RANDOMIZED, DOUBLE-BLIND TRIAL OF MP29-02 NASAL SPRAY COMPARED TO PLACEBO, AZELASTINE HYDROCHLORIDE NASAL SPRAY, AND FLUTICASONE PROPIONATE NASAL SPRAY IN THE TREATMENT OF PATIENTS WITH SEASONAL ALLERGIC RHINITIS (MP4006)

IND Number	77,363
Name of Product	MP29-02
Indication studied:	Seasonal Allergic Rhinitis
Developmental phase of study:	III
Study Design	Randomized, Double-blind, Parallel-group
First subject enrolled	08 Apr 2009
Last subject completed:	26 Aug 2009
Release date of report:	04 May 2010

Company/Sponsor signatory:

Meda Pharmaceuticals Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Meda Pharmaceuticals</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
MP29-02</td></tr>
<tr><td>Name of Active Ingredients:
Azelastine hydrochloride
Fluticasone propionate</td></tr>
<tr><td colspan="3">Title of Study:
Randomized, Double-Blind Trial of MP29-02 Nasal Spray Compared to Placebo, Azelastine Hydrochloride Nasal Spray, and Fluticasone Propionate Nasal Spray in the Treatment of Patients with Seasonal Allergic Rhinitis (MP4006)</td></tr>
<tr><td colspan="3">Principal Investigator:
Investigators: A list of study investigators is provided in Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Study center(s): A total of 49 sites in the United States participated in this study.</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 08 Apr 2009
Date last patient completed: 26 Aug 2009</td><td>Phase of development: III</td></tr>
<tr><td colspan="3">Objectives: The objective of this clinical trial was to compare the efficacy and safety of the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray (MP29-02) compared to placebo and to each product alone.</td></tr>
</table>

Methodology: This was a Phase III, randomized, double-blind, placebo-controlled, parallel-group study in subjects with moderate-to-severe seasonal allergic rhinitis (SAR). The study began with a 7-day, single-blind, placebo lead-in period (Day -7 to Day 1). Subjects were instructed to take placebo lead-in medication twice daily (1 spray per nostril), approximately every 12 hours. On Day 1, subjects who satisfied the symptom severity requirements and continued to meet all of the study inclusion/exclusion criteria were randomized in a 1:1:1:1 ratio to receive 1 spray per nostril twice daily of MP29-02, azelastine hydrochloride, fluticasone propionate, or placebo nasal spray.

Efficacy was assessed by the change from baseline in the subject-reported 12-hour reflective Total Nasal Symptom Score (TNSS). On Days 1 through 14, subjects rated the instantaneous and reflective TNSS symptoms of sneezing, nasal congestion, runny nose, and nasal itching; the instantaneous and reflective total ocular symptom score (TOSS) symptoms of itchy eyes, watery eyes and eye redness; the symptom of postnasal drip was rated reflectively, twice daily (AM and PM) in a diary prior to the dose of study medication. Symptoms were scored on a 0 to 3 scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms), such that the maximum daily symptom severity score was 24 for the TNSS and 18 for the TOSS. Additional secondary efficacy variables included reflective individual nasal and ocular symptom scores, as well as change from Baseline to Day 14 in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Subjects ≥ 18 years of age completed the RQLQ on Day 1 (prior to dosing) and Day 14. Subjects returned to the clinic on Day 7 for an interim evaluation. After completing the 2-week double-blind treatment period, subjects returned to the clinic on Day 14 (or at time of early termination) for an end-of-study evaluation. Safety and tolerability assessments were made on Days 7 and 14. Tolerability was evaluated by subject-reported adverse events (AEs), nasal examinations, and vital signs assessments.

Number of subjects (planned and analyzed):

A total of 1800 subjects were planned to be enrolled in this study. Overall, 1801 subjects were randomized to treatment. Results from all 1801 subjects (451 each in the MP29-02 and placebo groups, 449 in the azelastine group, and 450 in the fluticasone group) were included in the final safety population.

Diagnosis and main criteria for inclusion: Male and female subjects, 12 years of age and older with a minimum 2-year history of SAR and a positive skin test to a prevailing individual seasonal pollen during the previous year were eligible for this study. At Screening, subjects with a 12-hour reflective TNSS of at least 8 out of a possible 12 and a congestion score of 2 or 3 were eligible for single-blind period enrollment. On Day 1, subjects were eligible for randomization if, for the 3 days prior to randomization and on the morning of randomization, the sum of the 7 consecutive reflective AM and PM TNSS assessments were equal to or greater than 56, with a nasal congestion score equal to or greater than 14, and they had an instantaneous TNSS score of at least 8 and a congestion score of at least 2 at time point zero, just prior to beginning the onset of action assessment.

Test product, dose and mode of administration, batch number:

MP29-02
Mode of administration: Topical/intranasal spray
Dose: 548 mcg total daily dose of azelastine hydrochloride, and 200 mcg total daily dose of fluticasone propionate
Regimen: 1 spray per nostril twice daily (AM and PM)
Batch Number: G70454

Duration of treatment: 2 weeks of treatment

Reference therapies, dose and mode of administration, batch number:

Azelastine hydrochloride
Mode of administration: Topical/intranasal spray
Dose: 548 mcg total daily dose
Regimen: 1 spray per nostril twice daily (AM and PM)
Batch Number: G71093

Fluticasone propionate
Mode of Administration: Topical/intranasal spray
Dose: 200 mcg total daily dose (vehicle only)
Regimen: 1 spray per nostril twice daily (AM and PM)
Batch Number: G71092

Matched placebo
Mode of Administration: Topical/intranasal spray
Dose: 0 mcg total daily dose (vehicle only)
Regimen: 2 sprays per nostril once daily (AM)
Batch Number: GPL7028

Criteria for evaluation:

The primary objective of this study was to evaluate the efficacy of MP29-02 (fixed dose combination of azelastine hydrochloride and fluticasone propionate solution) at a dosage of 1 spray per nostril twice daily compared to each individual component and placebo at a dosage of 1 spray per nostril once daily.

Primary efficacy endpoint:

- Change from baseline in the 12-hour reflective TNSS for the entire double-blind period compared to placebo.

Secondary efficacy endpoints:

- Change from baseline in instantaneous TNSS for the entire 14-day study period;
- Change from baseline in 12-hour reflective individual symptom scores for the entire 14-day study period;
- Daily change from baseline in the 12-hour reflective and instantaneous TNSS for the 14-day study period;
- Onset of Action: change and percent change from baseline in instantaneous TNSS compared to placebo over the 4-hour period following initial administration of study drugs;
- Change from baseline in 12-hour reflective and instantaneous TOSS for the entire 14-day study period;
- Change from baseline in 12-hour reflective individual ocular symptom scores for the entire 14-day study period;
- Change from baseline in 12-hour reflective postnasal drip for the entire 14-day study period;
- Daily change from baseline in 12-hour reflective postnasal drip for the entire 14-day study period;
- Change from baseline to Day 14 in the RQLQ, including overall score and 7 individual

domains, in subjects age 18 or older.

Safety: Safety was assessed by incidence, type and severity of adverse events, as well as by clinical assessments such as a focused nasal examination and vital signs measurements. For female subjects of childbearing potential, a negative urine pregnancy test was required for study participation.

Statistical methods: All statistical conclusions were based on a .05 level of significance and all statistical tests were 2-sided. A repeated-measures analysis was performed on the primary efficacy variable, change from baseline in 12 hour reflective TNSS for the entire 14-day study period compared to placebo that included all changes in 12-hour reflective TNSS in an analysis of covariance (ANCOVA) model with unspecified covariance structure for the ITT population. The model contained study day as the within-subject effect, treatment group and site as the between-subject effect, and baseline as a covariate.

In order to adjust for multiplicity, a gatekeeping strategy was employed. The MP29-02 – placebo comparison was first tested at the .05 significance level. If this was significant, then the MP29-02 – azelastine comparison was also done at the .05 level. If the MP29-02 – azelastine comparison was not significant at the .05 level, no comparison of MP29-02 to fluticasone was made; otherwise the comparison was made at the .05 level. Once these 3 test comparisons were shown to be significantly different in favor of MP29-02, the reflective TOSS was examined in the same order specified for TNSS.

All secondary efficacy analyses were performed as described for the primary efficacy endpoint. Only the ITT population was used. For RQLQ, the change from baseline to Day 14 was calculated for the overall score and for the individual domains. Assumptions of the ANCOVA model were checked including site by treatment interaction. Further sensitivity analyses comprised raw data analysis without imputation and analyses of the PP population.

The incidence of AEs was summarized by body system and preferred term overall as well as by maximum severity and relationship to study drug. The incidence of treatment-related AEs was summarized by body system and preferred term.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary Efficacy Variable:

- In the primary efficacy variable of change from baseline in the 12-hour reflective TNSS, MP29-02 had an LS mean change of -5.53. Changes in the azelastine, fluticasone and placebo groups were -4.82, -4.89 and -3.40, respectively. The difference in the LS mean change from baseline in the reflective TNSS between MP29-02 and the placebo treatment group was statistically significant ($P \leq .001$). The differences in the LS mean change from baseline between MP29-02 and azelastine and between MP29-02 and fluticasone were also statistically significant ($P = .016$ versus azelastine; $P = .029$ versus fluticasone).

Secondary Efficacy Variables:

- The change from baseline in the instantaneous TNSS for the entire 14-day study period was statistically significant for MP29-02 versus placebo ($P < .001$).
- In individual nasal symptom scores, the LS mean improvements for MP29-02 were statistically significant for all symptoms versus placebo ($P < .001$).
- The daily change from baseline values in the 12-hour reflective and instantaneous TNSS demonstrated continuous improvement in the active treatment groups over the 14-day study period. The improvement in subjects in the MP29-02 group was significantly better

versus subjects in the placebo group on all study days ($P < .001$).

- Beginning 30 minutes after the first dose of study medication and continuing through the end of the 4-hour assessment, subjects who received MP29-02 showed significantly more improvement in TNSS when compared to subjects who received placebo ($P \leq .008$).
- The change from baseline in reflective and instantaneous TOSS for the entire 14-day study period was statistically significant ($P < .001$) with MP29-02 versus placebo.
- For the individual ocular symptoms of itchy eyes, watery eyes and eye redness, MP29-02 significantly improved symptoms when compared to placebo ($P < .001$).
- For postnasal drip, the LS mean improvements for MP29-02 were statistically significant when compared to placebo ($P < .001$), azelastine ($P = .047$) and fluticasone ($P = .009$).
- In the adult-administered RQLQ, the improvements observed for MP29-02 were superior to placebo in all domains and in the overall score, with $P < .001$ for each category.

MP29-02 demonstrated statistical significance when compared to placebo and to the monotherapy components in the primary endpoint of this study, the overall change from baseline to Day 14 in the reflective TNSS. The inclusion of a treatment-by-site interaction term had no relevant impact on estimates of treatment differences or *P* values. Neither had missing values, as indicated by the raw data analysis, or protocol violations, as indicated by the analysis of the PP subset of patients. Thus, the results of the sensitivity analyses further confirm the results of the primary analysis.

This improvement in reflective TNSS with MP29-02 was statistically significant compared to placebo beginning on Day 2 (the first timepoint evaluated), and remained significant over the entire 14-day study period.

There was evidence of a contribution of each component to the efficacy of the combination drug across all of the secondary analyses, including evaluation of individual nasal and ocular symptoms. In addition, the adult RQLQ score for MP29-02 was significantly improved over placebo for overall score and for each individual RQLQ domain.

SAFETY RESULTS:

MP29-02 nasal spray administered as a single spray per nostril twice daily was well tolerated for the 14-day study period of this trial. Overall, among 1801 subjects in the Safety Population, 198 treatment-related, treatment-emergent adverse events (TR-TEAEs) were reported: 76 in the MP29-02 group [reported in 50 subjects (11.1%)], 62 in the azelastine group [reported in 45 subjects (10.0%)], 35 in the fluticasone group [reported in 28 subjects (6.2%)], and 25 in the placebo group [reported in 18 subjects (4.0%)]. The most common TR-TEAEs reported were dysgeusia (bitter taste), headache, and epistaxis. The majority of all AEs were mild in nature.

There were no deaths reported during the study period. Two subjects experienced SAEs during this study. One subject in the MP29-02 group reported a lacerated right hand, 7 days after the start of the double-blind Treatment Period; this SAE was judged to be unlikely related to study drug administration, and the subject continued in the study following a 2-day dose interruption. A subject in the placebo group experienced an SAE of pyogenic arthritis of the right elbow, beginning on Study Day 1. This event was considered to be unlikely related to study drug administration, and the subject discontinued from the study due to this AE.

Fifteen subjects who received study medication withdrew from the study due to AEs: 3 each in the MP29-02 and fluticasone groups, 4 in the azelastine group and 1 in the placebo group. The reasons for discontinuation varied among subjects. Two severe AEs were cited as reason for discontinuation, and included an event of sinusitis in a subject in the placebo group, and an event of pyogenic (bacterial) arthritis in the right elbow in a different subject in the placebo group. Eight subjects discontinued due

to AEs that were possibly or probably related to study treatment. Those events included nausea and epistaxis (in 2 subjects in the MP29-02 group); headache, postnasal drip, abdominal discomfort, dysgeusia, mucosal excoriation and nasal mucosal disorder (in 3 subjects in the azelastine group); mucosal erosion (in 2 subjects in the fluticasone group); and mucosal erosion (placebo group).

In the focused nasal examinations, the number and severity of examination findings was greatest at Screening and decreased as the study progressed.

Overall, the subjects on this study experienced few events. All study treatments were well tolerated.

CONCLUSIONS:

MP29-02 nasal spray is an investigational drug consisting of a fixed-dose combination of 2 approved medications (azelastine hydrochloride and fluticasone propionate) administered 1 spray per nostril twice daily.

Because azelastine and fluticasone have distinctly different mechanisms of action, it was hypothesized that the combination would produce a superior improvement in TNSS as compared to either component alone. This hypothesis was supported by the efficacy findings from this prospectively designed trial: MP29-02 was significantly better than placebo in improvement in TNSS, and also was also significantly better than either of the monotherapy agents alone. Moreover, MP29-02 was better than placebo in reducing TOSS. The results of this study also demonstrated that each component of MP29-02 made a contribution to the overall efficacy. Results were confirmed with sensitivity analyses. Secondary endpoints also supported the results of the primary analysis.

MP29-02 was well tolerated for the 14-day study period of this trial. The most common TR-TEAEs with MP29-02 were dysgeusia (bitter taste), headache, and epistaxis. The majority of all AEs were mild in intensity. In general, TR-TEAEs were generally quantitatively and qualitatively similar between the active treatment groups. There were no deaths and only 2 serious adverse events in this study. Only 3 subjects discontinued MP29-02 due to an adverse event. There were no remarkable findings for vital signs and nasal examinations.

Based on the results of this double-blind, placebo-controlled trial, MP29-02 provided a benefit compared to placebo and each of its individual components.

Date of the report: 04 May 2010

NAME OF FINISHED PRODUCT: Dymista® Nasenspray			

SUPPLEMENTARY INFORMATION TO SYNOPSIS

Study No.: **MP4006** **Report No.:** **not applicable**

Eudra-CT No.: **not applicable** **IND No.:** **77,363**

Substantial amendments (protocol amendments and premature interruption and/or discontinuation):

No.	Date issued	In force	Modifications
1	23 January 2009	Upon approval by IRB/EC	Protocol Amendment 1: For changes see Amendment 2
2	25 March 2009	Upon approval by IRB/EC	Protocol Amendment 2 included changes to the methodology, increase in study sites and sample size, changes to some inclusion criteria, more specific details on procedures, and some administrative modifications.

Principal Investigator (site 637) and study centers: Cf. next pages

Publication (reference):

Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol 2012;129:1282-9.

Site Number	Investigator	Institution	Street	City	State	Zip
601	n.n.	Allergy and Asthma Research	333 Londonderry Drive	Waco	TX	76712
602	n.n.	Diagnostic Research Group	4410 Medical Drive	San Antonio	TX	78229
603	n.n.	Bensch Research Associates	4632 Georgetown Place	Stockton	CA	95207
604	n.n.	Clinical Research Institute	2805 Campus Dr	Plymouth	MN	55441
605	n.n.	Bernstein Clinical Research Center	8444 Winton Road	Cincinnati	OH	45231
606	n.n.	Southern California Research	27800 Medical Center Road	Mission Viejo	CA	92691
607	n.n.	East Tennessee Center for Clinical Research	801 Weisgarber Road	Knoxville	TN	37909
608	n.n.	Allergy Research Foundation	11620 Wilshire Blvd.	Los Angeles	CA	90025
609	n.n.	Allergy & Asthma Care of Waco	221 Jewell Dr.	Waco	TX	76712
610	n.n.	Allergy, Asthma & Immunology Associates	7514 E. Monterey Way	Scottsdale	AZ	85251
611	n.n.	Allergy and Clinical Immunology Associates	180 Fort Couch Road	Pittsburgh	PA	15241
612	n.n.	Allergy, Asthma Research Center	2414 Babcock Rd	San Antonio	TX	78229
613	n.n.	The Asthma and Allergy Center	401 E. Gold Coast Road	Papillion	NE	68046
614	n.n.	AABI Associates Medical Group	11180 Warner Avenue	Fountain Valley	CA	92708
615	n.n.	Pharmaceutical Research & Consulting, Inc	5499 Glen Lakes Dr.	Dallas	TX	75231
616	n.n.	Central Texas Health Research	705-A Landa St.	New Braunfels	TX	78130
617	n.n.	Intermountain Clinical Research	150 South 1000 East	Salt Lake City	UT	84102
618	n.n.	Allergy & Asthma Center of Austin	10801 N. Mopac Expy	Austin	TX	78759
619	n.n.	Allergy and Asthma Clinical Research, Inc.	130 La Casa Via	Walnut Creek	CA	94598
620	n.n.	Clinical Research Institute	825 Nicollet Mall	Minneapolis	MN	55402
621	n.n.	Clinical Research Institute of Southern Oregon, PC	3860 Crater Lake Ave.	Medford	OR	97504
622	n.n.	The Clinical Research Center, LLC	1040 North Mason Rd	St. Louis	MO	63141
623	n.n.	North Carolina Clinical Research	2615 Lake Drive	Raleigh	NC	27607
624	n.n.	AARA Research Center	9900 N. Central Expway	Dallas	TX	75231
625	n.n.	RESEARCH Asthma, Sinus & Allergy Centers	65 Mountain Blvd Ext	Warren	NJ	07059
626	n.n.	Western Sky Medical Research	2121 Wyoming Avenue	El Paso	TX	79903
627	n.n.	Allergy & Asthma Medical Group & Research Center	9610 Granite Ridge Dr	San Diego	CA	92123

Site Number	Investigator	Institution	Street	City	State	Zip
628	n.n.	Allergy & Asthma Care Center of So. Cal	3816 Woodruff Ave	Long Beach	CA	90808
629	n.n.	Northeast Medical Research Associates, Inc.	49 State Road	N. Dartmouth	MA	02747
630	n.n.	Asthma & Allergy Associates	2709 N. Tejon Street	Colorado Springs	CO	80907
631	n.n.	Sneeze, Wheeze & Itch Associates, LLC	2010 Jacobssen Drive	Normal	IL	61761
632	n.n.	Colorado Allergy and Asthma Centers, PC	125 Rampart Way	Denver	CO	80230
633	n.n.	Princeton Center for Clinical Research	24 Vreeland Drive	Skilman	NJ	08558
634	n.n.	Clinical Research Center	317 N. El Camino Real	Encenitas	CA	92024
635	n.n.	Family Allergy & Asthma	1700 Bluegrass Avenue	Louisville	KY	40215
636	n.n.	Allergy Associates Medical Group	6386 Alvarado Court	San Diego	CA	92120
637	**Paul Ratner, MD**	Sylvana Research Associates	7711 Louis Pasteur Dr.	San Antonio	TX	78229
638	n.n.	National Allergy, Asthma, & Urticaria Centers of Charleston, PA	1879 Savage Rd.	Charleston	SC	29407
639	n.n.	Clinical Research Atlanta	980 Johnson Ferry Rd.	Atlanta	GA	30342
640	n.n.	Asthma, Nasal Disease & Allergy Research Center of New England	95 Pitman Street	Providence	RI	02906
641	n.n.	Allergy and Asthma Consultants of NJ-PA	555 Second Ave.	Collegeville	PA	19426
642	n.n.	Atlantic Research Center, LLC	802 West Park Ave.	Ocean	NJ	07712
643	n.n.	Storms Clinical Research Institute	1625 Medical Center Point	Colorado Springs	CO	80907
644	n.n.	Allergy, Asthma, & Clinical Research Center	4200 W. Memorial Road	Oklahoma City	OK	73120
645	n.n.	Asthma, Inc.	4540 Sand Point Way NE	Seattle	WA	98105
646	n.n.	Allergy & Asthma Associates	3410 Far West Blvd.	Austin	TX	78731
647	n.n.	Clinical Research Atlanta	175 Country Club Dr.	Stockbridge	GA	30281
648	n.n.	Kansas City Allergy and Asthma	8675 College Blvd	Overland Park	KS	66210
649	n.n.	Sneeze, Wheeze & Itch Associates, LLC	2010 Jacobssen Drive	Normal	IL	61761