcerations or septal perforations were observed. The incidence of abnormal ocular findings on ophthalmologic examination also was low for both groups (Table V). There was evidence of a posterior subcapsular cataract in 3 subjects in the MP29-02 group at month 6, which was considered mild and unlikely related to the study drug. All 3 subjects were discontinued from the study as per protocol. One subject in the MP29-02 group had evidence of moderate glaucoma at month 6 and was discontinued from the study, and one subject had a mild subcapsular cataract at month 12; both events were considered possibly related to study medication. Three subjects in the FP group had posterior subcapsular cataracts at the 12-month ophthalmologic examination, 2 of these were later found to be present at screening (randomized in error), and the third was considered mild and unrelated to study medication. One subject in each group reported moderate eye pain during the study, which, in both cases, was considered possibly related to treatment.

**Plasma cortisol measurements.** As shown in Table VI, mean  $\pm$  SD fasting serum cortisol was similar between treatment groups at baseline, month 6, and month 12. There also was no appreciable reduction in serum cortisol from baseline after 12 months of continuous treatment with either MP29-02 ( $-0.08 \pm 5.5$  mcg/dL) or FP ( $-1.04 \pm 5.0$  mcg/dL).

**Clinical laboratory and vital signs assessments.** The mean hematology, chemistry, and urinalysis values obtained at month 12 or upon early discontinuation were comparable with values determined at screening and were similar between the 2 treatment groups. There were no discontinuations due to abnormal laboratory values. In general, the mean changes in vital sign measurements from baseline to month 6 and to month 12 or early termination were similar in both treatment groups and were not considered clinically important.

## DISCUSSION

The design and sample size of this study fulfilled the requirements for evidence of long-term safety.<sup>7</sup> Both MP29-02 and intranasal FP were well tolerated. The AE profile was similar in both treatment groups, with a similarly low incidence of TRAE. The most common TRAEs were dysgeusia (2.5%) in the MP29-02 group and headache (4.3%) in the FP group. Changes in mean values of hematology, chemistry, and quantitative urinalysis

parameters at month 12 compared with values at screening were not appreciably different between treatment groups. Similarly, changes from baseline in serum cortisol levels were not substantially different between groups over a 52-week period.

Fluctuations in signs and symptoms are expected in patients with chronic rhinitis. In this long-term study, typical fluctuations in signs and symptoms during the course of rhinitis were generally not considered AEs. The focus of the nasal and ocular examinations was on any new finding, any clinically significant findings, or any worsening of a previously identified condition either reported on a nasal examination or by the patient. Findings of this nature were considered AEs. The incidence and the intensity of nasal examination findings in the 2 treatment groups were comparable and were reduced at month 6 and month 12 compared with screening values. Notably, the incidence of epistaxis in both groups was highest at screening (2.2% in MP29-02 group and 1.9% in the FP group). Reductions in the incidence of adverse nasal examination findings could be evidence of reductions in nasal inflammation, a possible beneficial effect of adhering to the treatment regimen over an extended period. Prevalence rates of cataract in India are double the rates in the United States; however, the overall incidence of any evidence of cataract in this study (0.8%) was below the expected incidence in the Indian general population over a 1-year period.<sup>8</sup>

Similar results have been reported in long-term studies by using intranasal corticosteroids.<sup>9-11</sup> For example, a 12-month study by Rosenblut et al<sup>10</sup> in 806 adult and adolescent subjects with perennial AR showed that intranasal fluticasone furoate was well tolerated with an incidence of most AEs (with the exception of epistaxis) similar to that observed with placebo. There was no clinically meaningful difference between fluticasone furoate and placebo in terms of mean changes in ophthalmic parameters, nor was there any evidence of clinically relevant systemic corticosteroid exposure.<sup>10</sup>

In the present long-term study, the most frequently reported AEs considered possibly or probably related to treatment were dysgeusia in the MP29-02 group and headache in the FP group. These AEs also were the most frequently reported after MP29-02 or FP use in subjects with moderate-to-severe SAR who were treated for 14 days.<sup>1-4</sup> An interim analysis of the data was conducted at 6 months, and the AE profile of MP29-02 at 12 months compared well with 6 months, and there was no evidence of any late-occurring AEs. When considering that the type and incidence of AEs were similar in this 1-year study and in the 14-day studies indicate that the incidence of AEs did not increase over time with continued exposure, further demonstrates the safety of MP29-02 for long-term treatment of SAR.

Although chronic use of orally inhaled corticosteroids has been associated with suppression of the hypothalamic-pituitary-adrenal axis,<sup>12,13</sup> chronic use of intranasal FP has been shown to be safe; recommended dosing has not produced clinically significant suppression of the hypothalamic-pituitary-adrenal axis.<sup>12,14,15</sup> In the current study, an analysis of fasting plasma cortisol levels showed no difference between the MP29-02 and FP treatment groups and, most importantly, no reduction between fasting plasma cortisol values at baseline compared with month 6 and month 12 or early

termination was detected. The open-label design of this study is a limitation and could have introduced bias. However, the open-label design, combined with the 52-week study duration and minimal clinical visits makes the trial as real to life as possible, and so the results obtained here are likely those achieved in everyday clinical practice. The absence of a placebo control also may be a limitation; however, FP, a commonly used intranasal corticosteroid for the treatment of AR with a well characterized safety profile was used as an active control. In conclusion, MP29-02 was well tolerated in this study. There was no evidence of unusual, unexpected, or late-occurring AEs, and no adverse nasal or ocular examination findings or laboratory assessments that would preclude the long-term use of MP29-02 in the treatment of AR.

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