Disclaimer: This study was originally sponsored by ALTANA Pharma AG and was acquired from Takeda by AstraZeneca. For additional information regarding this study, please contact the AstraZeneca Clinical Study Information Center at information.center@astrazeneca.com.

1 Title Page

Clinical Study Report No. 198/2006

Version **(1.0)**

Title: Comparison of Ciclesonide (80 µg Once Daily in the Evening) and Fluticasone propionate (100 µg Twice Daily) in Patients with Mild to Moderate Asthma		Version date:	26-Feb-2007
		INN:	Ciclesonide
		Project No. / List No.:	BY9010
		Compound No.:	B9207-015
		Batch No.: CIC 40 µg MDI: CIC placebo MDI: FP 50 µg MDI: FP placebo MDI:	 1BGA006 0BGA003 X48 FBG004
Study Protocol No.:	**BY9010/M1-142**	Development phase:	IIIb
EudraCT No:	2004-001072-39	Indication studied:	Asthma
Study initiation date:	02-Dec-2004	Date of early termination:	not applicable
Study completion date:	09-Jan-2006	Summary of modifications:	not applicable

Name and country of investigators:
48 centers in Austria, Canada, Germany, Poland, and South Africa
Coordinating 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

Sponsors contact persons:
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.

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2 Synopsis

Title of the study: Comparison of ciclesonide (80 µg once daily in the evening) and fluticasone propionate (100 µg twice daily) in patients with mild to moderate asthma

Investigator(s) and study center(s): A total of 48 main investigators participated in this international study at 48 centers located in Austria, Canada, Germany, Poland, and South Africa.

Coordinating investigator:

Publication (reference): Not applicable

Studied period: 02-Dec-2004 to 09-Jan-2006

Clinical phase: IIIb

Objectives:

The aim of the present study was to compare the efficacy of 80 µg ciclesonide od in the evening (CIC80, ex actuator) vs. 100 µg fluticasone propionate bid (FP200, ex valve) on lung function, time to the first asthma exacerbation, asthma symptoms, use of rescue medication, and quality of life in patients with mild to moderate asthma.

In addition, the study was to provide information on the safety and tolerability of treatment with ciclesonide.

Methodology:

The study was conducted using a randomized, double-blind, double-dummy, parallel-group design. Patients were randomized to one of two treatments groups (CIC80 or FP200) in a 1:1 randomization scheme. The study consisted of a 2- to 4-week baseline period (Visits B0, B2, Visits B3, B4 optional), and a treatment period of 24 weeks (Visits T0, T2, T4, T8, T16 and T24). During the treatment period the patients were thus asked to visit the investigation site at intervals of 2, 4, 8, 16, and 24 weeks after the randomization visit T0). A follow-up period subsequent to the treatment period was included, if necessary.

Patients included in the study were treated with ICSs (inhaled glucocorticosteroids) at a maximum daily dose of 250 µg FP or equivalent during the last 4 weeks directly preceding Visit B0. The ICSs were withdrawn at Visit B0. During the baseline period, eligible patients were treated with rescue medication (salbutamol) only. During the treatment period the patients received either a daily dosage of 80 µg ciclesonide administered once daily in the

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evening or a daily dosage of 200 µg fluticasone propionate administered twice daily (in the morning and in the evening).

FEV_1 [forced expiratory volume in one second], FVC [forced vital capacity]) was measured at each study visit. Home morning and evening PEF (peak expiratory flow), asthma symptom scores, and use of rescue medication were recorded in patient diaries throughout the study period.

At Visits B2/T0, T8, T16 and T24 or premature study termination an EQ-5D (Euro-Quality of Life 5 Dimensions) Questionnaire[1] and a self-administered AQLQ(S) (Standardized Asthma Quality-of-Life Questionnaire) were completed by the patients. Data on health economics were collected at Visits B0, T2, T4, T8, T16, and T24 or premature study termination[1].

Adverse events were documented at each study visit. During each visit an oropharyngeal inspection was performed for the assessment of oral candidiasis. Vital signs (BP [blood pressure], HR [heart rate]), physical examinations, and clinical laboratory tests were performed at study start (Visit B0) and at the end of the treatment period (Visit T24 or T_{end} in case of premature study termination). Vital signs were also assessed at Visits T8 and T16. All asthma exacerbations were recorded as AEs (adverse events).

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

According to the sample size calculation 480 randomized patients were needed.

Analyzed sets:

	Enrolled	Safety set	Full analysis set	Valid cases set
CIC80		240 (38.4%)	240 (38.4%)	216 (34.6%)
FP200		240 (38.4%)	240 (38.4%)	207 (33.1%)
Total	625 (100.0%)	480 (76.8%)	480 (76.8%)	423 (67.7%)

Percentages based on the total set (N = 625). If not given in Table 15.1.1.2, percentages were calculated by the author.
CIC80 = CIC 80 µg od, FP200 = FP 100 µg bid

Diagnosis and main criteria for inclusion:
At Visit B0:

- male and female outpatients aged 12 to 75 years inclusive;
- written informed consent;
- history of bronchial asthma for at least 6 months;
- good health with the exception of asthma;
- treated with ICS with a maximum daily constant dosage of 250 µg fluticasone propionate or equivalent during the last 4 weeks directly prior to B0;
- FEV_1 = 80 - 105% of predicted.

[1] Results from the EQ-5D and the health economics assessment will be presented in a separate report.

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At randomization (Visit T0):

For entry into the treatment period (Visit T0) patients had to fulfill the following randomization criteria:

- FEV_1= 61 - 90% of predicted;
- a decrease of FEV_1 by at least 10% of initial referred to B0 after withdrawal of the ICS;
- a reversibility of FEV_1 ≥12% (or at least 200 mL) of initial after inhalation of 200 - 400 µg salbutamol;
- asthma nighttime symptoms occurred during not more than 2 nights within 7 consecutive days directly preceding T0;
- daytime symptom score was not ≥3 on more than 3 d within 7 consecutive days directly preceding T0.

Test product, dose, mode of administration, batch no.:

Ciclesonide HFA (hydrofluoralkane)-MDI (metered dose inhaler), 80 µg/d (ex actuator), once daily in the evening, oral inhalation, 1BGA006.

Reference product, dose, mode of administration, batch no.:

Fluticasone propionate HFA-MDI, 200 µg/d (ex valve), twice daily, oral inhalation, X48.

Duration of treatment: 24 weeks

Criteria for evaluation:

Primary variable:

- FEV_1 [L] (T_{end} vs. T0)

Secondary efficacy variables:

- FEV_1 [L] (other visits); FVC [L]; FEV_1, FVC % of predicted [%] ; proportion of patients with asthma exacerbations; morning and evening PEF absolute [L/min] and predicted [%]; diurnal PEF fluctuation [%]; asthma symptom score sum [0, 1,…, 8]; use of rescue medication [puffs/d]; percentage of asthma-controlled days [%] ; AQLQ(S) domain and overall scores [1, 2,…, 7].

Safety variables:

- treatment exposure [d]; AEs; laboratory work-up; vital signs (blood pressure and heart rate); physical examination.

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Statistical methods:

CIC80 was tested for non-inferiority to FP200 for the primary variable difference in FEV_1 (T_{end} vs. T0).

Results of analyses of secondary variables were to be interpreted in an exploratory manner.

For the non-inferiority tests, the PP (per protocol) analysis was stipulated as the primary analysis. For superiority tests, the ITT (intention-to-treat) analysis was primary. For all statistically analyzed variables, both the PP and ITT analyses were performed and reported. The overall level of significance was set to 5%, two-sided (type I error of $\alpha = 0.05$), which in the case of one-sided hypotheses corresponded to 2.5%, one-sided.

The primary variable FEV_1 was evaluated using an ANCOVA (analysis of covariance) including baseline value (value at randomization visit T0) and age as covariates, and treatment, sex and center pool as fixed factors. Within-treatment and between-treatment comparisons of secondary lung function variables (absolute and predicted values), home PEF, and AQLQ(S) scores were performed by means of an analogous ANCOVA model. For non-inferiority tests the non-inferiority acceptance limits of -200 mL for FEV_1 and FVC, -25 L/min for home morning and evening PEF, and -0.5 scores for AQLQ(S) were pre-defined.

A further model that includes a treatment-by-country pool interaction term was performed in order to assess the interaction term.

Non-parametric within- and between-group comparisons of the diary variables diurnal PEF fluctuation, asthma symptom scores, use of rescue medication, percentage of asthma symptom-, rescue medication-, and nocturnal awakening-free days, and of the percentage of asthma-controlled days, were done using the modification of Wilcoxon's signed-rank test according to Pratt and the Mann-Whitney U-test, respectively.

Adverse events, blood pressure, heart rate, physical examination, and laboratory values were evaluated by means of descriptive statistics.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Overall, the treatment groups of the VCS (valid cases set) compared well and the demography for the FAS (full analysis set) was similar to the VCS.

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Demographic and other baseline characteristics (VCS, FAS)

		VCS		FAS	
		CIC80 (N = 216)	**FP200 (N = 207)**	**CIC80 (N = 240)**	**FP200 (N = 240)**
Age [years]	Median (range)	41 (12, 75)	40 (12, 75)	42 (12, 75)	41 (12, 75)
Sex [n (%)][a]	Female	126 (58.3)	132 (63.8)	140 (58.3)	150 (62.5)
	Male	90 (41.7)	75 (36.2)	100 (41.7)	90 (37.5)
ICS pretreatment (µg/day) up to Visit B0 expressed as BDP equivalent	Mean ± SD	438 ± 101	440 ± 102	436 ± 101	443 ± 103
FEV_1 at T0 [L][b]	Mean ± SD	2.371 ± 0.611	2.370 ± 0.599	2.389 ± 0.608	2.368 ± 0.597
FEV_1 at T0 [% of predicted][b]	Mean ± SD	75.6 ± 6.9	75.8 ± 6.3	75.5 ± 6.9	76.0 ± 6.7
FEV_1 reversibility (% increase)	Mean ± SD	16.8 ± 7.4	16.9 ± 7.1	16.7 ± 7.3	16.8 ± 7.1

[a] Percentages are based on the number of patients in a treatment group.
[b] Values are based on the number of patients with data available.
CIC80 = CIC 80 µg od, FAS = full analysis set, FP200 = FP 100 µg bid, n = number of patients with data available, N = number of patients, SD = standard deviation, VCS = valid cases set

Efficacy results

In both treatment groups, FEV_1 increased from baseline to the end of treatment (LSMean [least squares mean]: CIC80: 0.462 L, FP200: 0.521 L, PP analysis). Confirmatory testing demonstrated non-inferiority of CIC80 to FP200 (p = 0.0002, one-sided, 95% CI [confidence interval] -0.138, 0.019, PP analysis). The ITT analysis confirmed the results from the PP analysis.

The number of patients with asthma exacerbations was comparable for the two treatment groups (CIC80: 5 patients [2.1%], FP200: 5 patients [2.1%], FAS).

The results for the secondary variables FVC and home PEF reflected those for the primary variable FEV_1. Thus, FVC and morning and evening PEF values increased during the treatment period (PP and ITT analysis). Non-inferiority of CIC80 to FP200 was shown exploratorily for FVC (p = 0.0003) as well as morning and evening PEF (p = 0.0018 and p = 0.0003, respectively, all one-sided, PP analysis). The ITT analysis yielded comparable results.

In both treatment groups, asthma symptom scores (daytime, nighttime, and sum), use of rescue medication, and asthma control variables improved during the treatment period (PP and ITT analysis). No statistically significant between-treatment difference was shown for the CIC80 to FP200 comparison with regard to asthma symptom scores, use of rescue medication, and asthma control variables (PP and ITT analysis).

The AQLQ(S) overall and individual domain scores increased during the treatment period in both treatment groups (PP and ITT analysis). CIC80 was non-inferior to FP200 with regard to the AQLQ(S).

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Safety results

The following table gives an overview of treatment-emergent AEs and SAEs (serious AEs).

Treatment-emergent AEs (SAF)

	CIC80 (N = 240)	FP200 (N = 240)	Total (N = 480)
Number of patients (%)[a] with:			
AEs	106 (44.2)	103 (42.9)	209 (43.5)
SAEs: all	2 (0.8)	2 (0.8)	4 (0.8)
deaths	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested by the investigator	12 (5.0)	20 (8.3)	32 (6.7)
AEs leading to discontinuation	4 (1.7)	8 (3.3)	12 (2.5)

[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.
CIC80 = ciclesonide 80 µg od, FP200 = fluticasone propionate 100 µg bid, N = number of patients in each treatment group, SAF = safety set.

The most frequently reported treatment-emergent AEs in each treatment group were related to the MedDRA (Medical Dictionary for Regulatory Activities) SOC (system organ class) infections and infestations and included nasopharyngitis and upper respiratory tract infection. On the preferred term level nasopharyngitis was the most frequently documented AE in both groups (CIC80: 10.8% of patients, FP200: 10.4% of patients).

Most AEs were mild or moderate in intensity. For five patients in each group severe AEs were documented (CIC80: benign prostatic hyperplasia, musculoskeletal chest pain, asthma [2 patients], dermatitis allergic; FP200: renal colic, asthma, headache, syncope vasovagal and asthma, medulloblastoma).

The investigator assessed a likely relationship to the study medication for more patients with AEs in the FP200 group (8.3%) than in the CIC80 group (4.6%). The sponsor considered the AEs in 2.5% of the patients under CIC80, and in 3.8% of the patients under FP200 as likely related to study medication. In addition, the investigator assessed one AE (dyspnoea) in one patient from the CIC80 treatment group as definitely related to the study medication. The sponsor did not rate any AE as definitely related to the study drug.

Four SAEs were reported during the treatment period: two in two patients (0.8%) in the CIC80 group (benign prostatic hyperplasia and asthma) and two in two patients (0.8%) in the FP200 group (syncope vasovagal and medulloblastoma). One SAE in the CIC80 group (asthma) and one SAE in the FP200 group (medulloblastoma) led to study withdrawal. All SAEs in both treatment groups were assessed as unrelated to study medication.

Asthma was the most common AE leading to study discontinuation in each of the groups.

In the CIC80 treatment group, the investigator considered one AE leading to withdrawal of one patient as likely related to study medication (dyspnoea). In the FP200 treatment group

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also one AE leading to study discontinuation of one patient (throat irritation) was assessed as likely related to study medication by the investigator.

No general trend towards a clinically relevant change in any hematology or biochemistry variable was evident in either treatment group.

Conclusions

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