2 Synopsis

Title of the study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Using the Environmental Exposure Chamber (EEC) to Assess the Onset of Action of Ciclesonide Applied as a Nasal Spray (200 mcg once daily) in the Treatment of Seasonal Allergic Rhinitis (SAR) in Patients 18 Years and Older (Protocol BY9010/M1-406).

Investigator: [redacted] Allied Research International, 4520 Dixie Road, Mississauga, Ontario, L4W 1N2, Canada

Coordinating investigator: Not applicable. This was a single-site study.

Study center: [redacted] Allied Research International, 4520 Dixie Road, Mississauga, Ontario, L4W 1N2, Canada

Publication (reference): N/A.

Studied period (years): First patient in: November 22, 2004

Last patient's last visit: February 12, 2005

Clinical phase: Phase 3

Objectives: The primary objective of this placebo-controlled EEC study was to determine the time to onset of action of ciclesonide, applied as a nasal spray (200 mcg once daily) in patients with SAR.

Methodology: This was a randomized, double-blind, placebo-controlled, single-center, parallel-group study conducted in an EEC. The EEC is a validated outpatient clinical research facility designed to allow controlled exposure to airborne pollen particles with consistent airborne pollen particle counts between 3000 to 4000 pollen grains/m^3, documented by conducting assessments every thirty minutes using seven Rotational Impaction Samplers.

Patients were recruited in eight cohorts, each consisting of 35 to 89 patients.

The trial design included three Study Phases:

- Screening Phase (Study Phase I: one visit; Visit B0);
- Priming Phase (Study Phase II: at least 1 and up to 5 visits; Visits B1-B5);
- Treatment Phase (Study Phase III: one visit; Visit T0).

Patients were seen on an outpatient basis at the Screening Visit (B0), one or more Priming Visits (B1-B5) and a single Treatment Visit (T0). Informed consent was obtained at the Screening Visit (B0) prior to performing any protocol assessments or procedures. Demographic information, medical history and concomitant medication details were recorded and a physical examination (including measurement of vital signs) and a nasal examination were performed at this visit (B0). A positive skin prick test for short ragweed was required; this was conducted either at the Screening Visit (B0) or the first Priming Visit (B1), or both, if the patient had no documented positive test within 12 months before the Screening Visit (B0).

Eligible patients were asked to complete a minimum of one and up to a maximum of five priming visits in the EEC (Visits B1-B5), as determined by the investigator, based upon their nasal symptom development during such priming sessions. As a patient's rate of symptom development and ability to maintain this minimum level of symptoms varied, subjects were asked to return for subsequent priming session(s) 1-11 days prior to Treatment Visit (T0), as determined by the investigator. During each Priming Visit (Visits B1-B5) symptoms were assessed at 30-minute intervals from 0.5 to 3 hours after ragweed pollen exposure (3500 $\pm$ 500 grains/m^3). To be eligible for study treatment, each patient had to have a minimum of one (1) or a maximum of two (2) successful Priming Visits. A qualifying symptom score was defined as a patient-assessed instantaneous Total Nasal Symptom Score (TNSS) of 6 or greater and a score of 2 or greater for rhinorrhea or nasal congestion at 1.5 hours after ragweed pollen exposure (Priming Visit qualifying time point). The TNSS was the sum of the symptom scores rated on a scale of 0-3 for each of four symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion. The time span considered in determination of instantaneous TNSS was defined as the evaluation of the patient's symptom severity over the 10 minutes immediately prior to the evaluation time point.

During the single Treatment Visit (T0) symptoms were assessed at the -1.5, -1, -0.5 (Treatment Visit qualifying time point), 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hour time points. The first symptom assessment occurred 30 minutes after the initial pollen exposure (-1.5 hour). A qualifying symptom score was defined as a patient-assessed instantaneous TNSS of 6 or greater and a score of 2 or greater for rhinorrhea or nasal congestion at the qualifying time point (-0.5 hour). A single dose of study medication (either ciclesonide 200 mcg or placebo) was then administered at 0 hour time point.

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

The total number of patients randomized was 503, 251 to ciclesonide and 252 to placebo. Five hundred two patients received study medication, 251 in each treatment group. All patients who received study medication were included in the safety analyses and in the intention-to-treat analyses.

Diagnosis and criteria for inclusion: The study population defined in the protocol consisted of male and female patients in general good health, 18 years of age and older, with a history of seasonal allergic rhinitis (SAR) to ragweed pollen allergen for a minimum of two years immediately preceding the study. Patients had a positive skin prick test to short ragweed pollen.

Test product: Ciclesonide

Dose: 200 mcg (50 mcg /actuation, 2 actuations/nostril), one time dosage

Mode of administration: Intranasal spray

Batch No.: 2812406/0140181000

Duration of treatment: One day

Reference product: Placebo

Dose: 2 actuations per nostril, one time dosage

Mode of administration: Intranasal spray

Batch No.: 2812102/0140161000

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the time to onset of action of ciclesonide, as measured by a difference from placebo in the change from baseline in patient-assessed instantaneous TNSS following treatment. Secondary efficacy endpoints were changes in TNSS from baseline at each time point, changes in individual nasal symptom scores from baseline at each time point, the proportion of patients exhibiting good/excellent response at each time point (defined as all components of the patient-assessed TNSS scored as mild or less in severity).

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

Statistical methods: Sample size calculations were based on a standard deviation for the change from baseline in TNSS of 2.7. According to the study protocol, the required sample size of 241 patients per treatment group provided 90% power to demonstrate a difference of 0.8 at any time point in TNSS using a one-sided alpha level of 0.025.

The primary efficacy endpoint was the time to onset of action of ciclesonide. Onset of action was defined as the first time point at which ciclesonide nasal spray 200 mcg/day was significantly different from placebo where a following time point was also statistically

different from placebo. Statistical significance was based on comparison to a one-sided alpha level of 0.025. Changes from baseline in instantaneous TNSS at each time point were analyzed using ANCOVA with covariates of treatment and baseline TNSS. Baseline was defined as the instantaneous TNSS at the last pre-treatment evaluation (0 hour time point) during the Treatment Visit (T0).

Changes from baseline in individual nasal symptom scores at each time point were analyzed using ANCOVA adjusting for treatment and baseline. The proportion of patients exhibiting good/excellent response at each time point was analyzed using logistic regression with adjustment for treatment and baseline TNSS.

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

SUMMARY

Summary:

Efficacy Results: The onset of action of ciclesonide nasal spray in SAR was determined to occur within one hour, since the differences between ciclesonide and placebo in instantaneous TNSS at Hour 1 and every post-baseline hour time point thereafter were statistically significant ($p<0.025$). At Hour 1, the difference between ciclesonide and placebo was 0.5 (95% CI: 0.08, 0.93; $p=0.010$). Improvements in instantaneous TNSS were seen in both treatment groups at every post-baseline time point and generally increased over the 12-hour period. At Hour 12, the difference was 0.9 (95% CI: 0.41, 1.34; $p<0.001$). All treatment differences in TNSS were ≥ 0.5, a difference defined *a priori* as being clinically meaningful.

At Hour 1 after treatment, 12.4% of the ciclesonide group and 8.0% of the placebo group reported a good/excellent response (i.e. each component of the instantaneous TNSS scored as being mild or less in severity). At Hours 2 and 3, the proportion of patients reporting a good/excellent response was similar in the two treatment groups, but at all subsequent time points, a higher proportion of ciclesonide-treated patients reported a good/excellent response. At Hour 12, the odds of a good/excellent response in patients treated with ciclesonide were nearly 5-times greater than for patients treated with placebo (odds ratio 4.9; 95% CI: 2.2, 11.0; $p<0.0001$). Mean improvements in each of the individual components of the TNSS (nasal stuffiness/congestion, nasal itching, sneezing and runny nose) were seen after ciclesonide treatment that were greater than those seen with placebo at all post-baseline time points.

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 7.2% in the ciclesonide group and 14.3% in the placebo group. AEs judged to be treatment-related or likely to be treatment-related by the investigator were reported by few patients, 0.8% in each treatment group. No patients experienced an SAE during the study and no patients were discontinued from the study due to a treatment-emergent AE. There were no clinically meaningful differences between placebo and ciclesonide in the numbers and types of AEs. The most frequently reported (2% or more of patients in either group) AEs were headache (ciclesonide 2.0%, placebo 4.0%) and increased systolic blood pressure (ciclesonide 0.8%, placebo 2.4%). The majority of treatment-emergent AEs were of mild intensity and none were of severe intensity. Mean values for vital sign measurements were similar for ciclesonide and placebo. Fewer patients in the ciclesonide group than in the placebo group (1.2% compared with 7.2%) had changes in vital sign values to outside the protocol-defined range after treatment. No clinically significant findings on physical examination or nasal examination were observed.