AstraZeneca

D5252C00004

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Pulmicort HFA pMDI

ACTIVE INGREDIENT: budesonide

Trial title (number): A Randomised, Open-Label, Active-Controlled, Parallel Group, Single-Centre, 4-Week Study to Evaluate the Safety of High Dose Budesonide after Multiple Dosing with Investigational HFA Metered Dose Inhaler and Conventional CFC Metered Dose Inhaler (Pulmicort®) in Healthy Subjects.(D5252C00004)

Developmental phase: I
First subject recruited: 02 February 2004
Last subject completed: 05 May 2004
Approval date: 19 May 2005

OBJECTIVES

Primary objective:
To investigate the effect on the hypothalamo-pituitary-adrenal (HPA) axis of treatment with high dose budesonide (1600 µg/day) administered by SkyePharma (SKP) hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) compared to AstraZeneca (AZ) chlorofluorocarbon (CFC) pMDI over 4 weeks using 12-hour overnight urinary cortisol corrected for creatinine (urinary cortisol/creatinine ratio [UCC]) in healthy subjects.

Secondary objectives:
To determine the local irritation when switching from AZ CFC pMDI to SKP HFA pMDI using clinical symptoms (e.g., cough, stridor, dysphonia).
To compare the safety of budesonide when administered by SKP HFA pMDI and AZ CFC pMDI using incidence of adverse events (AEs) and vital signs.

METHODS

This Phase I randomised, open-label, active-controlled, parallel group, single-centre study was designed to evaluate the safety of high dose budesonide (1600 µg/day) administered over 4 weeks after multiple dosing with SKP HFA pMDI compared with AZ CFC pMDI.
Prior to the Baseline Visit (Run-In Day 7), all subjects were to undergo a Run-In Period of one week during which they were to receive budesonide delivered via AZ CFC pMDI (1600 µg/day). On Run-In Day 7, subjects were to be randomised to one of two treatment groups: budesonide (1600 µg/day)

delivered by SKP HFA pMDI or AZ CFC pMDI. Study drug was to be administered at 800 µg/day BID (1600 µg/day) over a 4-week period. Clinic visits were to occur at Weeks 1, 2, 3, and 4, during which safety assessments (AEs and vital signs) were to be made. Urine was to be collected overnight during a 12-hour period starting the night before the Run-In Period (Pre-Run-In UCC), the night before the Treatment Period (Run-In Day 7 UCC), the night after one day of treatment (Day 1 UCC), and at the end of treatment (Day 28 UCC).

A total of 48 male and female subjects (24 subjects per group) were randomised in this study. All 48 subjects completed the study as planned and were included in the per-protocol (PP), intent-to treat (ITT), and safety populations.Males and females, 18 to 45 years of age, who gave written informed consent and who had normal findings in general physical examination, medical history, routine clinical laboratory screening, and spirometry (forced expiratory volume [FEV1] greater than 80% of predicted values). The subjects were not to have a history of respiratory tract infection or a history of steroid medication use (systemic or topical) within 4 or 8 weeks, respectively, prior to the Screening Visit.

SKP HFA pMDI 200 µg/actuation.
Each subject was to dose him or herself.
Subjects were to receive budesonide 1600 µg/day (4 actuations BID) via SKP HFA pMDIs.

AZ CFC pMDI 200 µg/actuation.
Each subject was to dose him or herself.
During the Run-In Period, all subjects were to receive budesonide 1600 µg/day (4 actuations BID) via AZ CFC pMDIs. After randomisation to the treatment group, subjects were to receive budesonide 1600 µg/day (4 actuations BID) via AZ CFC pMDIs.

Each subject was to undergo a medical screening examination within28 days prior to the Run-In Period. The study duration for each volunteer was to be approximately10 weeks including pre-study and post-study assessments

The primary safety outcome variable was to be the UCC for the assessment of suppressive effects on HPA axis function of high dose budesonide administered by SKP HFA pMDI and AZ CFC pMDI. Urine was to be collected in 12-hour fractions following the Screening (= Pre-Run-In) and pre-Treatment Period Baseline Visits (= Run-In Day 7), and on Days 1 and 28 of the Treatment Period.

Secondary safety endpoints were to include the incidence of treatment-emergent AEs and changes in vital signs during the Treatment Period.
Adverse events were to be monitored at every visit and at the Follow-Up examination. Vital signs (blood pressure, heart rate) were to be determined at the Screening Visit, the Pre-Run-In Baseline Visit, on Treatment Days 1, 8, 15, 22, and 29, and at the Follow-Up medical examination. Laboratory monitoring (haematology, clinical chemistry and urinalysis) was to be carried out at the Screening Visit, the Pre-Run-In Baseline Visit, and at the Follow-Up medical examination. For female subjects, a serum pregnancy test was to be performed at the Screening Visit, at the Pre-Run-In Baseline Visit, on Treatment Days 1, 8, 15, 22, and at the Follow-Up examination. If the interval between the Pre-Run-In Visit and the first dosing of the Run-In Period was longer than 2 days, the following additional study

assessments were to be performed: urine drug screen, alcohol breath test, and serum-HCG test for female subjects.

Summary statistics for the pharmacodynamic parameters, urinary creatinine, cortisol, UCC, and the changes from the respective baseline were to be performed by treatment group and study day.

In order to investigate the effects of SKP HFA pMDI and AZ CFC pMDI at a high dose level (1600 µg/day), an analysis of variance (ANOVA) on the changes of UCC as identified above was to be performed, including the respective baseline value and treatment group as fixed effects. The residual variance from the analysis was to be used to construct 90% confidence intervals for the differences between the treatment groups. Distributional assumptions were to be checked by inspection of residual plots of studentised residuals versus normal order scores to examine normality and studentised residuals versus fitted values to examine homogeneity. If the residuals from the analysis did not meet the assumptions of normality, the analysis was to be performed for the log-transformed data.

The summary tables for AEs were to be broken down by treatment group, system organ class and preferred term. Additional tables were to be generated by treatment group for the relationship of AEs to study medication and for the severity of AEs. Adverse events in the Run-In and Treatment Periods were to be summarized separately.

Summary statistics for the vital signs parameters (systolic and diastolic blood pressure and heart rate), electrocardiogram (ECG) parameters, and laboratory data were to be presented by treatment group and study day. In addition shift tables were to be generated for all laboratory parameter.

RESULTS

Summary of Pharmacodynamics:

- Following treatment with AZ CFC pMDI during the Run-in Period, the mean UCC decreased from 4.67 nmol/mmol to 3.52 nmol/mmol.
- There was no change in mean UCC after the switch from the AZ CFC pMDI to the SKP HFA pMDI (after one day of treatment).
- Following randomisation, the mean UCC in the SKP HFA pMDI treatment group was 3.39, 3.38 and 1.81 nmol/mmol on Run-In Day 7, Treatment Day 1, and Treatment Day 28, respectivly. In the AZ CFC pMDI treatment group, the mean UCC was 3.65, 3.31, and 4.47 nmol/mmol on Run-In Day 7, Treatment Day 1, and Treatment Day 28, respectivly.
- Excluding Subject 39 in the AZ CFC pMDI group (due to the extremely high variability observed), the mean UCC in the AZ CFC pMDI group was 2.69, 3.39, and 2.48 nmol/mmol on Run-In Day 7, Treatment Day 1, and Treatment Day 28, respectively.
- Using log-transformed data, there were no statistically differences between the treatment groups with respect to Day 1 UCC (with or without Subject 39).
- Using log-transformed data, the difference in UCC between the two treatments were statistically different on Treatment Day 28 (estimated ratio of 0.69, 90% confidence interval [0.49, 0.98]). When Subject 39 in the AZ CFC pMDI group was excluded from the analysis (due to the extremely high variability observed), the difference in UCC between

the two treatment groups was not statistically significant (estimated ratio of 0.74, 90% confidence interval [0.52, 1.05]).

Summary of Safety:

- Twenty one subjects (44%) reported 49 AEs during the Run-In Period. During the Treatment Period, 14 subjects (58%) in the SKP HFA pMDI group reported 37 AEs and 18 subjects (75%) in the AZ CFC pMDI reported 78 AEs.
- The most frequently reported AEs were headache and pharyngolaryngeal pain. Headache was more frequently reported after administration of the AZ CFC pMDI than after administration of the SKP HFA pMDI (50% and 33%, respectively). Pharyngolaryngeal pain was reported by 7 subjects (29%) after treatment with the AZ CFC pMDI and after treatment with the SKP HFA pMDI.
- A difference between the two treatment groups was observed concerning the occurrence of gastrointestinal disorders (two subjects [8%] after treatment with the SKP HFA pMDI and 10 subjects [42%] after treatment with the AZ CFC pMDI).
- The majority of AEs were mild in severity.
- There were no SAEs, deaths, or AEs that led to treatment discontinuation.
- The Investigator judged the majority of AEs to be related to study drug.
- Local irritations (dry mouth, dry lips, tongue disorder, nasopharyngitis, and all symptoms coded under Respiratory, Thoracic and Mediastinal Disorders, like cough, dry throat, dyspnoea, hoarseness, rhinitis) were reported by fewer subjects in the SKP HFA pMDI group than in the AZ CFC pMDI group (9 [38%] and 13 [54%] subjects, respectively).
- There was no increased incidence of local AEs after switching from the AZ CFC pMDI to the SKP HFA pMDI.
- No clinically relevant findings were observed for haematology, biochemistry or urinalysis data, vita signs, or ECGs.

REFERENCE

Abrstract ERS 2005

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Pulmicort™ (budesonide), Healthcare Professionals should view their specific country information