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Clinical Study Report No. 295/2006

Version (1.0)

Title: Evaluation of parameters of the small airways and their changes under treatment with ciclesonide (320 µg once daily) versus placebo in patients with asthma	Version date: 13-Dec-2006 INN: Ciclesonide Project No. / List No.: BY9010 Compound No.: B9207-015 Batch No.: CIC 160 µg MDI: 4BGA004, 4BGA006 CIC Placebo MDI: 0BGA001, 0BGA003
Study Protocol No.: **BY9010/M1-131**	Development phase: IIIb
EudraCT No: not applicable	Indication studied: Asthma
Study initiation date: 13-Jan-2004	Date of early termination: 12-May-2006
Study completion date: 12-May-2006	Summary of modifications: not applicable
Name and country of investigators: One center in The Netherlands Principal investigator:	
Name of sponsor's responsible medical officer: ALTANA Pharma AG (RCS/P1), Byk-Gulden-Str. 2, 78467 Konstanz, Germany	
Person(s) responsible for study report: ALTANA Pharma AG (RCO/R1), Byk-Gulden-Str. 2, 78467 Konstanz, Germany	
Sponsor's contact persons for regulatory approval application: See accompanying letter of the regulatory approval application	
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)	
Archiving responsibility for essential documents: Department RCO/CT at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.	
This report is strictly confidential. Disclosure of contents to third parties is not permitted except by written consent of ALTANA Pharma AG, 78467 Konstanz, Germany.	

2 Synopsis

Title of the study: Evaluation of parameters of the small airways and their changes under treatment with ciclesonide (320 µg once daily) *versus* placebo in patients with asthma

Investigator and study center:

Principal investigator:

Publication (reference): Not applicable

Studied period: 13-Jan-2004 (first patient in) to 12-May-2006 (last patient out)

Clinical phase: IIIb

Objectives:

The aim of this pilot study was to investigate main indicators of the small airways before treatment with ICS (inhaled corticosteroids), and to evaluate their changes after 5 to 6 weeks of treatment with 320 µg/day ciclesonide in comparison with placebo.

A further aim was to evaluate measures of small airways involvement in relation with other variables such as bronchial hyperresponsiveness to AMP (adenosine-5'-monophosphate) and MCh (methacholine), lung function, regional air trapping visualized by low-dose CT (computed tomography) scanning, and non-cellular markers of inflammation in central and more peripheral airways. Furthermore, it was of interest to gain information about the reproducibility of the different variables of small airways in the placebo group.

Methodology:

Monocenter, double-blind, randomized, parallel group pilot study consisting of a 4-week pre-baseline period (for patients pretreated with ICS alone or in combination with LABAs [long-acting β_2-agonists]), a 2 to 3-week baseline period and a 5 to 6-week treatment period.

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

It was planned to randomize 20 patients (10 per treatment group) who complete the trial.

Analyzed sets:

	Enrolled	Randomized	Safety set	Full analysis set
CIC320		9	9	9
PLAC		7	7	7
Total	44	16	16	16

CIC320 = ciclesonide 320 µg once daily, PLAC = placebo.

Diagnosis and main criteria for inclusion:

Inclusion criteria at Visit P0, if patients were currently pretreated with ICS (alone or in combination with LABAs), or inclusion criteria at Visit B0, if patients were not pretreated with ICS:

- written informed consent was given;
- outpatients of either sex;
- age 18 to 60 years;
- history of bronchial asthma;
- FEV_1 (forced expiratory volume in 1 second) ≥60% of predicted, measured at least 6 hours after the last use of rescue medication (eg [for example] salbutamol);
- atopy shown by positive Phadiatop® or skin prick test to common allergens (historic tests were accepted, if results were available and test was done within 3 years prior to the start of study);
- stable asthma (no exacerbation or relevant respiratory tract infection within 2 months prior to the study);
- patients who were in good health with the exception of asthma.

Additional inclusion criteria at Visit P0:

- patients who had been pretreated with ICS of up to 800 µg/day budesonide or equivalent (ie [*id est*] up to 1000 µg BDP [beclomethasone dipropionate] as chlorofluorocarbon formulation, or 400 µg BDP as hydrofluoralkane formulation [eg Qvar®, produced by 3M], or 500 µg fluticasone propionate), if ICS had been taken alone or in combination with LABA;
- FEV_1 >1.25 L.

Additional inclusion criteria at Visits B0 and B1:

- FEV_1 ≥60% of predicted, measured at least 6 hours after the last use of rescue medication (eg salbutamol; at Visit B0 for patients who had withdrawn ICS at Visit P0);
- FEV_1 >1.25 L prior to each bronchial challenge test;
- PC_{20} (provocative concentration causing a 20% fall in FEV_1) ≤4.9 mg/mL to MCh (at Visit B0) and PC_{20} ≤40 mg/mL to AMP (at Visit B1);

- steroid-naïve patients or patients who had withdrawn ICS at least 4 weeks prior to entry into the baseline period, taking short-acting β_2-agonists (eg salbutamol) for rescue medication only.

Randomization criteria at Visit T0:

- FEV_1 ≥60% of predicted, measured at least 6 hours after the last use of rescue medication (eg salbutamol);
- PC_{20} MCh at Visit B2 was within two doubling doses compared to the respective measurement at Visit B0.

Test product, dose, mode of administration, batch no.: Ciclesonide 160 µg/puff (ex actuator) MDI (metered dose inhaler), 320 µg od (once daily), oral inhalation, 4BGA004 and 4BGA006

Reference product, dose, mode of administration, batch no.: Placebo MDI, od, oral inhalation, 0BGA001 and 0BGA003

Duration of treatment: 5 to 6 weeks

Criteria for evaluation:

The following variables were to be analyzed in an exploratory manner:

- ΔFVC% (percentage fall in forced vital capacity) at PC_{20} AMP, ΔFVC% at PC_{20} MCh (variables of primary interest);
- ΔSVC% (percentage fall in slow vital capacity) at PC_{20} AMP, ΔSVC% at PC_{20} MCh;
- PC_{20} MCh and PC_{20} AMP;
- regional air trapping in relation to lung volume assessed by low-dose CT scanning before and after MCh challenge tests;
- bronchial and alveolar exhaled NO (nitric oxide) assessed by multiple flow testing;
- closing volume [mL] and slope of phase III [%N_2/mL] from single breath nitrogen test;
- lung function variables (FEV_1, FVC, $FEF_{50\%}$ [forced expiratory flow after 50% of vital capacity], $FEF_{25-75\%}$ [mean forced expiratory flow between 25 and 75% of vital capacity], SVC, ratio FVC/SVC);
- non-cellular inflammatory markers derived by bronchoscopy (eg ECP [eosinophil cationic protein], IL [interleukin]-6, IL-8, TARC [thymus and activation-regulated chemokine], TNF-α [tumor necrosis factor alpha], LTB4 [leukotriene B4], as well as IL-4 and IL-5, if possible) in central and peripheral airways;
- safety and tolerability (physical examination, BP [blood pressure], HR [heart rate], AEs [adverse events], laboratory work-up).

Statistical methods:

It should be noted that this study was terminated prematurely and, thus, an abbreviated Clinical Study Report was compiled. Efficacy data were only listed, ie these data were not analyzed by ALTANA Pharma.

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

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

In total, 16 patients were randomized and included in the FAS (full analysis set; ciclesonide 320 µg od: N = 9, placebo: N = 7). Nine randomized patients terminated the study prematurely (ciclesonide 320 µg od: n = 4, placebo: n = 5).

The median age was 36 years (range 19 to 56) in the ciclesonide treatment group and 44 years (range 21 to 53) in the placebo group (see Table below). At the time of randomization mean FEV_1 % of predicted was 94.1 and 100.6 in the ciclesonide and the placebo treatment group, respectively (FAS).

Demographic and other baseline characteristics by treatment (FAS)

		CIC320 (N = 9)	PLAC (N = 7)
Age [years]	Median (range)	36.0 (19.0, 56.0)	44.0 (21.0, 53.0)
Sex [n (%)][a]	Male	5 (55.6)	2 (28.6)
	Female	4 (44.4)	5 (71.4)
Weight [kg]	Mean ± SD	78.1 ± 14.1	69.7 ± 11.1
Height [cm]	Mean ± SD	177.9 ± 11.8	171.7 ± 4.2
Duration of asthma [months]	Mean ± SD	283.4 ± 90.3	225.3 ± 86.9
FEV_1 % of pred. at T0 [L]	Mean ± SD	94.1 ± 12.0	100.6 ± 14.9

[a] Percentages are based on the number of patients in a treatment group.
CIC320 = ciclesonide 320 µg once daily, FAS = full analysis set, N = number of patients in respective treatment group, n = number of patients, PLAC = placebo, pred. = predicted, SD = standard deviation, T0 = randomization visit.

Efficacy

This study was terminated prematurely since the required number of 20 completed patients could not be achieved in a feasible period of time. Thus, the efficacy data obtained during the study were not analyzed by ALTANA Pharma.

Safety

A summary of treatment-emergent AEs is given in the following table:

Frequency of treatment-emergent AEs (safety set)

Number of patients (%)[a] with:	n (%)[a] CIC320 (N = 9)	PLAC (N = 7)	Total (N = 16)
AEs	3 (33.3)	1 (14.3)	4 (25.0)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
AEs not yet known to be recovered	1 (11.1)	0 (0.0)	1 (6.3)
Changes in study medication due to AEs	0 (0.0)	0 (0.0)	0 (0.0)
Changes in conc. medication due to AEs	0 (0.0)	0 (0.0)	0 (0.0)

[a] Percentages are based on the total number of patients in a treatment group.

[b] AEs assessed as 'likely' or 'definitely' related to the study medication by the investigator.

AE = adverse event, CIC320 = ciclesonide 320 µg once daily, conc. = concomitant, N = number of patients in each treatment group, n = number of patients with events, PLAC = placebo, SAE = serious adverse event.

AEs were reported during the treatment period by 3 of 9 (33.3%) patients treated with ciclesonide and by 1 of 7 (14.3%) patients treated with placebo.

The treatment-emergent AEs occurring in this study included the following: one episode each of blood creatine phosphokinase increased, headache, dermatitis together with eczema in the ciclesonide 320 µg od group and pulmonary function challenge test abnormal in the placebo group. There was no pattern with regard to the type and the distribution of these AEs. All of the AEs were of mild or moderate intensity and all of the events were assessed as being 'unrelated' or 'unlikely' related to the study drug by the investigator since the AEs were either intercurrent diseases or there were evident alternative reasons including pre-existing conditions.

No deaths or SAEs were reported during the treatment period of this study. Furthermore, no randomized patient discontinued prematurely due to an AE.

Overall, for all clinical chemistry and hematology variables analyzed, the median changes from baseline were small and not clinically relevant. Physical examination, BP and HR measured during treatment did not reveal any influence of the study medication.

Conclusions:

Date of report: 13-Dec-2006