2. Synopsis of study report: No. 147/2005

Study Code:
BY9010/M1-408

Report Version:
1.0

Title of the study:
Investigation of Potential Additive Inhibitory Effects on HPA-Axis of Ciclesonide Nasal Spray when Administered Concomitantly with Orally Inhaled Beclomethasone Dipropionate (HFA-BDP) in Patients (18-60 Years) with Perennial Allergic Rhinitis (PAR)

Investigator:
[redacted]

Study center:
San Antonio, TX.

Coordinating investigator:
Not applicable.

Study center:
One center in the United States.

Publication (reference):
None up to the present time.

Studied period (years):
First patient in: December 27, 2004
Last patient/last visit: April 18, 2005

Clinical phase:

Phase 3.

Objectives:

The primary objective of this study was to demonstrate that there were no clinically relevant additive inhibitory effects on the HPA-axis when ciclesonide nasal spray was concomitantly administered with orally inhaled HFA-BDP. The secondary objectives of this study were to evaluate the safety and tolerability of the combined dosing regimen of orally inhaled HFA-BDP and ciclesonide nasal spray.

Methodology:

This study was designed as a randomized, placebo- and active-controlled, double-blind, parallel-group, non-inferiority study conducted at a single investigational site in the United States that enrolled male and female patients (18-60 years) with PAR.

The study consisted of 3 periods followed by a single administration of 2 mg dexamethasone:

- A Screening Period of up to 10 days (Visit S0 to S1) during which patients gave informed consent, including Health Insurance Portability and Accountability Act (HIPAA) authorization, and underwent screening determinations;
- A 10-day Run-in Period (Visits B0 to B1) during which all patients received HFA-BDP and placebo nasal spray;
- A 43-day Treatment Period (Visits T0 to T3) during which patients received HFA-BDP with randomized study treatment;
- Visits T3 to T4 (Days 53 to 54), which began with the administration of dexamethasone followed by a 24-hour period to determine post-dexamethasone cortisol levels.

The study was largely performed on an outpatient basis, but involved 3 periods of in-house evaluation: at the conclusion of Screening and the beginning of Run-in (Visits S1 to B0, Days −1 through Day 1); at the conclusion of Run-in and the beginning of randomized treatment (Visits B1 to T0, Day 10 through Day 11); and at the conclusion of randomized treatment through follow-up (Visits T2 to T4, Days 52 through Day 54). During these periods, patients were confined for two 24-hour in-patient and one 48-hour in-patient visit to assess 24-hour plasma cortisol and urinary cortisol levels.

Each period of the study is described in greater detail below:

During the Screening Period, patients were evaluated for eligibility to enter the trial. The following assessments/procedures were performed to determine eligibility: medical history, including recent use of prescription and over-the-counter medication; physical examination including an ear-nose-throat (ENT) examination, patient assessment of nasal symptoms, a

skin prick test for a relevant allergen; and collection of blood samples for clinical laboratory determinations. At the conclusion of the Screening Period, the patients were confined for 24 hours to measure plasma cortisol levels at periodic intervals (at 0, 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours) and to determine 24-hour urinary excretion of cortisol over this same time span.

During the 10-day Run-in Period all patients self-administered orally inhaled HFA-BDP 320 mcg twice daily, plus a single-blind placebo nasal spray once daily. Prior to self-administering the study medications each morning, the patients performed their 24-hour reflective nasal symptom evaluations which rated 4 symptoms: runny nose, sneezing, nasal itching, and nasal congestion, on a severity scale ranging from 0 to 3. These evaluations were recorded on the patients' daily study diary cards. At the conclusion of the Run-in Period, the patients were confined for 24 hours to measure plasma cortisol levels at periodic intervals [pre-HFA-BDP administration for that day (Hour 0) and 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours after the first administration of HFA-BDP of the day] and to determine 24-hour urinary excretion of cortisol over this time span.

At the conclusion of the Run-in Period, patients meeting the following criteria were randomized:

- Patient continued to be in general good health, meeting the selection criteria;
- Patient had not experienced an adverse event that would result in failure to continue to meet selection criteria;
- Patient had not used any of the prohibited concomitant medications during the Screening or Run-in Period;
- Patient achieved a 24-hour reflective Total Nasal Symptom Score (TNSS) of 4 or greater (out of a possible 12) on at least 5 out of the last 7 days during the 10-day Run-in Period;
- Each patient had adequately completed the PAR Assessment Diary (failure was defined as missing one or more of the entries on more than 3 days during the Baseline Period).
- Patient had compliance with study medication usage (both inhaled and intranasal) within the range of 80% to 120% during the Run-in Period as assessed by patient diary.

During the 43-day Treatment Period patients continued to use orally inhaled HFA-BDP and also self-administered one of the following randomly assigned additional treatments: ciclesonide nasal spray (200 mcg once daily [2 actuations of 50 mcg/nostril]) or placebo nasal spray (2 actuations per nostril once daily). Patients also continued to perform their daily morning nasal symptom evaluations, recording their symptom ratings on the study diary cards. The patients returned to the site on Day 31 for interim Visit T1. At this visit, medication compliance was assessed, patient diaries were collected and reviewed, recent use

of prescription and over-the-counter medication use was evaluated, patients were queried regarding any adverse events they may have experienced, and an ENT examination was performed. Additional study diary cards, HFA-BDP canisters, and investigational nasal spray were dispensed.

The patients returned on Day 52 for a final 48-hour in-house confinement (Visits T2 through T4 on Days 52, 53, and 54). Procedures and assessments included: patient diary review; evaluation of recent prescription and over-the-counter medication use; physical examination, including an ENT examination; and collection of blood samples for routine clinical laboratory determinations as well as 2 successive plasma cortisol (at pre-HFA-BDP administration for that day [Hour 0] and 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours after the first administration of HFA-BDP of the day) and 24-hour urine cortisol determinations. A serum pregnancy test was performed in females of childbearing potential.

On the last treatment day, Day 53, all patients also received an oral 2 mg dexamethasone tablet in addition to the daily dose of HFA-BDP and randomized nasal spray. In order to establish the sensitivity of the study, plasma cortisol AUC (0, 24h) values obtained after administration of dexamethasone (2 mg) on Visit T3 (Day 53) were compared to AUC (0, 24h) values obtained at Visit T4 (Day 54). Plasma cortisol levels were measured immediately following the administration of dexamethasone and prior to administration of HFA-BDP. Thereafter, blood samples were collected 3, 6, 8, 10, 12, 14, 16, 18, 21, 22, and 24 hours after the first administration of HFA-BDP of the day. Another 24-hour urine specimen was collected for measurement of urinary cortisol excretion.

For this study, the Contract Research Organization, Pharmaceutical Product Development (PPD; Austin, TX), was responsible for data management and data transfer to the sponsor. Clinical laboratory services were provided by MDS Pharma Services, Toronto, Canada.

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

The total number of patients randomized was 111: 56 in the 200 mcg ciclesonide group and 55 in the placebo group. All patients were included in the intention-to-treat (ITT) and safety analyses, and 105 were included in the per-protocol (PP) analyses: 51 in the 200 mcg ciclesonide group and 54 in the placebo group.

Diagnosis and criteria for inclusion:

The study population consisted of male and female patients (age 18-60 years), with a history of PAR for a minimum of 1 year preceding the Screening Visit (S0).

Test product: Ciclesonide

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

Mode of administration: intranasally (spray)

Batch Nos.: 2812406/0140181000

2812406/0140191000

Duration of Treatment: 43 days (with ciclesonide nasal spray)

Reference Product: Placebo

Dose: 2 actuations/nostril, once daily

Batch Nos.: 2812102/0140171000

Criteria for evaluation:

The primary purpose of this study was the evaluation of the effect upon the hypothalamic-pituitary-adrenal (HPA) axis when ciclesonide nasal spray is administered concomitantly with orally inhaled HFA-BDP.

Primary Safety Variable

- Plasma cortisol

Other Safety Variables

- Urinary free cortisol
- Adverse events
- Physical examination
- ENT examination
- Vital signs (blood pressure, pulse)
- Clinical laboratory values (hematology/chemistry)

Although this was a safety study and there was no declared primary efficacy endpoint, the following efficacy measures were evaluated:

- AM patient-assessed 24-hour reflective Total Nasal Symptom Score (TNSS) over 6 weeks of treatment and at selected time points, and
- Individual nasal symptoms over selected time points.

Statistical methods:

Sample Size Determination

In a previous study with ciclesonide MDI (BY9010/FHP013), a 4-period crossover study in which the plasma cortisol values during each subject's placebo nasal spray period served as a baseline, the standard deviation for the change from baseline in the weighted average (0, 24h) of plasma cortisol concentration was estimated to be 1.62 mcg/dL. This translates to a 24-hour AUC of 38.8 mcg·h/dL. The standard deviation of the treatment difference in a parallel group setting was thus 54.9 mcg·h/dL.

To choose delta, the non-inferiority boundary, the data from study BY9010/FHP013 was again used. The mean plasma cortisol concentration from the placebo nasal spray period represented as a 24-hour AUC value was 181.4 mcg·h/dL. Assuming that the effect of HFA-BDP is to reduce cortisol by approximately 25%, it was estimated that the mean at the end of B1 (Day 10) would be approximately 136.1mcg·h/dL. Since no minimum clinically meaningful effect on cortisol is commonly recognized, standard bioequivalence bounds of a 20% difference were used to determine delta. Based on the BY9010/FHP013 study, delta was calculated to be 20% of 136.1 mcg·h/dL, or 27.2 mcg·h/dL.

In order to have 90% power to demonstrate non-inferiority of ciclesonide 200 mcg nasal spray to placebo nasal spray using a one-sided alpha level of 0.025 and assuming no true difference exists, it was estimated that 45 evaluable (per-protocol) patients per group would be needed (1). In order to account for patient withdrawals, patients with irregular plasma cortisol profiles at S1, and patients with major protocol violations, 53 patients per group were to be randomized. Regular 24-hour plasma cortisol profiles were defined as those with the highest cortisol concentrations occurring in the morning hours between 3:00 AM and 9:00 AM.

The planned sample size was 106 patients (53 per treatment group) in order to obtain 45 evaluable patients per treatment group.

Analysis of the Primary Variable:

Plasma cortisol AUC (0, 24h):

- AUC (0, 24h) was calculated using the trapezoidal rule. Up to one intermittent missing value was allowed between 2 measurements, but if there was a missing value at the start or end, the AUC was not calculated for that patient.
- The change from baseline Visit B1 values to Visit T2 (Day 52) in plasma cortisol AUC (0, 24h) values was analyzed using analysis of covariance (ANCOVA) with adjustment for the baseline AUC value, treatment, gender, and age.
- The primary comparison was the evaluation of potential non-inferiority of the ciclesonide nasal spray treatment group to the placebo nasal spray group using the per-protocol (PP) analysis.
- In order to validate the sensitivity of the study, an important additional comparison using this measure was the comparison of the End of Treatment Visit T3 (Day 53) plasma cortisol AUC (0, 24h) values obtained after administration of dexamethasone (2 mg) to the Visit T4 (Day 54) AUC (0, 24h) values.
- The effect of HFA-BDP over the Run-in Period was also examined by comparing the data from the Start of Run-in (Day 1; B0) to the data obtained at End of Run-in (Day 10; B1).

The additional safety variables defined in the protocol, adverse events (AEs), physical exams, vital signs, and nasal exams, have been summarized by incidence.

Since the primary objective of this study was the evaluation of safety, and the trial was not designed to assess efficacy, it was not expected that significant differences between ciclesonide and placebo would be observed for TNSS. Hence, no formal hypothesis was written for the evaluation of efficacy. Therefore, interpretation of the efficacy results has been based upon 95% confidence intervals, using a repeated measures ANCOVA model for the changes from baseline in the weekly averages for TNSS. Summary statistics including the mean, standard deviation, median and range have been calculated for TNSS and for change from baseline in TNSS and for each individual nasal symptom.

Summary

Summary:

There were no additive inhibitory effects on the HPA axis, compared to placebo when ciclesonide nasal spray was concomitantly administered once daily for 6 weeks with orally inhaled HFA-BDP.

- Twice-daily administration of 320 mcg orally inhaled HFA-BDP resulted in decreases in mean plasma cortisol AUC (0, 24h) over the 10-day Run-in Period.
- Addition of ciclesonide 200 mcg once daily or placebo for 6 weeks resulted in no additional reduction in mean cortisol AUC (0, 24h), and ciclesonide treatment was shown to be non-inferior to placebo.

- Decreases in cortisol seen after administration of dexamethasone on the last treatment day demonstrated that further suppression of the HPA axis by ciclesonide would have been possible.
- Similar results were seen with plasma cortisol AUC (0, 12h) and AUC (12, 24h)
- In contrast to the results with plasma cortisol, decreases in urine cortisol over the Treatment Period were observed. However, the changes were comparable between treatment groups.

Additionally, the results of this study indicated that ciclesonide when given intranasally once-daily for 6 weeks for the treatment of SAR, was well tolerated and showed no clinically meaningful differences from placebo in the incidence of AEs or other safety assessments.

No notable changes from the baseline values occurred over the 6-week Treatment Period, either in the TNSS or in the individual symptom scores. There were no significant differences in efficacy between the 2 treatment groups at any time point.