Pharma ALTANA

Summary of Clinical Study Results (Final version) V1.0
BY9010/M1-137
Clinical Study Report 117/2006

EudraCT Number: not applicable

ClinicalTrials.gov Identifier: NCT00163397

Title of the study: A comparative study of inhaled ciclesonide 160 µg/day vs budesonide 400 µg/day in patients with asthma

Investigator(s) and study center(s): Nine study sites were initiated; four in Malaysia and five in Taiwan.

Publication (Reference): Not yet published.

Studied period: 04-Jun-2004 (first patient in) to 28-Jul-2005 (last patient out)

Clinical phase: IIIb

Objectives:

- To compare the effect of 160 µg ciclesonide/day with 400 µg budesonide/day on lung function, symptoms and use of rescue medication including the onset of effect in patients with bronchial asthma.
- To provide information on safety and tolerability of ciclesonide.
- To generate efficacy and safety data in Taiwanese and Malaysian patients.

Methodology:
This was a randomized, double-blind, double-dummy, two-arm parallel group multi-center study. It included a baseline/washout period (1 to 4 weeks duration), a double-blind treatment period (12 weeks duration), and follow-up of AEs (adverse events), if necessary.

At the first baseline period visit (B0), the patient's ICS (inhaled corticosteroid) pretreatment was withdrawn and the patient received salbutamol MDI (metered dose inhaler) to be used as a rescue medication, when needed. A physical examination, vital signs (including electrocardiogram) measurements, standard clinical laboratory tests including pregnancy test in female patients of childbearing potential were done at first baseline and last treatment visit. Medical history and previous medications of the patients were documented at study entry, while AEs, concomitant medications and pregnancy test results were documented throughout the study. Patients who fulfilled the randomization

criteria after the baseline period were randomized into a 12-week treatment period and received od (once daily) in the evening either 160 µg ciclesonide given by a MDI or 400 µg budesonide given by Pulmicort Turbohaler®.

During the treatment period, patients recorded their daily use of rescue medication, daytime and nighttime asthma symptoms, and morning and evening PEF (peak expioratory flow) readings in a diary. Patients returned to the study site for efficacy and safety assessments at the end of week 4, 8, and 12.

During all baseline visits starting with B1, and at the last treatment visit, patients completed the Asthma Quality of Life Questionnaire (AQLQ)[S]).

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

Planned sample size: a total of 120 patients were planned for randomization, 60 patients per treatment group. A total of 125 patients were randomized, with 64 patients in the ciclesonide group and 61 patients in the budesonide group.

Analyzed data sets:

	Enrolled n	Randomized n	Safety set n	Full analysis set n	Valid cases set n
Ciclesonide 160 µg od		64	64	64	51
Budesonide 400 µg od		61	61	61	50
Total	160	125	125	125	101

od = once daily; n = number of patients

Diagnosis and main criteria for inclusion:

Male and female patients who met the following criteria at baseline Visit B0 were eligible to participate in the study:

- written informed consent had been obtained;
- outpatients, between 18 and 75 years of age, inclusive;
- had a history of persistent bronchial asthma as defined by ATS (American Thoracic Society) criteria, 1987, for at least 6 months;
- treated with an ICS (dosage: up to 250 µg fluticasone propionate or equivalent) within 4 weeks prior to baseline;
- FEV_1 = 80-105% of predicted measured at least 4 hours after the last use of rescue medication (eg salbutamol);
- in good health, with the exception of asthma.

Patients had to fulfill the following additional randomization criteria before entry into the treatment period (Visit T0):

- FEV_1 was ≥60 to ≤90% predicted when rescue medication (salbutamol [MDI]) had been withheld for at least 4 hours;
- a decrease of FEV_1 by at least 10% of initial referred to B0 after withdrawal of the ICS had been shown;
- either a reversibility of FEV_1 ≥15% initial after inhalation of 200 to 400 µg salbutamol had been demonstrated (either during the baseline period or within the last 3 months prior to the start of the baseline period) or the diurnal PEF fluctuation was ≥15% during at least 3 days during the last 7 days of the baseline period.

Test product, dose, mode of administration: Ciclesonide HFA-MDI, 160 µg/day (ex actuator), once daily, oral inhalation.

Reference product, dose, mode of administration: Budesonide DPI 400 µg/day, once daily, oral inhalation.

Duration of treatment: 12 weeks

Criteria for evaluation:

The primary efficacy variable was the change in FEV_1 absolute value (difference between T0 and T_{end}).

Secondary efficacy variables included: FEV_1 % of predicted; FVC and PEF absolute and % of predicted values; morning and evening home PEF (absolute and % of predicted values); diurnal PEF fluctuation; asthma symptom score; use of rescue medication; percentages of asthma symptom-free, rescue medication-free, nocturnal awakening-free days; asthma control (percentage of asthma symptom-free plus rescue medication-free days); drop-out rate due to asthma exacerbation; time until first asthma exacerbation; AQLQ(S).

Safety variables included: physical examination findings; vital signs data (incl. ECG); clinical laboratory test results; AEs.

Statistical methods:

The primary variable difference in FEV_1 (endpoint *versus* Visit T0) was analyzed in a closed testing procedure. First a test of non-inferiority of ciclesonide 160 µg/day od *versus* 400 µg/day budesonide od was performed by means of an ANCOVA model. Besides the treatment, the following factors and covariates (all fixed) were included in the model at the 2.5%-level, one-sided: value at T0 (baseline), age, sex, and country. The PP (per protocol) was the primary analysis for this non-inferiority trial. The non-inferiority acceptance limit was set to -200 mL. If and only if non-inferiority was shown, a subsequent test for superiority of ciclesonide 160 µg/day od over budesonide 400 µg/day od was performed without adjustment of the significance level.

The variables FVC and PEF measured at investigators site, morning and evening home PEF, and AQLQ(S) were analyzed by an ANCOVA model comparing 160 µg/day od *versus* 400 µg/day budesonide od. The non-inferiority acceptance limit for FVC was set to -200 mL and for morning and evening PEF to -25 L/min, and for AQLQ(S) to -0.5.

Diurnal PEF fluctuation, asthma symptom score, use of rescue medication, percentage of symptom-free, rescue medication-free, nocturnal awakening-free, and asthma controlled days were analyzed by nonparametric methods.

Time until first asthma exacerbation was analyzed by a logrank test and Kaplan-Meier, respectively.

Vital signs, AEs, and laboratory work-up were all analyzed descriptively.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

The ciclesonide and budesonide treatment groups had similar demographic and baseline characteristics. Most patients were female and the median age of the valid cases set was 49 years and 46 years in the ciclesonide and budesonide group, respectively. The treatment groups were well balanced with respect to baseline lung function (FEV_1 absolute and % of predicted range) at Visit B0 and at randomization Visit T0 (mean FEV_1 % of predicted at T0: 71.1% and 72.3% in the ciclesonide and budesonide group, respectively [valid cases set]). Also height, weight, smoking habits, race, duration of asthma, ICS pretreatment, and reversibility characteristics were well balanced between both treatment groups.

Study results

Efficacy results:

Primary efficacy variable: difference in FEV_1 (absolute)

The primary variable FEV_1 increased by 0.418 L in the ciclesonide 160 µg od pm group and 0.426 L in the budesonide 400 µg od pm group (95% CI [L]: ciclesonide 0.323, 0.513, budesonide 0.314, 0.539; PP analysis). The analysis of between-treatment differences demonstrated non-inferiority of ciclesonide treatment to budesonide (one-sided $p = 0.0021$). This result was confirmed by the ITT analysis.

Secondary efficacy variables:

For FVC (absolute) increases of 0.421 L and 0.480 L (PP analysis) were observed for ciclesonide and budesonide, respectively. The between-treatment differences missed non-inferiority of ciclesonide to budesonide in the PP analysis (one-sided $p = 0.0251$; not confirmed by ITT analysis: one-sided $p = 0.0001$).

The between-treatment differences showed non-inferiority of ciclesonide to budesonide for morning and evening home PEF (one-sided $p = 0.0022$ and $p = 0.0012$, respectively, PP analysis; confirmed by ITT analysis).

Decreases in median asthma symptom score sums from W0 to $W_{end/last}$ were observed for both treatment groups No statistically significant difference between the treatment groups was observed for the PP or ITT analyses.

No statistically significant differences in decrease in rescue medication use were observed between the treatment groups in the PP or ITT analyses.

Between-treatments, no statistically significant differences were observed for the increase of the median percentage of symptom-free days, rescue medication-free days, asthma control days (defined as symptom-free and rescue medication-free days) and nocturnal awakening-free days during the treatment period (PP and ITT).

With respect to the improvement in the overall AQLQ(S) score, the PP analysis of between-treatment differences demonstrated non-inferiority of ciclesonide treatment to budesonide (one-sided p = 0.0001). This result was confirmed by the ITT analysis.

No asthma exacerbation (LOE) was observed in either treatment group.

Overall the efficacy data support that ciclesonide 160 µg od pm and budesonide 400 µg od pm compare well.

Safety results

The median exposure time to study medication was 84.0 days for the ciclesonide and budesonide treatment groups.

During the baseline period, 23 patients (14.4%) experienced a total of 29 AEs. The most common AEs during the baseline period were upper respiratory tract infection, asthma, and cough.

Summary of treatment-emergent AEs (safety analysis set)

	Number (%) of patients					
	CIC160 (N = 64)		BUD400 (N = 61)		Total (N = 125)	
Number of patients (%)[a] who experienced	Patients n (%)	Number of Events	Patients n (%)	Number of Events	Patients n (%)	Number of Events
AEs	41 (64.1)	72	29 (47.5)	49	70 (56.0)	121
SAEs: all	4 (6.3)	6	4 (6.6)	7	8 (6.4)	13
deaths	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs with likely relationship (per investigator)[b]	3 (4.7)	4	0 (0.0)	0	3 (2.4)	4
AEs leading to discontinuation	1 (1.6)	1	0 (0.0)	0	1 (0.8)	1
AEs not yet known to be recovered	8 (12.5)	9	6 (9.8)	7	14 (11.2)	16
AEs that resulted in study medication change	1 (1.6)	1	0 (0.0)	0	1 (0.8)	1
AEs that resulted in concomitant medication change	29 (45.3)	44	23 (37.7)	29	52 (41.6)	73

[a] Percentages are based on the total number of patients in a treatment group, [b] AEs assessed as likely related or definitely related by the investigator. AE=adverse event, BUD400=budesonide 400 µg once daily in the evening, CIC160=ciclesonide 160 µg once daily in the evening, N=number of patients in the respective treatment group, n=number of patients, SAE=serious adverse event.

Overall, 121 treatment-emergent AEs were reported by 70 (56.0%) patients. The percentage of patients with AEs was higher in the ciclesonide group (64.1%) than in the budesonide group (47.5%). The most common treatment-emergent AEs belong to the PTs (preferred terms) upper respiratory tract infection (ciclesonide group: 26.6% of patients, budesonide group: 19.7% of patients), asthma (ciclesonide group: 4.7% of patients, budesonide group: 6.6% of patients), and headache (ciclesonide group 3.1% of patients, budesonide group: 4.4% of patients).

The majority of AEs were mild or moderate in intensity and only one event from all resolved AEs recovered with sequelae (PT glaucoma). There were no AEs assessed by the investigator as definitely related to the study medication. Four events (PTs cheilitis with headache, reflux oesophagitis, nasopharyngeal disorder) were considered as likely related to study medication by the investigator. No events of candidiasis or dysphonia were reported during the study. One patient in the ciclesonide group discontinued the study due to an AE (cheilitis).

No deaths occurred during the study. Eight patients experienced a total of 13 SAEs. The percentage of patients who experienced an SAE were similar in the ciclesonide group (6.3%) and budesonide group (6.6%). None of these SAEs were assessed as related to study medication; no patient discontinued the study due to an SAE.

No trends or major changes in laboratory values over time were observed for either treatment group. No clinical laboratory AE was assessed as related to study medication by the investigator. One event of elevated liver enzymes in the ciclesonide group and two events of elevated creatine phosphokinase (one event with additionally documented follow up investigations of CPK MB) in the budesonide group were considered serious but assessed as unrelated to study medication by the investigator.

Mean blood pressure and heart rate were stable throughout the study and there were no clinically relevant differences between the treatment groups.

Physical examination findings were unremarkable at baseline and at the end of the study. One patient in the ciclesonide group had a documented ECG abnormality (atrio-ventricular heart block) at the end of the treatment period that was assessed by the investigator as clinically relevant but unrelated to study medication, as this problem was noted already prior to the patient's entry into the study.

In conclusion, administration of ciclesonide 160 µg od pm for 12 weeks did not show safety concerns in this population of Asian patients. The safety data seen in this study are comparable to the safety data in Caucasians.

Information provided by ALTANA Pharma (03-December-2006).