2. Synopsis

Title of the Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Using the Environmental Exposure Unit (EEU) 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.

Investigator: [redacted]

Study center: Kingston General Hospital, Kingston, Ontario, Canada. See

Publication (reference): Not applicable.

Studied period (years): First patient in: 08 February 2005

Last patient's last visit: 16 April 2005

Clinical phase: Phase 3

Objective: The primary objective of this placebo-controlled EEU 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 EEU. The EEU was designed to create the necessary conditions for even pollen dispersion by use of fans and controlled airflow. A pollen concentration of 3500 grains/m^3 was targeted which is consistent with peak outdoor levels. Pollen levels were recorded by sampling for 30 seconds at 30-minute intervals using seven Rotorod samplers.

Patients were recruited in four cohorts, each including 101 to 109 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. 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 allergen was required; this was conducted either at the Screening Visit (B0) or the first Priming Visit (B1) 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 EEU (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 could be 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 were required to demonstrate 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, itchy nose, 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): 420 patients were randomized, 210 to ciclesonide and 210 to placebo. All patients received study medication and were included in the intention-to-treat and the safety analyses.

Diagnosis and criteria for inclusion: The study analysis set 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. Additionally, for inclusion in the trial, patients were required to have a documented positive skin prick test to short ragweed pollen.

Test product: Ciclesonide

Dose: 200 mcg (50 mcg /actuation, 2 actuations/nostril), single dose

Mode of administration: Intranasal spray

Batch No.: 2812406/0140191000

Duration of treatment: One day

Reference product: Placebo

Dose: 2 actuations per nostril, single dose

Mode of administration: Intranasal spray

Batch No.: 2812102/0140161000 and 2812102/0140171000

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 score 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. Based upon this standard deviation, the required sample size of 206 patients per treatment group provides 85% 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 covariates of treatment and baseline. The proportion of patients exhibiting good/excellent response at each time point was analyzed using logistic regression with covariates of treatment and baseline TNSS.

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

SUMMARY

Efficacy Results: This study did not demonstrate an onset of action for a single dose of ciclesonide nasal spray (200 mcg). However, there was an appreciable difference favoring ciclesonide. A statistically significant ($p<0.025$) difference in change from baseline in instantaneous TNSS between ciclesonide and placebo in favor of ciclesonide was observed at Hour 6 but at not other time points from Hour 1 through Hour 12, in the ITT analysis. Additionally, although improvements from baseline in instantaneous TNSS were seen in both treatment groups and at each post-baseline time point through Hour 12 the difference between treatments in change from baseline in TNSS was numerically greater in the ciclesonide group than in the placebo group. Treatment differences over the 12-hour study period ranged from 0.1 to 0.7. The proportion of patients with a good/excellent response (i.e. each component of the instantaneous TNSS scored as being mild or less in severity) was numerically greater in the ciclesonide group than in the placebo group at each time point after treatment. Odds ratios for a better response with ciclesonide than placebo ranged from 1.1 at Hour 2 ($p=0.3223$) to 1.8 at Hour 8 ($p=0.0085$) and Hour 9 ($p=0.0108$).

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 8.1% in the ciclesonide group and 7.6% in the placebo group. No AEs judged to be treatment-related or likely to be treatment-related by the investigator were reported and no patients receiving treatment experienced an SAE during this single dose study. Three patients, two treated with ciclesonide and one treated with placebo were discontinued from the study due to treatment-emergent AEs, which all resolved without sequelae. 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) AE was headache (ciclesonide 2.4%, placebo 1.4%). The majority of treatment-emergent AEs were of mild or moderate intensity and few patients in either treatment group (ciclesonide 1.9% and placebo 2.4%) experienced treatment-emergent AEs of severe intensity. Mean values for vital sign measurements were similar for ciclesonide and placebo and no patients had changes in vital sign values to outside the protocol-defined range after treatment. Few clinically significant findings on physical examination or nasal examination were observed in either treatment group.