2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Clinical Trial Designed to Assess the Safety of Ciclesonide, Applied as a Nasal Spray at Three Dose Levels, 200 mcg, 100 mcg, or 25 mcg Once Daily for Six Weeks, in the Treatment of Perennial Allergic Rhinitis (PAR) in Pediatric Patients 2-5 Years of Age.

Investigator: [redacted] Arkansas Research Medical Testing Center, 1207 Rebsamen Park Road, Little Rock, Arkansas 72202.

Study center: 1 center in the US

Publication (reference): N/A

Studied period (years): First patient in: September 10, 2004
Last patient's last visit: April 25, 2005

Clinical phase: Phase 3

Objectives: The primary objective of the study was to demonstrate the safety of ciclesonide, administered as an intranasal spray formulation for six weeks at three dose levels, 200, 100, or 25 mcg, once daily (QD) versus placebo in the treatment of PAR in pediatric patients (age 2 to 5 years old).

The secondary objective of the study was to measure serum concentrations of ciclesonide and its active metabolite under steady state conditions at three time points corresponding to the presumed peak and trough exposure after six weeks of administration in pediatric patients (age 2 to 5 years old) with PAR.

In addition, reflective 24-hour AM Total Nasal Symptom Scores (TNSS) over the six weeks of treatment and at various time points and Overall Physician-Assessed Nasal Symptom Scores (PNSS) were assessed at Endpoint and various time points.

Methodology: This was conducted as a randomized, double-blind, placebo-controlled, single-center, parallel-group study of ciclesonide at doses of 200, 100, or 25 mcg administered via intranasal spray QD. A total of 120 patients (30 per treatment arm) were to be randomly assigned in a 1:1:1:1 ratio among the following 4 treatments: 200 mcg ciclesonide, 100 mcg ciclesonide, 25 mcg ciclesonide, or placebo. The study was conducted at one investigational center in the US.

The study consisted of three periods: a 3- to10-day Baseline Period, a 6-week Treatment Period, and a 7-day Follow-up Period. Patients were to be seen on an outpatient basis at the

Screening Visit (B0), Visit T3 (Day 21), and the Follow-up Visit (Day 50). Patients were to stay overnight at the investigational site for the Randomization Visit ($T0^{-1}$ through T0; Days 0 and 1, respectively) and the last Treatment Visit (T6 through $T6^{+1}$; Days 42 and 43, respectively).

No. of patients (total and for each treatment): The total number of patients randomized was 133: 33 in the 200 mcg ciclesonide group, 33 in the 100 mcg ciclesonide group, 33 in the 25 mcg ciclesonide group, and 34 in the placebo group. All patients were included in the Safety Analysis Set, 132 patients were included in the ITT Analysis Set, and 113 were included in the Per-Protocol (PP) Analysis Set.

Diagnosis and criteria for inclusion: Male and female patients, in general good health, aged 2 to 5 years, who had a history of PAR to a relevant perennial allergen for a minimum of 3 months immediately preceding the study were eligible for study participation. Patients were excluded if they had a history or physical findings of nasal pathology (within the last 60 days), biopsy (within the last 60 days), trauma, surgery, or atrophic rhinitis or rhinitis medicamentosa (within the last 60 days); a respiratory infection or disorder within the last 14 days; active asthma that required treatment with inhaled or systemic corticosteroids and/or routine use of beta-agonists or any controller drugs (theophylline, leukotrienes, etc.); or used systemic corticosteroids within the past 2 months. Additionally, patients were excluded if they particpated in an investigational drug trial within the previous 30 days, had an elevated intraocular pressure (IOP) at baseline > 21 mm Hg or required anti-epileptic treament.

Test product: Ciclesonide

Dose: 200 mcg (50 mcg/actuation) QD, 100 mcg (50 mcg/actuation) QD, 25 mcg (12.5 mcg/actuation) QD

Mode of administration: Ciclesonide was administered via intranasal spray. Each patient received two bottles (Bottles A and B) and parents/caregivers were instructed to administer one actuation per nostril from each bottle, QD.

Batch Nos.: 2812406/0140181000 (50 mcg) and 2812200/0140121000 (12.5 mcg)

Duration of treatment: six weeks

Reference product: Placebo

Mode of administration: Placebo was administered via intranasal spray. Each patient received two bottles (Bottles A and B) and parents/caregivers were instructed to administer one actuation per nostril from each bottle, QD.

Batch Nos.: 2812102/0140161000

Rescue Medication: Chlorpheniramine maleate syrup

Dose: 1mg/5mL

Mode of administration: One teaspoon (1 mg) every 4 to 6 hours; 1 mg not to exceed 12 mg/24 hours. Rescue medication was to be used on an as needed basis (prn).

Batch Nos.: Supplied commercially at investigational site.

Other Products: Proparacaine HCl ophthalmic 0.5% solution

Dose: 1 drop per eye

Mode of administration: 1 drop per eye approximately 2 to 3 minutes prior to intraocular pressure (IOP) measurement.

Batch Nos.: Supplied commercially at investigational site.

Criteria for Evaluation:

Analysis Sets: Three analysis sets were analyzed (ITT, PP, 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 PP analyses set is based on the valid cases set which excludes observations occurring after major protocol violations. The Safety analysis set consisted of all randomized patients who had received at least one dose of study medication.

Efficacy: The efficacy variables measured included the changes from baseline in reflective 24-hour AM TNSS over 6 weeks of treatment and at selected time points as well as the Overall Physician-Assessed Nasal Symptom Score (PNSS) at various time points.

Safety: Safety assessments included the following: review of spontaneous and elicited adverse events (AEs); vital sign measurements; physical examination findings, including ear, nose, and throat (ENT) examinations and IOP assessments; urine free cortisol (24-hour urine) and plasma cortisol levels; and clinical laboratory tests.

Pharmacokinetics (PK): Blood samples were collected at the T6 visit (pre-dose, and 2 and 5 hours post-dose) to assess PK characteristics of ciclesonide administered as an intranasal spray in this age group.

Statistical methods: For this study, no prospective calculations of statistical power were made. The sample size was selected to provide information on ciclesonide nasal spray safety, tolerability, and PK characteristics following multiple doses of ciclesonide.

As this was primarily a safety study, there was no primary efficacy measured. The 24-hour AM reflective TNSS and individual symptom questions for the 24-hour reflective TNSS were summarized over Days 1 through 42 and over each week. Baseline was defined as the mean TNSS over the last 7 days prior to randomization. Changes from baseline in the PNSS were summarized at Endpoint and at Visits T3 and T6. The measurement at Visit $T0^{-1}$ served as the Baseline for PNSS, and Endpoint was defined as the last visit during the treatment period with non-missing data.

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), drug-related AEs, and AEs leading to withdrawal were summarized by incidence, intensity, and causality.

Changes from Baseline in vital sign measurements were summarized using descriptive statistics by treatment group. Similarly, IOP and changes in IOP were examined using summary statistics. Changes from Baseline in 24-hour urine free cortisol and AM plasma free cortisol were summarized using descriptive statistics by treatment group and 95% confidence intervals (CIs) for treatment differences were provided. The CIs were based on an analysis of covariance (ANCOVA) model with factors of age, gender, treatment group, and baseline cortisol value. If enough serum concentrations of ciclesonide or its active metabolite were above the LLOQ (Lower Limit of Quantification) for any dose, PK parameters were to be estimated.

SUMMARY

Efficacy Results:

Although this was primarily a safety study, in an attempt to observe efficacy trends in the active dose groups compared to the placebo group, various efficacy measures were incorporated into the study design at the request of the FDA. These included: PNSS, 24-hour reflective TNSS and rescue medication usage.

The PNSS was derived from the physician query of parents/caregivers on the severity of the following AR symptoms: runny nose, itchy nose, congestion, and sneezing. At Baseline, the mean PNSS scores ranged from 5.6 in the placebo group to 7.0 in the ciclesonide 100 mcg group. At Endpoint, the estimated mean decrease from Baseline in overall PNSS was 2.93 (95% CI for treatment difference from placebo: -0.6, 1.7) for the ciclesonide 200 mcg group, 3.48 (95% CI for treatment difference from placebo: 0.0, 2.3) for the ciclesonide 100 mcg

group, 2.97 (95% CI for treatment difference from placebo: -0.5, 1.8) for the ciclesonide 25 mcg group, and 2.36 for the placebo group.

The parent/caregiver reflective 24-hour AM TNSS was defined as the sum of reflective (over the past 24 hours) scores for nasal stuffiness/congestion, nasal itching, sneezing, and runny nose from the parent/caregiver-rated diary. At Baseline, the mean 24-hour AM TNSS scores ranged from 4.5 in the ciclesonide 25 mcg group to 5.4 in the ciclesonide 100 mcg group. Over six weeks of treatment, the mean decrease from Baseline in the average reflective 24-hour AM TNSS was 1.5 for the ciclesonide 200 mcg group, 2.0 for the ciclesonide 100 mcg group, 1.5 for the ciclesonide 25 mcg group, and 1.6 for the placebo group.

The greatest improvements relative to placebo in TNSS were observed in the 100 mcg ciclesonide treatment group. While this could be suggestive of a treatment effect, the most likely explanation for this finding was the higher baseline symptom scores in this treatment group relative to the other groups. Since there was no model adjustment for baseline, some if not all of the greater mean change in the 100 mcg ciclesonide treatment group could also be explained by a regression to the mean.

Thus, although trends were observed, no definitive conclusions regarding efficacy can be drawn. This finding is not unexpected considering the subjective nature of the efficacy measures being evaluated, which were completed by a third party (parent or caregiver). Due to these reasons, assessment of symptoms in 2 to 5 year old children is considered to be unreliable for evaluation of efficacy.

Safety Results:

The overall mean number of days of study medication exposure was 40.9. One hundred twenty-nine (97.0%) of the 133 randomized patients completed the study.

Thirty (22.6%; 30/133) patients reported at least one treatment-emergent adverse event (TEAE): 6 (18.2%), 8 (24.2%), 7 (21.2%) and 9 (26.5%) in the ciclesonide 200 mcg, 100 mcg, 25 mcg and placebo, respectively. The most commonly reported adverse events were nasopharyngitis (4.5%), epistaxis (3.0%), cough (3.0%), and pyrexia (2.3%). In general, there were no appreciable differences among the treatment groups with respect to incidence of TEAEs and intensity. Most TEAEs were considered by the investigator to be mild or moderate in intensity. None led to premature discontinuation from the study.

Two (1.5%; 2/133) patients experienced TEAEs that were considered by the investigator to be likely related to study medication: 1 (3.0%; 1/33) patient in the ciclesonide 100 mcg group experienced epistaxis and 1 (2.9%; 1/34) patient in the placebo group experienced a headache. Neither incident required discontinuation of study medication.

One (0.8%; 1/133) patient experienced an SAE during the study. This involved a 2-year-old Caucasian male who was admitted to the hospital with "swollen lymph nodes", "severe abdominal cramping" and a temperature of 104º F approximately 4 weeks after receiving his last dose of study medication (ciclesonide 25 mcg). A CAT scan and a bone scan were conducted but were found to be inconclusive. After a period of observation, the patient was discharged.

Most patients experienced fluctuations in clinical laboratory tests within the normal range during the study. Generally, the observed changes to outside the normal range for the various clinical laboratory tests during the study period appeared to be random in nature. Mean changes in clinical laboratory tests throughout the study were similar in all treatment groups. Two (1.5%; 2/133) patients experienced an investigator-designated laboratory AE. However, these AEs were deemed by the investigator unlikely to be related to the study medication. Patient #5129 in the ciclesonide 200 mcg group and #5131 in the ciclesonide 100 mcg group experienced an increase in their alkaline phosphatase values. Patient #5129 exhibited a value of 274 IU/L during the Screening Period but 1577 IU/L at Visit T6. Subsequent repeat follow-up tests disclosed values of 488 and 321 IU/L. Patient #5131 exhibited a value of 235 IU/L during the Screening Period but 2264 IU/L at Visit T6. Subsequent repeat follow-up tests disclosed values of 462 and 278 IU/L. The investigator did not consider either of these observations to be a serious adverse event.

All abnormal vital signs, physical examination and ENT findings for patients in this study were regarded as not clinically significant at Baseline or at Endpoint. The majority of patients had Baseline examination findings consistent with PAR and related physical findings. No treatment related physical examination and ENT findings were observed in patients among the four treatment groups.

Intraocular pressure (mmHg) was measured at Visits B0, T3, and T6. There were no clinically meaningful mean changes from Baseline to Endpoint in any treatment group. The changes in intraocular pressure for the ciclesonide groups were numerically smaller than placebo.

Plasma and urine free cortisol:

An analysis of the urine free cortisol using the cortisol (creatinine corrected) analysis set demonstrated a similar estimated mean decrease from baseline of –6.87, -14.03, -13.54 and -6.76 for the 200 mcg, 100 mcg, 25 mcg and placebo groups, respectively. Although a non-significant dose related decrease for mean change from baseline in plasma cortisol was observed, this was most likely a spurious finding since the changes were small in magnitude (approximately 12% reduction) and were not confirmed by the more sensitive HPA axis assessment of urinary free cortisol.

PK Results:

Only 3 (1.1%) of 285 plasma samples obtained from ciclesonide-treated patients demonstrated detectable levels of ciclesonide. Thirty-eight (13.3%) of 285 plasma samples obtained from these ciclesonide-treated patients demonstrated detectable levels of the active metabolite of ciclesonide. The level of detectible values increased with higher dosages of ciclesonide with the greatest proportion of patients (12/31) with detectible levels of des-ciclesonide occurring at two hours post dosing in the 200 mcg ciclesonide treatment group. Despite these detectible levels, the highest value of des-ciclesonide observed at the 200 mcg ciclesonide dosage group was 39.11 pg/mL, while the highest detectable value for des-ciclesonide was 64.49 pg/ml observed in one patient receiving ciclesonide 25 mcg. This limited number of detectable values was insufficient to support a conventional pharmacokinetic assessment. There was no indication of a relationship between detectable levels of active metabolite and changes in 24-hour urinary cortisol.