1 TITLE PAGE Clinical Study Report No. 60/2008 Version 1.0

<table>
<tr><td rowspan="5">Title: Investigation of the Efficacy and Safety of Concomitant Administration of Ciclesonide Nasal Spray and Azelastine Nasal Spray in Patients (18 years or older) with Perennial Allergic Rhinitis (PAR) Not Adequately Controlled on an Intranasal Corticosteroid or Antihistamine Monotherapy</td><td>Version date: 22-Jan-2009</td></tr>
<tr><td>INN: Ciclesonide</td></tr>
<tr><td>Project No. / List No.: BY9010</td></tr>
<tr><td>Compound No.: TBN-15; BY9010</td></tr>
<tr><td>Batch No.: 350361000 (ciclesonide 50mcg /actuation), 0000002480 (azelastine 30mL, 0000001196 (azelastine placebo 30mL mcg/actuation), 350361000 (ciclesonide 50 mcg/actuation), and 0039K06A (cetirizine HCL 10 mg)</td></tr>
<tr><td>Study / Protocol No.: BY9010/M1-490</td><td>Development phase: IV</td></tr>
<tr><td>Study initiation date: November 16, 2006</td><td>Indication studied: Perennial allergic rhinitis</td></tr>
<tr><td>Study completion date: May 29, 2007</td><td>Date of early termination: N/A</td></tr>
<tr><td colspan="2">Name and country of investigators: (Appendix 16.1.4)</td></tr>
<tr><td colspan="2">Name of Sponsor's responsible medical officer:</td></tr>
<tr><td colspan="2">Person responsible for study report:</td></tr>
<tr><td colspan="2">Sponsors contact persons: See accompanying letter of the regulatory approval application</td></tr>
<tr><td colspan="2">Statement of GCP compliance:
This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)</td></tr>
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Department of Clinical Operations at Nycomed US, Inc., Florham Park, NJ, according to ICH Consolidated Guideline E6.</td></tr>
<tr><td colspan="2">This report is strictly confidential. Disclosure of contents to third parties is not permitted except by written consent of Nycomed US, Inc.</td></tr>
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2 SYNOPSIS

Title of the study: Investigation of the Efficacy and Safety of Concomitant Administration of Ciclesonide Nasal Spray and Azelastine Nasal Spray in Patients (18 years or older) with Perennial Allergic Rhinitis (PAR) Not Adequately Controlled on an Intranasal Corticosteroid or Antihistamine Monotherapy

Investigators: 39 centers in the USA. See Appendix 16.1.4 for further details.

Publication (reference): N/A

Studied period (years): First patient in: 16-Nov-2006
Last patient out: 29-May-2007

Clinical phase: Phase IV

Objectives:

The primary objective of this study was to evaluate the efficacy of the concomitant administration of ciclesonide nasal spray and azelastine nasal spray versus ciclesonide nasal spray alone in patients (18 years or older) with perennial allergic rhinitis (PAR) not adequately controlled on an intranasal corticosteroid or antihistamine monotherapy.

The secondary objective was to investigate the safety of the concomitant administration of ciclesonide nasal spray and azelastine nasal spray.

Methodology:

Number of Patients (total and for each treatment): The total number of patients randomized was 298: 151 in the 100 mcg ciclesonide/548 mcg azelastine BID (twice daily) group and 147 in the 100 mcg ciclesonide/placebo BID group. All patients were included in the Safety Analysis Set and in the ITT Analysis Set; 176 patients were included in the Per Protocol Analysis Set.

Diagnosis and criteria for inclusion: The study population consisted of male and female patients, 18 years of age and older, in general good health with a history of PAR to a relevant perennial allergen for a minimum of two years, confirmed by a positive skin sensitivity test to a known perennial allergen, who have been found to be not adequately controlled by intranasal corticosteroid or antihistamine monotherapy.

This study was conducted as a randomized, placebo-controlled, double-blind, parallel-group, efficacy and safety study.

The study consisted of two periods:

- Run-in Period (14 days), and a
- Treatment Period (28 days from Visit T0).

Informed consent/assent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained at the Screening Visit (B0) prior to performing any study procedures. Eligibility to enter the study was established by medical history, physical examination, 24-hour reflective nasal symptom assessment, and skin prick results. Patients were seen on an outpatient basis at all visits.

An Interactive Voice Response System (IVRS) was used for central randomization for all subjects fulfilling screening and randomization criteria and was also responsible for activation/deactivation of the site, allocation of drug to individual patients, drug supply management and early terminations/completions.

The initial phase of the study consisted of a 14-day Run-in Period during which the following treatments were administered:

- patients currently using intranasal corticosteroids (INCS) were given ciclesonide nasal spray 200 mcg administered as two sprays of 50 mcg/nostril once daily;
- patients currently using oral or intranasal antihistamines for their PAR symptoms were given cetirizine 10 mg once daily;
- patients who are not currently using any medications (montelukast or medications other than intranasal corticosteroids or oral antihistamines) for their PAR symptoms were given open-label cetirizine 10 mg once daily or ciclesonide nasal spray 200 mcg once daily. For these patients, the run-in medication assignment was made using an IVR system, based upon which group had fewer patients at the time of assignment. The objective was to allocate approximately 50% of patients to cetirizine and 50% to ciclesonide

nasal spray. (Note: patients who were simultaneously using both INCS and antihistamines at the time of screening were not eligible to enter the study.)

During this Run-in Period, patients recorded 12-hour reflective severity scores for their nasal symptoms (sneezing, runny nose, itchy nose and nasal congestion) and non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes and itching of ears or palate) in an electronic diary in the morning and approximately 12 hours later in the evening. In the morning, immediately after recording their nasal and non-nasal AR (allergic rhinitis) symptoms, patients self-administered their study medication.

Patients who were not adequately controlled on ciclesonide nasal spray or cetirizine at the end of the Run-in Period were defined as those patients having an average daily patient-reported reflective TNSS score greater than or equal to 6 over the last week of the Run-in Period. For these patients, the Run-in Period was followed by a 28-day Treatment Period.

At the inception of the Treatment Period, patients were randomly assigned via IVRS to one of the following double–blind treatments:

Ciclesonide nasal spray (50 mcg/spray, one spray per nostril) and placebo azelastine nasal spray (two sprays per nostril) administered twice daily approximately 1 minute apart, once in the morning and 12 hours later, in the evening.

or

Ciclesonide nasal spray (50 mcg/spray, one spray per nostril) and azelastine nasal spray (137 mcg/spray, two sprays per nostril) administered twice daily approximately 1 minute apart, once in the morning and 12 hours later, in the evening.

During the Treatment Period (Visit T0 through Visit Tend) 12-hour reflective nasal and non-nasal symptom severity scores were captured electronically twice daily by all patients, followed immediately thereafter by administration of the randomly assigned study medication. Post-randomization, these patients had a single treatment evaluation visit at the conclusion of the study (Visit Tend).

The primary efficacy variable was the average of AM and PM patient-reported reflective Total Nasal Symptom Score (TNSS) over the four weeks of treatment.

The key secondary efficacy variable was the total physician-assessed nasal symptoms score (PNSS) at Endpoint.

Other efficacy variables measured during the trial were:

- RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire) at Endpoint.

- Total patient-reported reflective non-nasal symptoms over four weeks of treatment.
- Individual reflective patient-reported nasal and non-nasal symptoms over four weeks of treatment and each week.
- Average reflective AM and PM TNSS for each Week.
- Reflective AM TNSS and PM TNSS separately over four weeks of treatment.
- Individual physician-assessed nasal symptoms at Endpoint.

Safety was evaluated by means of the following assessments:

- Spontaneous and elicited adverse events (AEs)
- Physical examinations, including ENT examinations
- Vital signs (blood pressure and pulse rate)
- Clinical laboratory tests (blood chemistry and hematology)

Statistical Methods:

Based on the BY9010/M1-402 study, it was assumed that the standard deviation for the change from baseline in TNSS over four weeks would be 1.95. Assuming that the post-randomization dropout in this trial would be similar, no adjustment for dropouts was made as this standard deviation was calculated using data that included dropouts. In order to have at least 80% power to detect a difference of 0.6 between the two treatment groups assuming a standard deviation of 1.95 and using a two-sided alpha of 5%, 170 randomized patients per group were required (Dixon, W.J., Massey, F.J., 1983). Randomization was stratified by both center and run-in medication.

Analysis of Primary Measure

The primary variable was change from baseline in the average AM and PM weekly Total Nasal Symptom Score. Weekly AM (PM) TNSS was defined as the average of the AM (PM) TNSS in the week and baseline was defined as the average AM and PM TNSS over the Run-in period up to seven days prior to randomization

The primary analysis was that performed on weekly averages over Weeks 1-4 using the ITT analysis set. Treatment groups were compared using repeated measures analysis of covariance with covariate adjustment for treatment, baseline, week, treatment by week interaction, and run-in medication. Week was treated as an unordered categorical variable. Patient was treated as a random factor. In conjunction with an autoregressive structure for the error term, this yielded a block diagonal AR(1) variance covariance matrix with an addition variance from the subject random effect added to each within-subject element. This variance structure reflected that observations closer in time are more correlated, but this correlation does not approach to zero as the observations become further apart. Estimated treatment differences and 95% confidence intervals for the treatment differences have been provided.

For any AM or PM TNSS as well as the average AM and PM TNSS, TNSS was set to missing if one or more symptom components were missing. Weekly average were calculated based on non-missing average AM and PM TNSS for each week. No imputation for missing data was performed as the extent of missing data was predicted to be low and the chosen analysis as a

maximum likelihood method is valid for missing-at-random missingness [Little and Rubin 2002].

Analysis of Key Secondary and Other Measures

Total non-nasal symptoms, and individual symptoms were analyzed in a manner analogous to the primary measure. Additionally, weekly averages were analyzed using ANCOVA with adjustment for center, run-in medication, treatment, and baseline. PNSS and RQLQ were analyzed using the same ANCOVA model.

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

Test product: Ciclesonide Nasal Spray

Dose: 100 mcg (50 mcg /actuation, 1 actuation/nostril), twice daily

Mode of administration: intranasally (spray)

Batch No.: 350361000

Duration of treatment: 28 days

Test product: Azelastine Nasal Spray

Dose: 548 mcg (137 mcg/actuation, 2 actuations/nostril), twice daily

Mode of administration: intranasally (spray)

Batch No.: 0000002840

Duration of treatment: 28 days

Reference product: Placebo for Azelastine Nasal Spray

Dose: 2 actuations per nostril, twice daily

Mode of administration: intranasally (spray)

Batch No.: 0000001196

SUMMARY - CONCLUSIONS

Summary:

Efficacy Results:

For the primary variable, the change in mean reflective TNSS over the four-week treatment period, Baseline TNSS scores were comparable between treatment groups: 8.75 ± 1.64 for the ciclesonide/azelastine combination and 8.62 ± 1.65 for ciclesonide/placebo. Over the four-week treatment period, mean change in TNSS from baseline was -2.30 for ciclesonide/azelastine versus -2.03 for ciclesonide/placebo, a difference of 0.269 (95% CI: -0.20, 0.74; p=0.263).

A similar magnitude of difference was observed for the key secondary variable, physician assessment of overall nasal symptoms (PNSS). Baseline PNSS scores were comparable between treatment groups: 8.36 ± 2.18 for the ciclesonide/azelastine combination and 8.42 ± 1.97 for ciclesonide/placebo. At Endpoint, mean change in PNSS from baseline was -3.03 for ciclesonide/azelastine versus 2.73 for ciclesonide/placebo, a difference of 0.302 (95% CI: -0.31, 0.92; p=0.334).

Subgroup analysis showed that the ciclesonide/azelastine combination produced a numerically larger effect than ciclesonide/placebo treatment among patients being treated with INCS or antihistamines at the time of screening, a difference of 0.864 (p=0.044) in TNSS over the treatment period. No difference in treatment response was observed in TNSS scores for patients not using either any member of either drug class at the time of screening for this study. Results for the PNSS were similar with an estimated difference of 0.71 in this subgroup and no appreciable difference in the group of patients not on AR medication at the time of screening.

Safety Results:

The mean number of days of study medication exposure was similar for the two treatment groups: 26.0 days for ciclesonide/azelastine group and 27.3 days for ciclesonide/placebo treatment group.

Among the 298 patients who were randomized, 39/151 patients (25.8%) in the ciclesonide/azelastine group and 38/147 patients (25.9%) in the ciclesonide/placebo group experienced at least one treatment-emergent adverse event (TEAE). AEs occurring in 2 percent or more of the patients treated with ciclesonide/azelastine were: dysgeusia (5; 3.3%), epistaxis (5; 3.3%), nasal discomfort (4; 2.6%), sinusitis (4; 2.6%), and upper respiratory tract infection (3; 2.0%). AEs occurring in 2 percent or more of the patients treated with

ciclesonide/placebo were: epistaxis (6; 4.1%), upper respiratory tract infection (5; 3.4%) nasal discomfort (4; 2.7%), sinusitis (3; 2.0%), and nasopharyngitis (3; 2.0%).

Two patients experienced serious adverse events (SAEs). Both occurred in the ciclesonide/placebo group. Patient 3863/90323 was randomized on February 14, 2007 after receiving ciclesonide during the Run-in Period. She experienced severe right-sided facial numbness that began on February 19, 2007. Study medication was discontinued on February 20, 2007. The patient recovered without sequelae by April 27, 2007. The investigator considered it unlikely that this SAE was related to study medication administration. Patient 4519/90296 was randomized on February 9, 2007 after receiving ciclesonide during the Run-in Period. She experienced a severe concussion accompanied by a skull fracture that was regarded as having no relationship to study medication administration. Despite the injury, the patient completed the study.

Twenty patients discontinued treatment due to AEs occurring during the study. Fourteen patients had received ciclesonide/azelastine with the most common reasons for discontinuation being nasal burning (3), sinusitis (3), and exacerbation of asthma (2). Among the 6 patients who discontinued from the ciclesonide/placebo group, the most common reason was upper respiratory infection (3).

Conclusions: