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ALTANA

Summary of Clinical Study Results (Final version) V1.0

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ClinicalTrials.gov Identifier: NCT00163384

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): 16 investigators at 16 study sites in South Korea.

Publication (Reference): Not yet published.

Studied period: 11-Feb-2004 (first patient in) to 19-May-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 Korean patients with bronchial asthma.
- To provide information on safety and tolerability of ciclesonide.

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, enrollment Visit B0, weekly Visits B1, B2, B3, and B4), a double-blind treatment period (12 weeks duration, randomization Visit T0, 4-weekly Visits T4, T8, T12), and, if necessary, a follow-up of AEs (adverse events).

At the first baseline period visit (B0), the patient's ICS (inhaled corticosteroid) pretreatment was withdrawn and the patient received salbutamol MDI (metered dose inhaler) to be used as a rescue medication, when needed.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 ECG [electrocardiogram]) measurements, and standard clinical laboratory tests (including pregnancy test in female patients of childbearing potential) were done at the first baseline and last treatment visit. Medical history and previous medications of the patients were documented at study entry; 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 expiratory flow) readings in a diary. Patients returned to the study site at the end of weeks 4, 8, and 12 for efficacy and safety assessments.

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

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

Planned sample size: a total of 240 patients were planned for randomization, 120 patients per treatment group. A total of 249 patients were randomized, with 124 patients in the ciclesonide group and 125 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		124	124	124	107
Budesonide 400 µg od		125	125	125	114
Total	333	249	249	249	221

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;
- Korean descent;
- 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: total daily dose up to 250 µg fluticasone propionate or equivalent) within 4 weeks prior to baseline;
- FEV_1 = 80-105% of predicted measured at least 4 h 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 h;
- 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 defined as the difference in absolute FEV_1 [L] values from baseline (T0) to endpoint or last FEV_1 measurement ($T12/T_{end}$).

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 days without asthma symptoms and without use of rescue medication); drop-out rate due to asthma exacerbation; time until first asthma exacerbation; AQLQ(S).

Safety variables included: physical examination findings; vital signs data (including 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 center (pool).

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 to be 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 od budesonide. The non-inferiority acceptance limit for FVC was set to -200 mL, 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 to be 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 (ciclesonide group 57%; budesonide group 67%). The median age of the valid cases set was 41 years and 43 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) at Visit B0 and at the randomization Visit T0 (mean FEV_1 % of predicted at T0: 79.0% and 78.9% in the ciclesonide and budesonide group, respectively [PP analysis]). Also height, weight, smoking habits, race (Korean only), duration of asthma, ICS pretreatment, and reversibility characteristics were well balanced between both treatment groups.

Study results

Efficacy results:

Primary efficacy variable: FEV_1 [L]

The primary variable FEV_1 increased by 0.345 L in the ciclesonide 160 µg od pm group and 0.479 L in the budesonide 400 µg od pm group (95% CI [L]: ciclesonide 0.271, 0.419, budesonide 0.406, 0.552; PP analysis). Non-inferiority of ciclesonide to budesonide was not shown, as the 95% CI included the stipulated non-inferiority acceptance limit of -200 mL (one-sided $p = 0.0753$, PP analysis). This result was confirmed by the ITT analysis.

Secondary efficacy variables:

For FVC (absolute) non-inferiority of ciclesonide to budesonide was shown for the PP analysis (one-sided $p = 0.0100$). This result was confirmed by the ITT analysis.

Non-inferiority of ciclesonide *versus* budesonide for morning and evening home PEF for both the PP and ITT analyses was shown (one-sided $p \leq 0.0001$ [morning and evening]).

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

No statistically significant differences in the decrease of rescue medication use were observed between the treatment groups (PP and ITT analysis).

The percentage of the variables asthma symptom-free days, rescue medication-free days, asthma symptom- and rescue medication-free days (patient perceived asthma control), and nocturnal awakening-free days increased in both treatment groups during the treatment period. No statistically significant between-treatment differences were observed for any of these variables (PP and ITT analyses).

With respect to the improvement in the overall AQLQ(S) score, the PP analysis demonstrated non-inferiority of ciclesonide treatment to budesonide (one-sided $p < 0.0001$), which was confirmed by the ITT analysis.
Ten patients (8.1%) in the ciclesonide group and five patients (4.0%) in the budesonide group full analysis set (FAS) experienced LOE during the treatment period of the study. The difference between both treatments was not statistically significant (two-sided p-value logrank test = 0.1715, ITT; confirmed by PP).

Overall statistically significant increases for the primary efficacy variable FEV_1 were observed with ciclesonide 160 µg od pm and budesonide 400 µg od pm, while non-inferiority of ciclesonide to budesonide was not demonstrated. It should be mentioned that in subgroup analyses by sex for FEV_1 absolute and % predicted as well as for the exacerbation rate unexpected different effect sizes in female and male patients were observed, for which there is no apparent explanation available.

For the other variables (clinic FVC, home PEF, asthma symptoms and use of rescue medication, as well as for quality of life) comparable efficacy was seen for ciclesonide 160 µg od pm and budesonide 400 µg od pm.

Safety results

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

During the baseline period, 44 patients (13.2%) experienced a total of 59 AEs. The most common AEs during the baseline period were URTI (upper respiratory tract infection) and asthma.

Overall, 157 treatment-emergent AEs were reported by 99 patients (39.8%). The percentage of patients with AEs was similar in both treatment groups (ciclesonide: 40.3%; budesonide: 39.2%). The most frequently occurring treatment-emergent AEs were URTI (ciclesonide group: 18.5% of patients; budesonide group: 12.0% of patients) and asthma (ciclesonide: 9.7% of patients; budesonide: 4.8% of patients).

Treatment-emergent AEs (safety set)

	Number (%)[a] of patients and number of events					
	CIC160 (N = 124)		BUD400 (N = 125)		Total (N = 249)	
Patients who experienced	**n (%)**	**n'**	**n (%)**	**n'**	**n (%)**	**n'**
AEs	50 (40.3)	82	49 (39.2)	75	99 (39.8)	157
SAEs: all	2 (1.6)	3	1 (0.8)	1	3 (1.2)	4
deaths	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs with likely relationship (per investigator)[b]	4 (3.2)	4	4 (3.2)	5	8 (3.2)	9
AEs leading to discontinuation	11 (8.9)	16	4 (3.2)	5	15 (6.0)	21
AEs not yet known to be recovered	4 (3.2)	5	8 (6.4)	11	12 (4.8)	16
AEs that resulted in study medication change	9 (7.3)	14	5 (4.0)	7	14 (5.6)	21
AEs that resulted in concomitant medication change	37 (29.8)	54	31 (24.8)	49	68 (27.3)	103

[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, n' = number of events, SAE = serious adverse event.

The majority of AEs were mild or moderate in intensity. Seven patients (5.6%) in the ciclesonide treatment group experienced at least one treatment-emergent AE that was assessed as severe (cardiac failure congestive [one patient], URTI [three patients], and asthma [six patients]); in the budesonide group this was reported for four patients (3.2%; URTI [one patient] and asthma [four patients]). Only one event from all resolved AEs recovered with sequelae (ciclesonide group: URTI). One AE in the budesonide group (bronchospasm) was assessed by the investigator as 'definitely related' to study medication. Four events in the ciclesonide group (pharynx discomfort, muscular weakness, blood creatine phosphokinase increased, dysphonia) and four events in the budesonide group (dysphonia [three cases], dyspepsia) were considered as 'likely related' to study medication.

Eight patients in the ciclesonide group and four patients in the budesonide group discontinued the study due to an asthma exacerbation; one patient due to worsening of asthma with simultaneous URTI (ciclesonide group), and one patient due to muscular weakness (ciclesonide group).

No deaths occurred during the study. Two patients (1.6%) in the ciclesonide group and one patient (0.8%) in the budesonide group experienced SAEs (three SAEs in total in the ciclesonide group [congestive cardiac failure and urticaria with simultaneous toxic skin eruption] and one SAE in the budesonide group [colonic polyp]). One patient in the ciclesonide group discontinued the study due to two simultaneous SAEs (urticaria with toxic skin eruption). None of the SAEs were assessed as related to study medication.

No major changes in laboratory values over time were observed for either treatment group. In the ciclesonide group one mild event of increase in blood creatine phosphokinase was assessed by the investigator as 'likely related' to study medication. However, this patient had an elevated CPK value at baseline already. One patient in each treatment group, who tested negative for pregnancy at baseline, had a positive pregnancy test during the

treatment period of the study. Both patients were withdrawn from further participation in the study immediately after confirmation of pregnancy.

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. No clinically relevant ECG readings appeared during the study in either treatment group.

In conclusion, administration of ciclesonide 160 µg od pm for 12 weeks did not reveal any unknown safety findings in this population of Korean patients. The safety data seen in this study are comparable to the safety data in Caucasians.

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