2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Clinical Trial Designed to Assess the Safety and Tolerability of Ciclesonide (200 mcg Once Daily), Applied as a Nasal Spray for Twelve Weeks, in the Treatment of Perennial Allergic Rhinitis (PAR) in Pediatric Patients 2-5 Years of Age

Investigators: [redacted]

Publication (reference): N/A

Studied period (years): First patient in: 22-Nov-2005

Last patient out: 26-Jun-2006

Clinical phase: Phase III

Objectives:

The primary objective of this study was to evaluate the safety and tolerability of ciclesonide 200 mcg administered once daily as an intranasal spray for 12 weeks, in pediatric patients (ages 2-5 years) with PAR.

The secondary objective of this study was to evaluate the efficacy of ciclesonide 200 mcg administered once daily as an intranasal spray for 12 weeks, in pediatric patients (ages 2-5 years) with PAR.

Methodology:

This was a randomized, double-blind, placebo-controlled, multi-center, parallel-group study of intranasally administered ciclesonide 200 mcg administered once daily for 12 weeks in which 125 patients were randomly assigned to 200 mcg ciclesonide or placebo. The study was conducted in pediatric patients with PAR at three investigational centers in the United States.

The study consisted of two periods:

- baseline period (7 to 14-d from Visit B0 to Visit T0);
- treatment period (84 ± 4-d from Visit T0).

Informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained from parent/caregiver on or before the Screening Visit (B0) and prior to performing any study procedures. Eligibility to enter the study was established by medical history, physical examination, skin prick results, and clinical laboratory evaluations. 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 pre-randomization criteria and was also responsible for activation/deactivation of the site, dispensation of drug, drug supply management and early terminations.

During the Baseline and Treatment Period, the parent/caregiver maintained a daily diary recording his/her evaluation of the patient's nasal symptoms. These nasal symptoms were to be based upon a 24-h retrospective assessment of four individual nasal symptoms: sneezing, runny nose, nasal itching, and nasal congestion. In addition, the parent/caregiver was to note any adverse events that occurred and record these in the space provided in the diary records. After completing this record each morning, 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
- placebo nasal spray (2 actuations per nostril, once daily).

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

Safety

- physical examinations at Visits B0 and T4;
- ENT examinations at all visits;
- spontaneous and elicited adverse events (AEs) at all visits;
- vital signs at all visits;
- cortisol (AM serum sample drawn prior to 9.00 am at Visits B0, T2, and T4);
- clinical laboratory parameters at Visits B0 and T4.

Efficacy

Since this was a safety study, there was no declared primary efficacy endpoint. However, efficacy measures were collected and included the following:

- daily morning Reflective (24-h) Total Nasal Symptom Score (TNSS) over 12 weeks of treatment and over other selected time points based on daily parent/caregiver diary data;
- physician assessment of nasal symptoms (PNSS) as derived from the investigator query of the parent/caregiver on the intensity of four allergic rhinitis symptoms (nasal discharge, nasal itching, nasal congestion, and sneezing) for the patients enrolled in the study at Visits B0, T0, T1, T2, T3, and T4.

Compliance with the assigned treatment regimen was assessed at each post-randomization visit (T1 through T4) by two methods. The primary measure of compliance relied upon the treatment administration information recorded in the daily diary by the parent/caregiver. A secondary measure consisted of the difference in each respective study medication bottle weight over each treatment interval. A new bottle was to be dispensed after each compliance evaluation.

Individual patient participation in the study concluded after the final assessments at Visit T4 at 84 ± 4-d.

No. of patients (total and for each treatment):

The total number of patients randomized was 125: 83 in the 200-mcg ciclesonide group and 42 in the placebo group. All patients were included in the Safety Analysis Set and 123 patients were included in the ITT Analysis Set.

Diagnosis and criteria for inclusion:

The study population defined in the protocol consisted of male and female patients in general good health, 2 to 5 years of age, with a history of PAR to a relevant perennial allergen for a minimum of 90-d immediately preceding the study.

Test product: Ciclesonide

Dose: 200 mcg (50 mcg/actuation, 2 actuations/nostril) once daily

Mode of administration: intranasally (spray)

Batch Nos.: 2812406/0410181000 and 2812406/0350361000

Duration of treatment: 12 weeks

Reference product: Placebo

Dose: 2 actuations per nostril, once daily

Mode of administration: intranasally (spray)

Batch Nos.: 2812102/0140171000

Rescue Medication: Loratadine syrup

Dose: 5mg/5mL

Mode of administration: 1 teaspoon (5 ml) once daily; 1 mg not to exceed 5 mg/24-h. Rescue medication was to be used on an as needed basis (prn).

Batch Nos.: Supplied commercially at investigational site.

Criteria for evaluation:

Analysis Sets: Two analysis sets were assessed (ITT and Safety). The ITT analysis set consisted of patients who had received at least one dose of study medication and had at least 1 post-baseline value of efficacy. The Safety analysis set consisted of all randomized patients who had received at least one dose of study medication.

Safety: Safety was assessed by spontaneous and elicited AEs, vital signs, cortisol (AM serum), clinical laboratory parameters, and physical examinations including ENT exams.

Efficacy: Changes from baseline in AM 24-h reflective Total Nasal Symptom Score (TNSS) over 12 weeks of treatment and over selected time points and a physician assessment of nasal symptoms at Endpoint and at each visit were assessed.

Statistical methods: For this study, no prospective calculations of statistical power were made. The sample size was selected to provide information on safety and tolerability following multiple doses of ciclesonide. A total of 102 patients were to be randomized with 68 patients assigned to ciclesonide nasal spray at a dose of 200 mcg per d and 34 patients assigned to placebo.

Local tolerability as assessed by changes in ENT examination findings over the study period were summarized by contingency 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. Changes from Baseline in AM serum cortisol were summarized using descriptive statistics by treatment group and 95% confidence intervals for treatment differences were provided. The confidence intervals were based on an ANCOVA model with factors of age, sex, treatment group, center, and baseline cortisol value.

As this was primarily a safety study, there was no declared primary efficacy measure. However, changes from baseline in the daily TNSS were analyzed over Days 1-84 and for each week using weekly averages within a repeated measurements ANCOVA model. Changes from baseline in the PNSS were analyzed at Endpoint and at each post-Baseline visit using ANCOVA.

Summary:

Efficacy Results: Since the primary objective of this study was the evaluation of the safety of ciclesonide nasal spray, the study was not adequately powered to detect differences in efficacy variables. However, the LS mean decrease from Baseline in the reflective 24-h AM TNSS averaged over 12 weeks of treatment was 2.32 for the ciclesonide group and 1.46 for the placebo group, providing an estimated difference of 0.86, $p = 0.021$, 95% CI: (0.13, 1.60). The LS mean decrease from Baseline in average reflective 24-h AM TNSS over each study week during Weeks 1-12 was numerically greater in the ciclesonide group for every weekly interval from Week 1 through Week 12. Furthermore, the overall change in TNSS was driven by contributions from all four symptom components.

Although there were large average changes from Baseline in both treatment groups, the PNSS derived from the physician query of parents/caregivers showed no consistent difference between treatment groups. Also, rescue medication usage was similar between the two treatment groups (mean: 0.6 ± 0.122 teaspoons on an average of 6.1-d during the study for ciclesonide versus 0.6 ± 0.129 teaspoons for an average of 5.2 study d for placebo).

Safety Results:

As summarized below, the results of this study demonstrated that ciclesonide administration at 200 mcg/d showed no meaningful differences versus placebo in the incidence of AEs or in other safety assessments:

- of the 125 patients included in the safety analyses, 73 (58.4%) experienced at least 1 treatment emergent adverse event (TEAE): 50 (60.2%) in the ciclesonide group and 23 (54.8%) in the placebo group. The intensity of these events was balanced between treatment groups;
- adverse events considered to be treatment-related (definitely or likely) by the investigator were reported by 3.2% (4/125) of patients overall. Three treatment-related AEs (3.6%; 3/83) were reported among patients in the ciclesonide group. One patient reported eye irritation and nasal discomfort (1), another experienced epistaxis and a third individual, hemoptysis. One (2.4%; 1/42) patient in the placebo group experienced nasal discomfort;
- three incidents resulted in discontinuation of study medication, two occurring in the ciclesonide group and one in the placebo group. Eye irritation and nasal discomfort were reported in one patient, and headache and dizziness in another receiving ciclesonide. A skin rash was reported in one patient in the placebo group;
- for AM serum cortisol, no appreciable difference between treatment groups were indicated by the 95% confidence intervals for the treatment differences from placebo;
- no relevant treatment-related findings were observed for the other safety assessments;
- no deaths or SAEs occurred in this study.

Date of report: 22-Mar-2007