2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial to Assess the Safety and Efficacy of Ciclesonide (200 mcg once daily) Applied as a Nasal Spray in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 12 Years and Older (Protocol BY9010/M1-402).

Coordinating investigator: [redacted]

Study center(s): 41 Centers in the U.S. and Canada.

Publication (reference): N/A

Studied period (years): First patient in: 12/18/2003
Last patient's last visit: 05/12/2004

Clinical phase: Phase 3

Objectives: The primary objective of this study was to demonstrate the efficacy of ciclesonide applied as a nasal spray once daily in patients with PAR. The secondary objectives were to evaluate quality of life and safety.

Methodology: This was a randomized, double-blind, placebo-controlled, multi-center, parallel-group study of intranasally administered ciclesonide 200 mcg once daily. Four hundred seventy-one patients were randomly assigned to either the ciclesonide group (238) or the placebo group (233). The study was conducted in adult and adolescent patients with PAR at 41 investigational centers in the United States and Canada.

The study consisted of three periods for all patients:

1. Baseline Period [7-14 days; Screening Visit (B0) to Randomization Visit (T0)]
2. Treatment Period [6 weeks; Randomization Visit (T0), Visit T3, and Visit T6]
3. Follow-up Period [at least 7 days; from the Tend Visit to the Follow-up Visit (F)]

All patients were seen on an outpatient basis. Informed consent, including Health Insurance Portability and Accountability Act (HIPAA) authorization, was obtained at the Screening Visit (B0). At the Screening Visit (B0) or Randomization Visit (T0) (or both), each patient was required to demonstrate evidence of a positive skin prick test to a relevant allergen, which is known to induce PAR, unless the patient had previously demonstrated a relevant positive skin prick test within the past 12 months prior to the Screening Visit (B0). In addition, each patient received an extensive physical examination and blood specimens were collected for hematology and blood chemistry evaluations and, where appropriate, a pregnancy test.

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The Randomization Visit (T0) took place 7-14 days later, in the morning before 10:00 AM. At the Randomization Visit (T0) patients were required to have a patient-assessed reflective total nasal symptom score (TNSS) (AM or PM) of at least 6 out of a possible 12 on at least 4 of the last 7 days of the Baseline Period to be randomized. Patients who had successfully completed all Screening Visit (B0) assessments and who continued to meet the eligibility criteria were asked to complete the respective age-appropriate adult or adolescent Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Patients were then randomized and given an allergic rhinitis assessment diary to record their rhinitis symptoms. Randomized patients received instructions on the proper use of the nasal spray, and instructions for completing diary cards, including the onset-of-action diary cards.

Study drug was dispensed and thereafter patients recorded their instantaneous nasal symptoms for the 0-hour time point in their Day 1 diary. Patients then self-administered the first dose of study medication in the presence of the investigator or a designee. Beginning 4 hours after the first dose, and continuing through Hour 12, patients performed hourly recordings of their instantaneous nasal symptoms scores in their patient diaries. Beginning on Day 2 of the Treatment Period, and continuing throughout the remaining treatment period, patients recorded twice daily (once in the morning and once in the evening) both reflective and instantaneous nasal symptoms and the times at which the scores were recorded.

Treatment Visits T3 and T6 were scheduled to occur before 10:00 AM, on Days 22 (± 2 days) and 43 (± 2 days), respectively, and the Follow-up Visit (F), on Day 50 (at least seven days after Visit T6 or Tend). During the 6-week treatment period, each patient was to have self-administered the daily dose of study medication each morning immediately after the AM assessment of symptoms.

At Visit T3, the RQLQ was completed. Also at this visit, an ENT examination and the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) was conducted, patient diary cards were reviewed and any use of prohibited drugs evaluated. Study medication was dispensed again.

At Visit T6, the RQLQ was completed again. Also each patient received a physical examination, including an ENT examination; the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) was conducted; patient diary cards were reviewed, and any use of prohibited drugs evaluated. In addition, blood specimens were collected for hematology and blood chemistry evaluations and, where appropriate, a pregnancy test.

At the Follow-up Visit (F), information on concomitant medications and AEs was recorded.

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No. of patients (total and for each treatment): The total number of patients randomized were 471: 238 in the ciclesonide group, and 233 in the placebo group. All patients were included in the intention-to-treat (ITT) and safety analyses, and 436 were included in the per-protocol (PP) analyses: 219 in the ciclesonide group, and 217 in the placebo group.

Diagnosis and criteria for inclusion: The study population defined in the protocol consisted of male and female patients in general good health, 12 years of age and older, with a history of PAR to a relevant perennial allergen for a minimum of two years 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.: 2812406/0330121000 and 2812406/0330131000

Duration of treatment: 6 weeks

Reference product: Placebo

Dose: 2 actuations per nostril, once daily

Mode of administration: intranasally (spray)

Batch Nos.: 2812102/0330131000 and 2812102/0330141000

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the average of the AM and PM patient-assessed reflective TNSS over Days 1-42 of treatment. The key secondary efficacy endpoints were: average of AM and PM patient-reported instantaneous TNSS over Days 1-42; PANS at Endpoint and combined adolescent and adult RQLQ at Endpoint.

Additional secondary efficacy variables were: time to onset of action; time to maximal effect; average and separate AM and PM patient-assessed reflective TNSS at selected time points (Days 1-42 [for separate AM and PM TNSS only]; 1-14; 15-28; 29-42); Average and separate, AM and PM patient-assessed instantaneous TNSS at selected time points (Days 1-42 [for separate AM and PM TNSS only]; 1-14; 15-28; 29-42.); individual nasal symptoms at selected time points (Days 1-42; 1-14; 15-28; 29-42.); individual components of the PANS and overall PANS at Visits T3 and T6; changes from baseline in RQLQ at Visits T3, T6, and Endpoint, as well as in each of the seven domains for the adult RQLQ and 6 domains for the adolescent RQLQ, and percent change from baseline in the average of patient-assessed AM and PM reflective TNSS.

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Safety: Safety was assessed by spontaneous and elicited adverse events (AEs), physical examinations including ENT examinations, vital signs and clinical laboratory tests.

Statistical methods: The primary null hypothesis was that there was no difference between intranasal ciclesonide and placebo in changes from baseline in the average AM and PM reflective TNSS over Days 1-42 in patients with PAR. The primary alternative hypothesis was that the treatment effects differ for this measure. Secondary and other hypotheses were framed in a similar manner. Type I error rates were strictly controlled across the primary and key secondary measures at the two-sided 0.05 level.

According to the study protocol the estimated sample size of 418 patients required for the ITT analysis (209 per treatment arm) was calculated for change from baseline in AM and PM reflective TNSS over Days 1-42 to ensure a power of 90% to correctly conclude that there is a difference between ciclesonide and placebo under the assumption of a common standard deviation of 2.2 and a difference between treatment groups of 0.7, using a two-sided alpha level of 5%.

The primary efficacy variable was the change from baseline in the average of AM and PM patient-reported reflective TNSS over Days 1-42 where baseline was defined as the average of the responses obtained during the Baseline Period up to seven days prior to randomization. The primary analysis was performed using the ITT population.
The clinical decision rule was addressed by the primary efficacy variable. Sequential testing was employed. If the study medication was found to be effective using a criterion of $p \leq 0.05$with respect to the primary efficacy measure, key secondary variables were tested for statistical significance. If the p-value from the test of the average of AM and PM patient-assessed instantaneous TNSS was ≤ 0.05, then PANS was examined. If the p-value for the test of PANS was ≤ 0.05, then the RQLQ result was examined. Thus, the type I error rate was strictly controlled for the primary and key secondary measures.

A repeated measures analysis of covariance model was used for analyses of the difference in treatment effects for the nasal symptom variables over multiple days with covariates of baseline, day and treatment by day. Day was treated as an unordered categorical variable. A first order autoregressive structure was used to model intra-patient correlation in combination 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. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated. No imputation for missing values was performed as the extent of missing data was expected to be low and the chosen analysis as a maximum likelihood method is valid for missing-at-random missingness

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Changes from baseline to Endpoint in the PANS and RQLQ evaluations were analyzed by univariate ANCOVA with the following effects in the model: baseline, center, and treatment.

Safety data were summarized by incidence, means, changes, and shifts depending on the measure.

SUMMARY

Summary:

Efficacy and Quality of Life Results: Once-daily intranasal administration of ciclesonide 200 mcg was effective for the treatment of PAR. Improvement from Baseline in the primary efficacy variable, average of AM and PM reflective TNSS for Days 1-42, was statistically significantly greater for ciclesonide than for placebo (decreases of 2.51 versus 1.89, respectively; treatment effect size 0.63; 95% CI 0.28, 0.97; $p<0.001$).

Results of key secondary variables were as follows: Improvement from Baseline in the average of AM and PM instantaneous TNSS for Days 1-42 of treatment was statistically significant for ciclesonide compared to placebo (-2.22 versus -1.68; treatment effect size 0.54, 95% CI 0.21, 0.88; $p=0.001$). At Endpoint, the decrease from Baseline in PANS was numerically greater for the ciclesonide group (2.05) than for the placebo group (1.67) [$p=0.051$ for the difference]. At Endpoint, the decrease from Baseline in RQLQ was 1.30 for the ciclesonide group and 1.01 for the placebo group. This treatment difference of 0.28 was not statistically significant due to the sequential testing procedure employed to control type I error (95% CI: 0.07, 0.50; $p=0.011$).

Safety Results: Of the 471 patients included in the safety analyses, 43% in the ciclesonide group and 47% in the placebo group experienced treatment-emergent AEs. AEs judged to be treatment-related or likely to be treatment-related by the investigator were reported by 11% in each treatment group. Potential imbalances in the incidence of AEs between groups were observed for epistaxis, which was more frequent in the ciclesonide group and upper respiratory infections, which were more frequent in the placebo group. No SAEs were reported for any patient in either treatment group. Discontinuation rates due to AEs were 4% for the ciclesonide group and 5% for the placebo group. No other treatment-related findings were observed for the other safety assessments.

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