2 SYNOPSIS

Title of Study: Onset of Action of Mometasone Furoate Nasal Spray vs. Placebo in Induced Allergic Rhinitis in an Allergen Exposure Unit (AEU) P03431.

Investigator(s): Robert Berkowitz, MD

Study Center(s): 1

Publication(s): 

Studied Period: 12/15/03 – 2/21/04
Clinical Phase: IV

Objective(s):

1. The primary objective was to determine the “onset of action” of mometasone furoate nasal spray (MFNS), ie, relief of the nasal symptoms, in subjects with ragweed pollen-induced allergic rhinitis in an AEU. The time of the onset of action was the first assessment time at which a consistent statistically significant difference between treatments in reduction from pre-dose baseline of the total nasal symptoms severity score was achieved.

2. The secondary objectives were to compare the effects of mometasone furoate nasal spray and placebo on the following endpoints:

- Changes/percent changes at the time of onset of action from baseline in the nasal congestion severity score, in the other individual nasal symptom severity scores, and in the nasal plus non-nasal symptoms severity scores.

- Proportion of subjects who have shown good/excellent therapeutic response at each timepoint.

Methodology: A randomized, placebo controlled, parallel-group, and double-blind single dose study to be conducted at a single center in conformance with Good Clinical Practices.

Number of Subjects: Randomized (N=340); Safety/ITT (N=340); MITT (N=287); PP (N=283)

Diagnosis and Criteria for Inclusion:

Subjects were eligible for enrollment if they:

- were ≥12 years old, of either gender, of any race;

- had a history of SAR to ragweed pollen for at least one year, as diagnosed by the investigator, another physician, or subject-provided history;

- had a positive skin test (prick) to short ragweed allergen. A positive test is defined as a wheal diameter ≥ 3 mm greater than with the diluent control;

- participated in 1 to 2 priming sessions (Phase II) with short ragweed pollen in the AEU and qualified to proceed to the treatment day session (Phase III). To qualify at priming, the subject had to meet the following symptom severity scores on any two diary cards within the first 2 hours of either of the two priming days:

  - ≥ 2 (moderate) for nasal congestion

  AND

  - ≥ 6 out of the maximum of 12 for combined nasal (congestion, sneezing, rhinorrhea, itching) symptoms

To qualify for dosing on the treatment day, the 90 minute diary after initiation of pollen exposure must have had the following severity scores:

- ≥ 2 (moderate) for nasal congestion
AND

- ≥ 6 out of the maximum of 12 for combined nasal (congestion, sneezing, rhinorrhea, itching) symptoms;
- had not participated in previous Nasonex Park study, P97019.

Test Product, Dose, Mode of Administration, Batch No(s): Mometasone furoate nasal spray, single dose of 200 mcg (2 sprays per nostril), batch no. 79229-101

Duration of Treatment: One dose

Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo nasal spray, single dose (2 sprays per nostril), batch no. 2-SP-22

Criteria for Evaluation:

Efficacy

The primary efficacy measurement in this study is the total nasal symptoms score (TNSS) which is the sum of scores of rhinorrhea, nasal stuffiness/congestion, sneezing and nasal itching.

The secondary efficacy measurements include:

Nasal Symptoms:
Rhinorrhea, nasal stuffiness/congestion, sneezing and nasal itching measured with a 4-point scale (0=None; 1=Mild; 2=Moderate; 3=Severe) after 90 and 120 minutes of pollen exposure on the treatment day and then every 60 minutes post-dose for 12 hours.

Non-Nasal Symptoms:
Eye itching, eye tearing and itching ears/palate measured with a 4-point scale (0=None; 1=Mild; 2=Moderate; 3=Severe) after 90 and 120 minutes of pollen exposure on the treatment day and then every 60 minutes post-dose for 12 hours.

TNSS:
Total non-nasal symptoms score (sum of the severity scores for the 3 non-nasal symptoms).

TSS:
Total symptoms score (sum of the 4 nasal symptom scores and the 3 non-nasal symptom scores).

Global Therapeutic Response:
Evaluation of global therapeutic response of symptoms measured with a 5-point scale (1=Excellent; 2=Good; 3=Fair; 4=Poor; 5=Failure) beginning 60 minutes post-dose on the treatment day and then every 60 minutes for the next 11 hours.

If the severity score for any nasal symptom/non-nasal symptom is missing, then TNSS/TNNSS and TSS was set to missing.

Statistical Methods:

Efficacy: The changes/percent changes of total nasal symptom scores (TNSS) at each time point from baseline were summarized and analyzed using a one-way ANOVA model containing the fixed effect of treatment. The 95% confidence interval for the difference between treatments (MFNS minus placebo) was calculated. In addition, the TNSS were analyzed with a repeated measurement model containing the effects of treatment, time, and treatment by time interaction, with the random effect of subject nested within treatment. The test of treatment effect used subject within treatment as an error term. The SAS procedure PROC MIXED was used. The between-treatment difference in the baseline data was examined using one-way ANOVA. If the baseline was unbalanced, the ANOVA model to adjust the baseline would be used for analysis.

The secondary efficacy measures, four individual nasal symptoms (rhinorrhea, nasal stuffiness/congestion, sneezing and nasal itching), three individual non-nasal symptoms (eye itching, eye tearing and itching ears/palate), TNSS, and TSS were analyzed with the same methods used for the primary efficacy.

The global therapeutic response was tabulated and tested using the Mantel-Haenzel test (general association). The percentage of excellent and good responses were collapsed and analyzed using binomial test.

Safety: The incidence of treatment-emergent AE and treatment-associated treatment-emergent AE were...
summarized by severity and treatment for each preferred term and body system. The occurrence of AE in subjects was evaluated with the Fisher exact test.

**SUMMARY - CONCLUSIONS:**

**RESULTS:**

**Efficacy:**

An additional population, the Modified Intent-to-Treat (MITT) population was defined for analyses, although this population was not included in the study protocol. The MITT population excluded subjects who dosed prior to the second baseline diary evaluation (120 minutes post pollen exposure).

All subjects in the MITT population (N=287) completed the study and were the basis of the efficacy evaluation. The mean total nasal symptom scores (TNSS) decreased in both treatment groups during the 12-hour treatment period. However, there is no difference in TNSS between treatment groups through the 12 hour period.

The individual nasal and non-nasal symptom scores, total non-nasal symptom scores, and the total nasal and non-nasal symptoms decreased during treatment, though the difference was not significant between placebo and MFNS subjects.

Both treatment groups had improvement after treatment from 1 to 4 hours, then remained stable on the global response; however, it was not statistically significantly different between these two groups.

**Safety:**

The most frequently reported AE occurred in the eye, respiratory system, and skin and subcutaneous tissue disorders. The highest incidence of AE in the MFNS treatment group was epistaxis (1.8%) and urticaria (1.8%) compared to 0.6% of placebo subjects for both epistaxis and urticaria. There were no subject discontinuations due to adverse events.

**CONCLUSIONS:**

This study provides evidence of the beneficial effect of MFNS on total and individual nasal symptom scores, total and individual non-nasal symptom scores, and total nasal plus non-nasal symptom scores. Additionally, MFNS was associated with improvements in evaluation of global therapeutic response. However, time of onset for MFNS was not demonstrated compared to placebo. Mometasone Furoate Nasal Spray was well tolerated; the most common incidence of AE on the medication was epistaxis and urticaria.

**Date of the Report:** 26 January 2005