2 Synopsis

Title of the study:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Clinical Trial to Assess the Long Term Safety of Ciclesonide, Applied as a Nasal Spray (200 mcg once daily), in the Treatment of Perennial Allergic Rhinitis (PAR) in Patients 12 Years and Older

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Study center(s): 35 centers in the United States.

Publication (reference): None

Studied period (years): First patient in: January 9, 2004
Last patient/last visit: April 29, 2005

Clinical phase: Phase 3.

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

Methodology: This study was conducted in the United States as a randomized, double-blind, placebo-controlled, multi-center, parallel-group study. A total of 663 patients were randomized, 441 in the ciclesonide group (200 mcg/day) and 222 in the placebo group.

The study consisted of two periods in which all patients participated: [1] Baseline period [7-14 days; Screening Visit (B0) to Randomization Visit (T0)] and [2] Treatment Period [up to 52 weeks; Randomization Visit (T0) up to the final Visit (T16 or T18)]. Patients were seen on an outpatient basis at the Screening Visit (B0), at the Randomization Visit (T0) 7-14 days

after Screening Visit, and at up to 10 subsequent treatment evaluation visits: T1 (Day22), T2 (Day 43), T4 (Day 85), T6 (Day 127), T8 (Day 169), T10 (Day 211), T12 (Day 253), T14 (Day 295), T16 (Day 337) and T18 (for those patients participating in the treatment extension) (Day 365).

During the study, each patient was evaluated 3 times for visual acuity and intraocular pressure (IOP), as well as lens opacity by an ophthalmologist (specifically trained in LOCS III lens opacity assessments). These evaluations were performed during the interval between the Screening Visit (B0) and the Randomization Visit (T0) and in close schedule proximity with the T8 (Day 169) and the T16 (Day 337) treatment evaluation visits.

No. of patients (total and for each treatment): Six hundred sixty-three patient were randomized, 441 to ciclesonide 200 mcg/day treatment and 222 to placebo. All patients were included in the Safety and ITT Analysis Sets.

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, confirmed via skin test, for a minimum of two years immediately preceding the study.

Test product: Ciclesonide

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

Mode of administration: intranasally (spray)

Batch No.: 2812406/0140181000, /0140191000, /0140201000, /0330131000, /0330141000, and /0330121000

Duration of treatment: up to 52 weeks

Reference product: Placebo

Dose: 2 actuations per nostril, once daily

Mode of administration: intranasally (spray)

Batch No.: 2812102/0140161000, /0140171000, /0330131000 and /0330141000

Criteria for evaluation:

Analysis Sets: Two analysis sets were analyzed (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 for efficacy. The Safety analysis set consisted of all randomized patients who had received at least one dose of study medication. In this trial, the ITT analysis set was identical to the Safety analysis set.

Efficacy: The efficacy variables measured included changes from baseline in reflective 24-hour AM Total Nasal Symptom Score (TNSS) as well as individual patient-assessed nasal symptoms analyzed over a period of 52 weeks of treatment and over other selected time periods. Percent change in patient's self-assessed reflective 24-hour TNSS; Physician Assessment of Overall Nasal Signs and Symptoms Severity (PANS) at Endpoint and at other selected time points. Combined Adult and Adolescent Rhinoconjunctivitis Quality of life Questionnaire (RQLQ) at Endpoint and at other selected time points, and resource utilization/health economics information were also measured throughout the study.

Safety: Safety assessment included the following: Spontaneously-reported and elicited adverse events (AEs), Physical examination findings, Vital signs, ENT examination findings, ECG findings, Clinical laboatory assessments, Urine (24-hour) and AM plasma cortisol (subset of patients randomized at pre-selected sites), as well as Eye examinations including: Intraocular Pressure (IOP) measurements, cataract assessment using LOCS III criteria, visual acuity and overall ocular health.

Statistical methods: Sample size was determined by the requirements of the ICH Guidelines that 300 patients be exposed to ciclesonide nasal spray for six months and 100 patients be exposed for one year. In order to account for withdrawals, 600 patients were to be randomized in a 2:1 ratio (400 ciclesonide: 200 placebo).

Since this was a safety study, there was no predefined primary efficacy measure. However, several measures of efficacy were included in the study. Changes from baseline in the daily 24-hour patient-assessed TNSS were summarized over Days 2-365 and over various other intervals throughout the study. Available nasal symptom scores for each day were averaged to create weekly values. The weekly values were then used in the analyses. Treatment groups were compared using repeated measures analysis with covariate adjustment for

baseline, treatment, week, and the treatment by week interaction. Estimated treatment differences and 95% confidence intervals for the treatment differences are provided. Individual patient-assessed nasal symptoms were analyzed in a similar fashion. Changes from Baseline in PANS and RQLQ were analyzed using ANCOVA with covariates of pooled center, baseline and treatment.

Adverse events, SAEs, drug-related AEs, and AEs leading to withdrawal were summarized by incidence. Changes from baseline in urine cortisol were examined using summary statistics. Clinical laboratory data and ECGs were examined using summary statistics, categorization by normal ranges, and shift tables. Physical examination findings were summarized in contingency tables. Vital signs and changes in vital signs were examined using summary statistics.

Ocular safety was evaluated using general ocular examinations, visual acuity, slit-lamp examination with assessments of lens opacity, and tonometry to measure intraocular pressure. Changes from Baseline for these measures were summarized by treatment group, and 95% confidence intervals on treatment differences were calculated based on an ANCOVA model with covariated of pooled center, baseline, treatment, age and gender.

SUMMARY

Summary:

Efficacy:

Once-daily intranasal administration of ciclesonide 200 mcg/day was shown to be effective for the treatment of PAR. Treatment differences in favor of ciclesonide for patient reported TNSS were demonstrated over the entire treatment period ($p<0.001$) and were already apparent over the first week of treatment ($p<0.001$). Each individual nasal symptom component of the TNSS contributed to the overall benefit seen with ciclesonide.

There were no appreciable differences between the treatment groups in overall or individual signs/symptoms of PANS.

Despite the baseline impairment of QOL being low, the change in the overall RQLQ was greater in the ciclesonide group than in the placebo group when measured as the change from Baseline to Endpoint, as well as to Visit T8 and to Visit T16. In a post hoc subgroup analysis in patients with a greater impairment of QOL at baseline, the treatment difference was 0.49 units which approached a clinically meaningful difference of 0.5.

The level of resource utilization was low during the trial with no evidence of a treatment difference observed.

Safety

Treatment-emergent AE incidence was similar in the 2 treatment groups: 75.1% in the ciclesonide group and 74.3% in the placebo group. For most adverse events, the pattern and incidence of AEs were comparable between the placebo and ciclesonide treatment groups and were expected of patients with AR or nasal corticosteroid treatment. The five most frequently reported AEs were upper respiratory tract infection, nasopharyngitis, epistaxis, pharyngolaryngeal pain, and sinusitis. The first two of these events occurred more frequently in the placebo treated patients whereas the latter three occurred more frequently in the ciclesonide treated patients. No adverse event of clinical concern was observed with long-term treatment with intranasal ciclesonide.

The majority of adverse events, regardless of treatment were mild to moderate in severity. Severe AEs were reported in 13.4% of the patients in the ciclesonide group and 11.7% in the placebo group. For the most part these AEs were not classified as drug related and did not lead to patient withdrawal.

Adverse events that were considered treatment related occurred with a greater incidence in the ciclesonide relative to the placebo group (17.0% versus 10.8%, respectively) . Most of these events were single occurrences or, if were reported in more than one patient, were expected and are commonly seen in AR patients or with topical corticosteroid administration (epistaxis and nasal discomfort). Only a few of these AEs led to study drug discontinuation. Although the number of AEs leading to discontinuation was slightly higher in the ciclesonide versus the placebo group (4.3% versus 2.7%, respectively), most of the AEs leading to discontinuation were single event cases and were considered to be unrelated to treatment by the investigator.

Serious AEs were comparable between groups (3.6% of patients in the ciclesonide group versus 2.7% patients in the placebo group) and all of the events were judged to be either not related or unlikely related to study treatment. None of the serious AEs resulted in death and, in all but 2 events in the ciclesonide group (multiple myeloma and acute renal failure) and 1 event in the placebo group (Brugada syndrome), the patient recovered without sequelae.

There were no notable mean changes from the Baseline value for any of the hematology or chemistry test results. Mean changes from Baseline in AM plasma cortisol and 24-hour urine free cortisol values were small and similar between treatment groups. No treatment-related adverse effects were observed based upon the analysis of ENT examination findings.

No treatment-related changes or differences from placebo were observed in IOP over the treatment period. No treatment-related changes from Baseline or differences from placebo in any of the four LOCS III parameters were observed. The lower end of the 2-sided 95% confidence interval for the treatment differences were all above the defined non-inferiority margins of -0.5 for nuclear opalescence and posterior subcapsular cataract and -0.8 for

cortical opacity. Thus, not only were no treatment differences observed, but these results demonstrated that clinically meaningful differences between treatments did not occur.