2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial Designed to Assess the Efficacy and Safety of Ciclesonide Applied as a Nasal Spray at Three Dose Levels (200 mcg, 100 mcg, or 25 mcg, once daily) in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 6-11 Years of Age.

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Study center: 74 centers in the US and Canada.

Publication (reference): Not applicable

Studied period (years): First patient in: June 4, 2004
Last patient's last visit: July 1, 2005

Clinical phase: Phase 3

Objectives: The primary objective of this study was to demonstrate the efficacy of ciclesonide, administered intranasally as a spray formulation at 3 dose levels (200 mcg, 100 mcg, or 25 mcg, once daily) vs placebo in the treatment of PAR in pediatric patients (ages 6-11 years). The additional objectives of this study were to demonstrate the safety of administering ciclesonide intranasally and to determine the optimal dose in pediatric patients (ages 6-11 years) with AR.

Methodology: This study was designed as a randomized, double-blind, parallel-group, placebo-controlled, multicenter clinical trial to be conducted in pediatric patients 6-11 years of age with PAR at 74 investigational centers in the United States and Canada. Six hundred sixty-five (665) patients were randomized, 165 to the intranasal ciclesonide 200 mcg group, 166 to the intranasal ciclesonide 100 mcg group, 169 to the intranasal ciclesonide 25 mcg group, and 165 to the placebo group.

The study consisted of three periods:

- Baseline Period (7-14 days; Screening Visit [B0] to Randomization Visit [T0]);
- Treatment Period (12 weeks; Randomization Visit [T0] to Visit T12);
- Follow-up Period (7 days after last treatment dose to the Follow-up Visit [F]).

Patients were seen on an outpatient basis at the Screening Visit (B0), Randomization Visit (T0) at 7-14 days after the Screening Visit, Visit T3 at Day 22, Visit T6 at Day 43, Visit T9 at Day 64, Visit T12 at Day 85, and Visit F at Day 92.

Visits B0, T6 and T12 were to have taken place before 10:00 AM. At Visit B0 or T0 (or both), all patients were required to demonstrate a positive skin prick test to an allergen, which is known to induce PAR, or to have documentation of a positive skin prick test for a PAR allergen within 12 months prior to the Screening Visit (Visit B0). All patients were required to have a history of PAR to a relevant perennial allergen for a minimum of 6 months immediately preceding the Screening Visit (B0).

Patients who successfully completed all screening assessments and who met all eligibility criteria received an allergic rhinitis assessment diary to record their allergic rhinitis symptoms. Patients were given written and verbal instruction for properly recording nasal PAR symptoms in the diary twice daily. At Visit T0, patients must have achieved a patient/caregiver-assessed reflective Total Nasal Symptom Score (TNSS) (AM or PM) of at least 5 out of a possible 12 on at least 4 of the last 7 days of the Baseline Period to be eligible for randomization. Patients must also have experienced at least 1 individual reflective nasal symptom that had an assessment of moderate intensity or greater on at least 4 of the last 7 days of the Baseline Period.

Randomized patients and their caregivers received instructions on completion of the diary cards and on the proper use of the nasal spray. Beginning on Day 1 of the Treatment Period, patients/caregivers recorded nasal (both reflective and instantaneous) symptoms twice daily, once in the morning and once in the evening (approximately 12 hours later). Rescue medication was provided to patients at the T6 visit for use between this visit and the T12 visit.

At all visits, ear, nose and throat (ENT) examinations were performed. At all but the post-treatment Follow-up Visit [F], the Physician Assessment of Nasal Signs and Symptoms Severity was conducted, and any use of prohibited drugs was evaluated. At Visits T0, T3, T6, T9, and T12, a patient compliance check was conducted, and patient diaries were reviewed. At Visits T0, T3, T6, T9, T12, and F, adverse events (AEs) and concomitant medications were recorded. A comprehensive physical

examination, including determination of vital signs, and blood collection for hematology, blood chemistry, and pregnancy assessment were performed at Visits B0 and T12. Intraocular pressure was measured at Visits B0, T6, and T12. One hundred forty four patients provided 24-hour urine samples for urine cortisol assessment at Visits T0, T6, and T12. Plasma cortisol was collected in this same subset at Visits B0 and T12. A subset of 72 of these 144 patients who underwent cortisol assessment also were to provide blood samples at Visit T6 for pharmacokinetic analysis.

No. of patients (total and for each treatment): The number of patients randomized was 665; 664 patients were included in the intention-to-treat (ITT) analyses, 665 included in safety analyses, and 546 had at least some efficacy data included in the per-protocol (PP) analyses.

Diagnosis and criteria for inclusion: The study population targeted in the protocol consisted of male and female patients in general good health, between the ages of 6 and 11, with a history of PAR for a minimum of 6 months immediately preceding the Screening Visit (B0). Patients also were to have required treatment for PAR in the past, were expected to require treatment for PAR throughout the study period, and were to have a demonstrated sensitivity to a perennial allergen.

Test product: Ciclesonide

Dose: 200 mcg, 100 mcg or 25 mcg once daily

Mode of administration: Intranasal spray

Batch Nos.: 2812200/0140121000 (12.5 mcg ciclesonide); 2812406/0140121000 and 2812406/0140191000 (50 mcg ciclesonide)

Duration of treatment: 12 weeks

Reference Product: Placebo

Dose: 0

Mode of administration: Intranasal spray

Batch Nos.: 2812102/0140171000 and 2812102/0140161000

Criteria for evaluation:

Efficacy: The primary efficacy measure was the average of AM and PM patient/caregiver-reported reflective TNSS over the first 6 weeks of treatment. Key secondary efficacy measures were average AM and PM patient/caregiver-reported reflective TNSS over the 12 weeks of treatment and Overall Physician Assessment of Nasal Symptom Severity at Endpoint (Weeks 1-6). Additional secondary efficacy measures were: average AM and PM patient/caregiver-reported reflective TNSS over Weeks 7-12 and by each week as well as individual symptom assessments; AM patient/caregiver-assessed TNSS and PM patient/caregiver-assessed TNSS Weeks 1-6, 7-12, 1-12 and by each week; overall reflective average AM and PM patient/caregiver-assessed TNSS over Week 1-6 and 1-12; average AM and PM instantaneous TNSS, AM instantaneous TNSS, PM instantaneous TNSS, and individual symptom questions for average of AM and PM instantaneous TNSS Weeks 1-6, 7-12, 1-12, and by each week; time to maximal effect; average AM and PM patient/caregiver-assessed reflective TNSS by each day over the 12 weeks; percent change in AM and PM patient/caregiver-assessed reflective TNSS: Weeks 1-6, 7-12, 1-12, and by each week; Overall Physician Assessment of Nasal Signs and Symptom Severity (PANS) at T3, T6, T9, T12, and Endpoint; average of overall signs and overall symptoms severity scores at T3, T6, T9, T12, and Endpoint; individual sign and individual symptom severity scores at T3, T6, T9, T12, and Endpoint; rescue medication usage over Weeks 7-12 by day.

Safety: Safety was assessed by spontaneous and elicited adverse events (AEs), physical examination including ENT examinations, vital signs, intraocular pressure (IOP) assessment, and clinical laboratory assessments, as well as AM plasma cortisol and urine cortisol (24-hour) in 144 patients.

Pharmacokinetics: Serum concentrations of ciclesonide and its active metabolite were measured following 6 weeks of treatment at pre-dose and at Hours 2 and 5 post-dose in a subset of 72 patients who were undergoing assessments of urine and plasma cortisol.

Statistical methods: It was assumed that the correlation between any 2 observations from the same subject was 0.7 after adjusting for day. It was further assumed that the standard deviation for a single observed change from baseline in the average of AM and PM TNSS was 2.3. Thus the standard deviation for the mean change from baseline over six weeks was estimated to be 1.9. Using this standard deviation, 159 patients per group provided 80% power to detect a difference between treatment groups of 0.6 in the change from baseline in the overall TNSS with a two-sided alpha level of 0.05.

The primary analysis was performed on weekly averages of the average AM and PM reflective TNSS over Weeks 1-6 using the intent-to-treat (ITT) analysis set. Treatment groups were compared using repeated measures analysis of covariance with covariate adjustment for pooled center, baseline, treatment, week, and the treatment-by-week interaction. Week was treated as an unordered categorical variable. A first order autoregressive [AR(1)] structure was used to model intra-subject correlation in conjunction with treating patient as a random effect. This yielded a correlation structure in which observations from the same patient were considered to be correlated, with observations closer in time being more correlated. Baseline was defined as the average AM and PM TNSS over the last seven days prior to randomization. Estimated treatment differences and 95% confidence intervals for the treatment differences were provided. No imputation for missing data was performed as the extent of missing data was predicted to be low and the chosen analysis, as a maximum likelihood method, was valid for missing-at-random missingness (1).

A sequential approach across the doses combined with a sequential approach across the measures was used in order to control type I error rates for each dose and each endpoint. Changes from Baseline for other diary measures examined over time were analyzed in a similar fashion to the primary endpoint. Changes from Baseline for individual time points from the patient/caregiver diary and changes in physician-assessed symptoms were analyzed using ANCOVA with covariates pooled center, treatment, and baseline. The time to maximal effect was defined as the number of days until the first treatment day on which the estimated difference between ciclesonide and placebo is at least 90% as large as the largest estimated difference.

Adverse events (AEs), serious adverse events (SAEs), drug-related AEs, and AEs leading to withdrawal were summarized by incidence. AM plasma and 24-hour urine cortisol and intraocular pressure (IOP) were analyzed using 95% confidence intervals created using ANCOVA with covariate treatment, baseline, pooled center, gender, and age. Lab data were examined using summary statistics, categorization by normal and alert ranges, and shift tables. Vital signs and changes in vital signs were examined using summary statistics.

SUMMARY

Efficacy Summary:

- A decrease from Baseline in the average AM and PM patient/caregiver-assessed reflective TNSS over Weeks 1-6 was observed in all 4 treatment groups. There were no appreciable treatment differences between the

ciclesonide 100 mcg, ciclesonide 25 mcg and placebo groups. There was an appreciable, but non-statistically significant difference, between the ciclesonide 200 mcg group and placebo of 0.31 (95% CI: -0.1, 0.8; p=0.164) for Weeks 1-6. Additionally, there was an appreciable difference between the ciclesonide 200 mcg group and the ciclesonide 25 mcg group of 0.40 (95% CI: -0.0, 0.8; p=0.072).

- Though there were no appreciable differences from placebo in the patient/caregiver-assessed reflective TNSS over Weeks 1-12, there was an appreciable difference between the ciclesonide 200 mcg group and the 25 mcg group of 0.38 (95% CI: -0.1, 0.8; p=0.096).

- There was a decrease from Baseline in the overall physician assessment of nasal symptoms in all 4 treatment groups at Endpoint. This decrease was greatest in the ciclesonide 200 mcg group, with a mean treatment difference from placebo of 0.80 (95% CI: 0.2, 1.4; p = 0.006).
- Differences in instantaneous TNSS were somewhat less than those observed in the reflective TNSS.
- Differences between ciclesonide 200 mcg and placebo for both the overall PANS (treatment difference: 0.79) and the physician assessment of signs (treatment difference: 0.74) were similar to that observed with the overall symptoms (treatment difference 0.80).
- In general, there was no evidence of a differential treatment effect due to gender, nor was there any indication of a differential treatment effect when the various racial subgroups were compared to the overall study population. However due to the small sample sizes in the Black and other race categories, no definitive determinations can be made with regard to treatment effects between these racial subgroups compared to the overall population.

Safety Summary:

- A slightly higher mean exposure was observed in the ciclesonide 200 mcg and 100 mcg groups versus the 25 mcg and placebo groups.
- A similar proportion of patients in the ciclesonide and placebo groups experienced treatment emergent AEs and the pattern and type of treatment emergent AEs were expected of a pediatric population with AR.
- A similar number of patients experienced AEs judged as likely or definitely related to treatment. The most commonly reported AE was epistaxis and occurred with the highest incidence in the placebo group.

- Adverse events resulting in discontinuation occurred with greatest incidence in the placebo group (6.1% versus 1.8%, 3.0%, and 2.4% in the ciclesonide 200 mcg, 100 mcg, and 25 mcg groups, respectively).
- Serious AEs were reported in 3 patients, 2 in the ciclesonide 200 mcg group and 1 in the placebo group. All of these were considered to be unlikely related or unrelated to treatment.
- There was a slightly higher mean change in blood potassium in ciclesonide 200 mcg group compared to the placebo group however no other notable mean changes from the Baseline or treatment differences for any of the hematology or chemistry test results were observed. With the exception of blood potassium, transitions from within the normal range to above or below the normal range were observed with similar frequency in all 4 treatment groups. Abnormalities in blood potassium were regarded as minor and considered unrelated to treatment by the investigator.

- Mean changes from Baseline in urine and plasma cortisol were small and not indicative of a treatment effect.
- Changes in intraocular pressure did not appreciably differ across treatment groups.

Pharmacokinetic Summary:

- The serum concentrations of ciclesonide and the active metabolite were below the lower limit of quantitation (25 pg/mL for ciclesonide and 10 pg/mL for the active metabolite) for the majority of samples tested. The highest value detected of the active metabolite, des-ciclesonide (M1, B9027-021)) was 44.93 pg/mL. These data support the low bioavailability of ciclesonide and des-ciclesonide in patients 6-11 years of age.