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 Seasonal Allergic Rhinitis (SAR) in Patients 12 Years and Older

Investigators:

[redacted]

Coordinating investigator:

[redacted]

Study center(s):

Austin, TX; San Antonio, TX; Kerrville, TX; San Antonio, TX; San Antonio, TX; and Austin, TX.

Publication (reference):

N/A

Studied period (years):

First patient in: 12/15/2003
Last patient's last visit: 03/03/2004

Clinical phase:

3

Objectives:

The primary objective of this study was to demonstrate the efficacy of intranasal ciclesonide once daily in the treatment of SAR. The additional objectives of this study were to assess quality-of-life measures and the safety of administering ciclesonide intranasally.

Methodology:

This study was conducted as a randomized, double-blind, parallel-group, placebo-controlled, multi-center clinical trial to assess the efficacy, safety, and effect on quality of life of once-daily, intranasally administered ciclesonide 200 mcg in adult and adolescent patients with SAR at six investigational centers in the United States. Three hundred twenty-seven patients were randomized, 164 to the intranasal ciclesonide 200 µg group and 163 to the placebo group.

The study consisted of three periods:

1. A Baseline Period of seven to 10 days (Screening Visit B0 to Randomization Visit T0);
2. A Treatment Period of four weeks (Randomization Visit T0 to last treatment visit T4); and
3. A Follow-up Period of seven days concluding with a final evaluation visit (Follow-up Visit F).

All patients were seen on an outpatient basis. Informed consent was obtained at Visit B0. Visit T0 took place seven to 10 days after Visit B0. Visits T2 and T4 took place on Days 15 and 29, respectively. Follow-up Visit F took place seven days after the last treatment visit (Day 36). Treatment visits 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 Mountain Cedar pollen, which is known to induce SAR, or to have documentation of a positive skin prick test for Mountain Cedar pollen within 12 months prior to the Screening Visit (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 and non-nasal SAR symptoms in the diary twice daily. At Visit T0, patients must have achieved a patient-assessed reflective total nasal symptom scores (TNSS; AM or PM) score of at least six out of a possible 12 on at least four of the last seven days of the Baseline Period in order to be randomized. Randomized patients received instructions on completion of the diary cards and on the proper use of the nasal spray. At this visit, patients recorded their instantaneous nasal signs and symptoms in their Day 1 diary, for the 0-hour time point. Then patient's were to have self-administered the first dose of study medication in the presence of the investigator or designee. Beginning four hours after the first dose, and continuing hourly through Hour 12, patients recorded their instantaneous nasal signs and symptom scores in their diary cards. In addition, at Hour 12, non-nasal signs and symptoms and reflective nasal symptom scores were recorded. Beginning on Day 2 of the Treatment Period, patients recorded nasal (both reflective and instantaneous) and non-nasal (reflective) symptoms twice daily, once in the morning and once in the evening (approximately 12 hours later).

At all visits, ear, nose and throat (ENT) examinations were performed. For the entire study period, pollen counts were recorded daily at the sites. At all but the post-treatment Follow-up Visit [F], the Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) was conducted, and any use of prohibited drugs was evaluated. At Visits T0, T2, and T4, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was completed, a patient compliance check was conducted, and patient diaries were reviewed. At Visits T0, T2, T4, 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 T4.

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

The number of patients randomized was 327. All 327 patients were included in the intention-to-treat (ITT) and safety analyses, and 304 were included in the per-protocol (PP) analyses. 164 patients were randomized to ciclesonide and 163 patients were randomized to placebo.

Diagnosis and criteria for inclusion:

The study population targeted in the protocol consisted of male and female patients in general good health, 12 years of age and older, with ongoing SAR for a minimum of two years immediately preceding the study season. Patients also were to have required treatment for SAR in the past, were expected to require treatment for SAR throughout the study period, and were to have a demonstrated sensitivity to Mountain Cedar pollen.

Test product:

Ciclesonide

Dose:

200 mcg once daily

Mode of administration:

Intranasal spray

Batch No.:

2812406-0330121000 (ciclesonide 50 mcg/spray) and 2812406- 0330131000 (ciclesonide 50 mcg/spray)

Duration of treatment:
Four weeks

Reference product:
Placebo (vehicle)

Dose:

0 mcg once daily

Mode of administration:

Intranasal spray

Batch No.:
2812102-0330131000 and 2812102-0330141000

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the average of AM and PM patient-reported reflective TNSS over the first two weeks (Days 1-14) of treatment. Secondary efficacy endpoints were instantaneous patient-reported TNSS over the first two weeks of treatment; PANS at Endpoint; and RQLQ (adult and adolescent combined) at Endpoint. Additional secondary efficacy endpoints were total non-nasal symptoms (reflective), individual nasal and non-nasal symptoms, time to onset of effect, time to maximal effect, average AM and PM TNSS at selected time points (second two weeks of treatment [Days 15-28], overall four weeks [Days 1-28], and each day), AM and PM TNSS separately at selected time points (first two weeks of treatment, second two weeks, overall four weeks, and each day), percent change from baseline in average reflective AM and PM TNSS, individual components of the PANS and PANS at selected time points, and the seven adult and six adolescent domains of the RQLQ analyzed separately.

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

Statistical methods: The primary efficacy variable was the change from Baseline in the average of AM and PM patient-reported reflective TNSS for Days 1-14, where Baseline was the average of the responses obtained during the Baseline Period up to seven days prior to randomization. According to the study protocol the required sample size of 302 patients (151 per treatment arm) was calculated for the primary endpoint 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 2.4 and a difference between treatment groups of 0.9 using a two-sided alpha level of 5%.

The clinical decision rule was addressed by the primary efficacy variable. Sequential testing was employed. If the medication was found to be effective with respect to the primary efficacy measure, key secondary variables were tested for statistical significance, starting with the instantaneous TNSS over Days 1-14. If the p-value from the test of the average of AM and PM patient-assessed instantaneous TNSS over Days 1-14 was ≤0.05, then PANS at endpoint was examined. If the p-value for the test of PANS at endpoint was ≤0.05, then the RQLQ at endpoint result was examined. 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 and non-nasal symptom variables over multiple days, with covariates of baseline, treatment, 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 and, 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. Baseline was defined as the appropriate value measured over the Baseline Period up to seven days prior to randomization. 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 was valid for missing-at-random missingness

An analysis of covariance model with covariates of center, treatment and baseline value was used to analyze PANS change from baseline to Endpoint and to Visits T2 and T4. Baseline was defined as the PANS value at the B0 visit. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated based on the ANCOVA model.

Changes from Baseline to Endpoint and to Visits T2 and T4 in RQLQ for adults and adolescents combined and separately as well as for each of the individual domains comprising the RQLQ were analyzed using ANCOVA with covariates of center, treatment and baseline value. Baseline was defined as the value at the T0 visit. Estimated treatment differences and 95% confidence intervals for the treatment differences were calculated based on the ANCOVA model.

The hourly assessment of instantaneous nasal signs and symptoms scores obtained on Day 1 and the morning (24-hour) assessment obtained the day after randomization were used to evaluate onset of action. The onset of action for intranasal ciclesonide was defined as the time from Baseline until the two-sided p-value for the test of a difference in the average of patient-assessed instantaneous TNSS between intranasal ciclesonide and placebo was less than 0.05. Additionally, the p-value for the test of a difference between treatments was to be

less than 0.05 for a time point after the first significant time point in order to confirm the onset of effect. For the evaluation of onset of action, Baseline was defined as the zero hour from the Day 1 patient diary. Treatment groups were compared on each day using ANCOVA with covariate adjustment for center, treatment, and baseline.

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 SAR, with statistically significant improvement from Baseline relative to the placebo group in the primary efficacy variable, average of AM and PM reflective TNSS for Days 1-14 and the secondary variable average of AM and PM instantaneous TNSS for Days 1-14 of treatment. At Baseline, the average AM and PM reflective TNSS was 8.96 and 8.83 for the ciclesonide and placebo groups, respectively. Over two weeks of treatment, there was a significantly greater decrease from Baseline in average reflective TNSS for the ciclesonide group compared with the placebo group (2.40 and 1.50, respectively; $p<0.001$). At Baseline, the average AM and PM instantaneous TNSS was 8.40 and 8.33 on a scale of 0 to 12 for the ciclesonide and placebo groups, respectively. Over two weeks of treatment, there was a significantly greater decrease from Baseline in average instantaneous TNSS for the ciclesonide group compared with the placebo group (2.15 and 1.28, respectively; $p<0.001$). While treatment differences in the secondary variables PANS and RQLQ at Endpoint were not statistically significant, there were appreciable differences observed at Visit T2.

Treatment differences, indicating greater improvement for ciclesonide than for placebo, were found for Days 15-28 and Days 1-28 in average of AM and PM reflective TNSS, average of AM and PM instantaneous TNSS, percent change in reflective TNSS, and separate AM and PM reflective and instantaneous TNSS and for Visit T2 in PANS, combined adult and adolescent RQLQ, and adult RQLQ.

Safety Results: There were no clinically meaningful differences between the placebo and the ciclesonide group in incidence of AEs or other safety assessments during the study.

- The incidence of treatment-emergent adverse events was 40.2% in the ciclesonide group and 39.3% in the placebo group.
- AEs judged to be treatment-related or likely to be treatment-related by the investigator were reported by 11.0% of the patients in the ciclesonide group and 9.8% in the placebo group.
- One patient, who was in the ciclesonide group, experienced a non-treatment-related SAE (increased heart rate).

- The rate of discontinuation due to AEs was 2.4% for the ciclesonide group and 3.1% for the placebo group.
- There were no clinically meaningful differences between placebo and active treatment in the numbers and types of AEs. The most frequently reported (2% or more of patients) AEs were nasal passage irritation, headache, epistaxis, ear pain, nasopharyngitis, pharyngitis, tympanic membrane disorder, and upper respiratory tract infection.
- One or more severe treatment-emergent AEs were reported by 7.9% of patients in the ciclesonide group and 4.3% of patients in the placebo group. One patient (in the placebo group) had a severe AE (headache) that was regarded as likely to be treatment-related; all others were judged not related or unlikely to be treatment-related.
- Potential imbalances in incidences of adverse events between groups were observed for epistaxis, headache, upper respiratory infection, and ear disorders. These may represent signals for further evaluations.