2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Clinical Trial Designed to Assess the Safety and Efficacy of Ciclesonide (200 mcg and 100 mcg, once daily) Applied as a Nasal Spray for Two Weeks in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 6 to 11 Years of Age

Investigator(s) and study center(s): 69 centers in the USA.

Publication (reference): N/A

Studied period: First patient in: 14-Mar-2006

Last patient out: 16-Oct-2006

Clinical phase: Phase III

Objectives: The primary objective of this study was to demonstrate the efficacy of ciclesonide, administered intranasally as a spray formulation at two dose levels (200 mcg and 100 mcg, once daily) compared with placebo in the treatment of SAR in pediatric patients (6-11 years of age, inclusive).

The secondary objective of this study was to demonstrate the local safety and tolerability of ciclesonide, administered intranasally as a spray formulation at two dose levels (200 mcg and 100 mcg, once daily) compared with placebo in the treatment of SAR in pediatric patients (6-11 years of age, inclusive).

Methodology: This was a randomized, double-blind, placebo-controlled, multi-center, parallel-group study of intranasally administered ciclesonide 200 mcg or ciclesonide 100 mcg administered once daily for 2 weeks in which 618 patients were randomly assigned to 200 mcg ciclesonide, 100 mcg ciclesonide or placebo. The study was conducted in pediatric patients with SAR at 69 investigational centers in the United States.

The study consisted of two periods:

- Baseline Period (7 to 14/21 days from Visit B0 to Visit T0 [21 days for patients on intranasal corticosteroids at Visit B0]);
- Treatment Period (14 + up to 4 days from Visit T0).

Informed consent/assent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained at the Screening Visit (B0) and prior to performing any study procedures. Eligibility to enter the study was established by medical history, physical examination, and skin prick results. Patients were seen on an outpatient basis at all visits.

An Interactive Voice Response System (IVRS) was used for central randomization for all subjects fulfilling screening and randomization criteria and was also responsible for activation/deactivation of the site, dispensation of drug, drug supply management and early terminations/completions.

During the Baseline and Treatment Period, AM and PM patient diary data was provided by the parent/caregiver, using a telephone-based system (IVRS). The parent/caregiver evaluated the patient's nasal symptoms over the 12 hours prior to the recording of the score (reflective scores) and over the last 10 minutes (instantaneous scores). The nasal symptoms evaluated were sneezing, runny nose, nasal itching, and nasal congestion. After completing this record each morning during the treatment period, the parent/caregiver was to administer to the patient the randomly assigned treatment:

- ciclesonide nasal spray (200 mcg once daily [2 actuations of 50 mcg/nostril]); or
- ciclesonide nasal spray (100 mcg once daily [2 actuations of 25 mcg/nostril]); or
- placebo nasal spray (2 actuations per nostril, once daily).

The following clinical variables were assessed at the stated times during this study.

Efficacy

The primary efficacy endpoint of this study was the average of AM and PM parent/caregiver-reported reflective Total Nasal Symptom Score (TNSS) over the 2-week treatment period.

Key secondary efficacy endpoints of this study were:

- Physician-assessed nasal symptom score at Endpoint;
- Average of AM and PM parent/caregiver-reported instantaneous TNSS over the 2-week treatment period;

Other efficacy measures included the following:

- Average of AM and PM parent/caregiver-reported reflective and instantaneous TNSS over the 2-week treatment period and by day;
- Reflective and instantaneous separate AM and PM parent/caregiver-reported TNSS over the 2-week treatment period;
- Average AM and PM parent/caregiver-reported reflective and instantaneous TNSS at each day over the 2-week treatment period;
- Individual symptoms of the average AM and PM reflective and instantaneous TNSS over the 2-week treatment period;
- Physician-assessed nasal signs and symptoms score at Endpoint;
- Physician-assessed nasal signs score at Endpoint;
- Individual symptoms of the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) at Endpoint;
- Individual signs of the PANS at Endpoint.

Safety

- Spontaneous and elicited adverse events (AEs) at all visits;
- Physical examinations at all visits;
- Ear, nose and throat (ENT) examinations at all visits;
- Vital signs at all visits.

Compliance with the assigned treatment regimen was assessed based upon the treatment administration information recorded in the electronic diary by the parent/caregiver.

Individual patient participation in the study concluded after the final assessments at Visit T1 at 14 + up to 4 days.

No. of patients (total and for each treatment) planned and analyzed: The total number of patients randomized was 618: 215 in the 200 mcg ciclesonide group, 199 in the 100 mcg ciclesonide group and 204 in the placebo group. All patients were included in the Safety Analysis Set and in the ITT Analysis Set. There were 551 patients in the Per Protocol Analysis Set.

Diagnosis and main criteria for inclusion: The study population defined in the protocol consisted of male and female patients in general good health, 6 to 11 years of age, with a

history of SAR to a relevant seasonal allergen (pollen) for a minimum of two years immediately preceding the study.

Test product, dose, mode of administration, batch no.: Ciclesonide

Dose: 200 mcg (50 mcg/actuation, 2 actuations/nostril) once daily or 100 mcg (25 mcg/actuation, 2 actuations/nostril) once daily.

Mode of administration: intranasally (spray)

Batch Nos.: 2812406/350381000 (ciclesonide 50 mcg/actuation), and 2812308/450081000 (ciclesonide 25 mcg/actuation)

Duration of treatment: 2 weeks

Reference product, dose, mode of administration, batch no.: Placebo

Duration of treatment:

Dose: 2 actuations per nostril, once daily

Mode of administration: intranasally (spray)

Batch Nos.: 2812102/450271000

Duration of treatment: 2 weeks

Criteria for evaluation:

Analysis Sets: Three analysis sets were assessed (total set, full analysis set and valid cases or Per-Protocol [PP] set). The total set consisted of all patients enrolled, including patients withdrawn prior to randomization and those randomized patients who never took study medication. The full analysis set consisted of patients who had received at least one dose of study medication. Intent-to-Treat (ITT) analyses were based on those patients in the full analysis set who had at least one post-baseline value for efficacy. The valid cases (PP) set

consisted of the full analysis set without any major protocol violations and was used for PP analyses.

Efficacy: The primary efficacy variable in this study was the average of AM and PM parent/caregiver-reported reflective TNSS over the 2 weeks of treatment. Key secondary efficacy endpoints of this study were: physician-assessed nasal symptom score at Endpoint and average of AM and PM parent/caregiver-reported instantaneous TNSS over the 2-week treatment period. Other effectiveness variables were: measures based on the parent/caregiver-reported reflective TNSS and its respective individual nasal symptoms; measures based on the separate AM and PM parent/caregiver-reported instantaneous TNSS and its respective individual symptoms; scores derived from the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) and its respective individual signs and symptoms.

Safety: Safety was assessed by spontaneous and elicited AEs, vital signs, and physical examinations including ENT exams.

Statistical methods:

Using an estimate of the standard deviation of the change from baseline of 2.4, 217 patients per group would provide 90% power to detect a difference between treatment groups of 0.75 in the change from baseline in overall TNSS with a two-sided alpha level of 0.05. As the number of withdrawals was anticipated to be low, and all randomized patients were to be included in the ITT analysis, it was planned to randomize 220 patients to each treatment group.

In order to control Type I error rates, a sequential approach across doses was used for the interpretation of the results for the primary efficacy measure. If the p-value for the difference in treatment effect between the 200 mcg dose and placebo was ≤ 0.05 then the 100 mcg dose versus placebo was examined. Additionally, to control Type I error rates for the key secondary measures, a sequential approach across the measures was combined with a sequential approach across doses as illustrated immediately below where both previous doses comparison and measures were required to be statistically significant in order to draw inferential conclusions.

Order of Testing for Determining Statistical Significance

Start →	200 mcg vs. Placebo	100 mcg vs. Placebo	200 mcg vs. 100 mcg
Days 1-14 Reflective TNSS	↓ →	↓ →	↓
Physician-Assessed Nasal Symptoms at Endpoint	↓ →	↓ →	↓
Days 1-14 Instantaneous TNSS	□ →	□ →	□

Note: Arrows indicate the order of testing, from left to right and from top to bottom.

Changes from baseline in the average of AM and PM parent/caregiver-reported reflective TNSS over the 2-week treatment period were analyzed using the ITT Analysis Set. Treatment groups were compared using repeated measures analysis with covariate adjustment for treatment, baseline, day and the treatment-by-day interaction. Treatment and day were treated as an unordered categorical variable. An AR(1) model in conjunction with treating patient as a random effect was used to model intra-patient correlation. Estimated treatment differences and 95% confidence intervals for the treatment differences were provided. Similar methods were used for the analysis of other variables based on the reflective TNSS and its individual symptoms and for variables based on the instantaneous TNSS and its individual symptoms. Changes from baseline in the physician-assessed nasal signs and symptom score and its associated individual signs and symptom scores were analyzed using analysis of covariance (ANCOVA) with adjustment for pooled center, treatment and baseline. Estimated treatment differences with 95% confidence intervals were provided for each treatment difference.

Local tolerability as assessed by changes in ENT examination findings over the study period were summarized by transition tables. Adverse events, SAEs, drug-related AEs, and AEs leading to withdrawal were summarized by incidence. Changes from Baseline in vital signs were summarized using descriptive statistics by treatment group.

SUMMARY

Summary:

Efficacy Results:

At Baseline, the mean average of the AM and PM reflective TNSS was similar in all treatment groups: 8.25 in the ciclesonide 200 mcg group, 8.41 in the ciclesonide 100 mcg group and 8.41 in the placebo group. A decrease from Baseline in reflective TNSS over the 2-week treatment period was observed in all treatment groups which was estimated to be significantly greater in the ciclesonide 200 mcg group than in the placebo group, with this difference being 0.39 (95% CI: 0.02, 0.76; p=0.040). Since this treatment difference was significant, the difference between ciclesonide 100 mcg and placebo was examined. The treatment difference for this comparison was not significant.

At Endpoint, defined as the last on treatment assessment, improvements from baseline were seen in all treatment groups for the physician-assessed nasal symptom score. Changes seen in the ciclesonide 200 mcg group were significantly greater than those seen with placebo with the estimated treatment difference between these two groups being 0.92 (95% CI: 0.38, 1.45; $p<0.001$). As the difference between ciclesonide 200 mcg and placebo was significant, results for the other key secondary efficacy variable, the average AM and PM instantaneous TNSS over the 2-week treatment period, were examined. Improvements from baseline were seen in all treatment groups over the 2-week treatment period. Changes seen in the ciclesonide 200 mcg group were significantly greater than those seen with placebo with the estimated treatment difference between these two groups being 0.37 (95% CI: 0.00, 0.73; $p=0.047$). Since the treatment difference for ciclesonide 100 mcg versus placebo was not significant for the primary efficacy variable, no inferential conclusions can be drawn for comparisons for this dose versus placebo for secondary efficacy variables.

On all treatment days, there was a larger numerical change from Baseline in the average AM and PM reflective TNSS for both ciclesonide treatments than for placebo and there was a trend for the differences to increase over time compared with placebo. A decrease from baseline in AM reflective TNSS over the 2-week treatment period and in PM reflective TNSS over the 2-week treatment period was seen in all treatment groups, with numerically greater changes seen with ciclesonide than with placebo. Analysis of separate AM and PM reflective TNSS over the 2-week treatment period showed appreciable differences between ciclesonide 200 mcg and placebo with the estimated treatment difference being 0.35 for AM reflective TNSS (95% CI -0.04, 0.74; $p=0.075$) and 0.42 for PM reflective TNSS (95% CI: 0.04, 0.80; $p=0.030$). Numerically smaller treatment differences were observed between ciclesonide 100 mcg and placebo.

Decreases in each of the average AM and PM reflective individual symptom scores were seen in all three treatment groups. The decreases over the 2-week treatment period were numerically larger for ciclesonide 200 mcg and ciclesonide 100 mcg than for placebo for each individual symptom. For nasal congestion, appreciable differences compared with placebo were seen for both ciclesonide 200 mcg (estimated treatment difference 0.13) and ciclesonide 100 mcg (estimated treatment difference 0.12). Appreciable treatment differences over the 2-week treatment period (ranging from 0.08 to 0.10) were also seen between ciclesonide 200 mcg and placebo for the other individual symptoms, indicating that all four individual symptoms contributed to the treatment difference observed in the reflective TNSS.

Results for the instantaneous TNSS were consistent with those for the reflective TNSS. On all treatment days, there was a larger numerical change from Baseline for both ciclesonide

treatments than for placebo and there was a trend for the differences compared with placebo to increase over time. A decrease from baseline in AM instantaneous TNSS over the 2-week treatment period and in PM instantaneous TNSS over the 2-week treatment period was seen in all treatment groups, with numerically greater changes seen with ciclesonide than with placebo. Decreases in each of the average AM and PM individual instantaneous symptom scores were seen in all three treatment groups. The decreases over the 2-week treatment period were numerically larger for ciclesonide 200 mcg and ciclesonide 100 mcg than for placebo for each individual symptom.

Consistent with the results for the physician-assessed nasal symptom score, the physician-assessed nasal signs and symptoms score showed a decrease in all three treatment groups at Endpoint, with numerically larger decreases in the ciclesonide treatment groups than in the placebo group. There was an appreciable estimated treatment difference (0.78) between ciclesonide 200 mcg and placebo (95% CI: 0.34, 1.22; $p<0.001$). Results for the physician-assessed signs score at Endpoint were also consistent with those for the physician-assessed nasal signs and symptom score and the physician-assessed nasal symptom score, with an appreciable estimated treatment difference (0.64) observed between ciclesonide 200 mcg and placebo (95% CI: 0.18, 1.09; $p=0.006$).

Examination of the results for individual physician-assessed symptoms revealed numerically greater improvements at Endpoint in each individual nasal symptom (nasal congestion, runny nose, nasal itch and sneezing) for both ciclesonide treatments compared with placebo. These changes were numerically larger for the 200 mcg/day treatment group than for the 100 mcg/day group for each individual nasal symptom. Numerically greater improvements at Endpoint in swollen nasal passages, presence of nasal secretions and evidence of post-nasal drip or throat irritation were observed for both ciclesonide treatments compared with placebo but not for discoloration of nasal passages. Again, these changes were numerically larger for the 200 mcg/day treatment group than for the 100 mcg/day group.

Safety Results:

The mean number of days of study medication exposure was similar for the three treatment groups, being 14.3 days for ciclesonide 200 mcg, 14.2 days for ciclesonide 100 mcg and 14.1 days for placebo.

Ninety-nine (16.0%; 99/618) patients reported at least one TEAE and the overall incidence was slightly higher in the placebo group (19.1%) than in the ciclesonide 100 mcg group (16.6%) or the ciclesonide 200 mcg group (12.6%). The most commonly reported TEAE was epistaxis reported by 1.4% with ciclesonide 200 mcg, 3.5% with ciclesonide 100 mcg and

3.9% with placebo. With the exception of nasal discomfort which was reported more frequently in the placebo group (3.4%) than in either ciclesonide group (0.5% in each group), there were no appreciable differences between the treatment groups with respect to incidence of TEAEs and no evidence for any dose-related differences. In general, there also were no appreciable differences between the treatment groups with respect to intensity of TEAEs. Only 8 patients (three in the ciclesonide 200 mcg group, three in the ciclesonide 100 mcg group and two in the placebo group) experienced TEAEs of severe intensity. AEs considered to be treatment-related (definitely or likely) by the investigator were reported by 4.7% (29/618) of patients overall. Five patients (2.3%) in the ciclesonide 200 mcg group, seven patients (3.5%) in the ciclesonide 100 mcg group and 17 patients (8.3%) in the placebo group experienced AEs considered to be treatment-related. Epistaxis was the TEAE that was most commonly reported as treatment-related, but the incidence was similar or greater in the placebo group (3.9%) than in either the ciclesonide 200 mcg group (0.9%) or ciclesonide 100 mcg group (3.0%). No other TEAE was reported as treatment-related for more than one patient in either ciclesonide treatment group.

Fourteen patients, three in the ciclesonide 200 mcg group, five in the ciclesonide 100 mcg group and six in the placebo group experienced TEAEs that led to premature discontinuation from the study. In five patients (one in the ciclesonide 100 mcg group and four in the placebo group), the TEAEs that led to premature discontinuation were considered by the investigator to be related to study treatment. In the ciclesonide 100 mcg group the patient experienced nasal disorder (irritated nasal turbinates), epistaxis, nasal discomfort (nasal burning) and throat irritation and in the placebo group the patients experienced epistaxis (two patients), nasal discomfort (nasal irritation), and hypersensitivity (increased allergy symptoms).

Two deaths occurred during the study, both of which were unrelated to study treatment. Two patients who were cousins (Patient 4751/6623 and Patient 4751/6652) died from injuries sustained in an automobile accident. Patient 4751/6623 (ciclesonide 100 mcg group) had completed the study Treatment Period and Patient 4751/6652 (ciclesonide 200 mcg group) was on Day 12 of treatment. No other serious adverse events occurred during this study.

In all treatment groups, only small mean changes in vital signs were observed. Transitions in ENT findings were similar for patients among all treatment groups. Few transitions from normal to abnormal in physical examinations occurred and findings were similar for patients among all treatment groups.