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Clinical Study Report No. 349/2005

Version 1.0

Title: A comparison study of inhaled ciclesonide 200 µg/day vs fluticasone propionate 200 µg/day in children with asthma	Version date: 10-Jul-2006 INN: Ciclesonide Project No. / List No.: BY9010 Compound No.: B9207-015 Batch No.: CIC 80 µg MDI: 2BGA003, 2BGA004 CIC placebo MDI: 0BGA001, 0BGA002 FP 50 µg MDI: D036108, D040214 FP placebo MDI: FBG002, FBG003
Study Protocol No.: **BY9010/M1-205**	Development phase: III
EudraCT No: not applicable	Indication studied: Asthma
Study initiation date: 14-Jun-2003	Date of early termination: not applicable
Study completion date: 01-Dec-2004	Summary of modifications: not applicable

Name and country of investigators:

14 investigators at 14 centers located in India

Name of sponsor's responsible medical officer:
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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 RCD/C1 at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

2 Synopsis

Title of the study:

A comparison study of inhaled ciclesonide 200 µg/day vs fluticasone propionate 200 µg/day in children with asthma

Investigators: 14 investigators at 14 centers in India.

Coordinating investigator: not applicable

Study center(s): Multicenter study at 14 investigational sites in India.

Publication (reference): Not yet published

Studied period (years): 14-Jun-2003 (first patient in) to 01-Dec-2004 (last patient out)

Clinical phase: Phase III

Objectives:

The objective of this study was to evaluate and compare the efficacy and safety of ciclesonide HFA 134-a (hydrofluoralkane) MDI (metered dose inhaler) 160 µg/d (ex actuator) with FP HFA 134-a MDI 200 µg/d (ex valve) in children with persistent asthma.

Methodology:

The present study has a randomized, double-blind, double-dummy, 2-arm, parallel group design. It consisted of a baseline period of 2 to 4 weeks, a 12-week treatment period, and a follow-up period if applicable. Patients had to use salbutamol as rescue medication throughout the study (baseline and treatment period). At Visit T0 eligible patients were randomized either to treatment with ciclesonide 160 µg od (once daily, evening), or FP 100 µg bid (twice daily) (at a 1:1 ratio). Both treatments were inhaled by using a spacer (AeroChamberPlus^{TM}) together with the MDIs.
Lung function (FEV_1, PEF) via spirometry was measured at all baseline and treatment visits. Throughout the study patients recorded their morning and evening PEF, use of rescue medication, and asthma-related symptoms in a paper diary. AEs and use of concomitant medication were documented by the investigator throughout the study. At study Visits B0 and $T12/T_{end}$ and at follow-up visits if applicable, standard laboratory investigations and physical examination (including vital signs) were performed.

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

	Enrolled	Randomized	SAF&FAS	VCS
CIC		254	254	231
FP		260	258	233
Total	**591**	**514**	**512**	**464**

CIC = ciclesonide 160 µg once daily, FAS = full analysis set, FP = fluticasone propionate 100 µg twice daily, SAF = safety set, VCS = valid cases set.

No patient was randomized more than once, therefore the SAF (safety set) was identical to the FAS (full analysis set).

Diagnosis and criteria for inclusion:

Inclusion criteria (at Visit B0)

Patients of whom the parent(s) or legal guardian(s) gave written informed consent and who fulfilled the following criteria were considered for inclusion into the study:

- male or female outpatients, aged 4 to 15 years inclusive;
- female patients who were postmenarchal or became menarchal during the study had to either start practicing safe contraception or abstinence. Patients who did not start practicing birth control measures were allowed to continue with the study provided that the parent(s) or legal guardian(s) was informed about the risk if the patient became pregnant during the course of the study. If the continued participation of a patient who was postmenarchal or became menarchal was regarded as a risk by either the investigator or the parent(s)/legal guardian(s), the patient was withdrawn from the study. A serum pregnancy test was performed at the start and the end of the study in all female patients who were 10 years or older;
- patients with a documented diagnosis of persistent asthma for at least six months;
- FEV_1 (forced expiratory volume in one second) % of predicted, measured at least 4 h after the inhalation of a short-acting β_2-agonist (eg salbutamol) or at least 24 h after the inhalation of salmeterol or formoterol or intake of a fixed combination of a LABA (long-acting β_2-agonist) and an ICS (inhaled corticosteroid):
    - ♦ 50 to 90% in patients who were not using any medication for asthma other than rescue medication prn (as needed);
    - ♦ 80 to 100% in patients who were treated with inhaled steroids for the past 30 d at doses not more than the following:
        - BDP (beclomethasone dipropionate): 400 µg/d (HFA formulation of BDP: 200 µg/d);
        - budesonide: 400 µg/d;
        - FP: 200 µg/d;

- ♦ 50 to 100% in patients treated with theophylline, cromones (cromoglycate, nedocromil), leukotriene-antagonists, lipoxygenase-inhibitors, ketotifen, LABA, anticholinergics, but without concurrent steroid treatment;

- patients who were on combination therapy of a LABA plus an ICS had to have not received budesonide or FP in a daily dose of more than 200 µg and 100 µg, respectively. In addition, the patient had to receive the fixed dose combination in the same dose for at least 30 d before B0;
- patients who were treated with anti-asthma drugs such as ICS, theophylline, cromones (cromoglycate and nedocromil), leukotriene antagonists, lipoxygenase inhibitors, anticholinergics and ketotifen must have had the medication for at least 30 d and at the same dosage before baseline;
- patients who, with the exception of asthma, were in good health;
- patients with no asthma exacerbation or relevant lung diseases (eg lower respiratory tract infection) during the past 30 d before B0;
- patients with no more than one inpatient hospitalization for asthma in the last one year but not within the last six months.[1]

Randomization criteria (at Visit T0)
Patients were randomized if the following criteria were fulfilled:

- FEV_1 of 50 to 90% of predicted following a 4 h withhold of salbutamol MDI;
- reversibility of FEV_1 by at least 12% of predicted following the inhalation of 200 µg to 400 µg salbutamol with spacer (AeroChamberPlus™) without face mask. If no reversibility test was shown during baseline (up to and including B4), a documented historically reversibility test during the last 12 months before B0 was used. Alternatively during baseline (first time at B1) diurnal PEF (peak expiratory flow) fluctuation of 15% or more on 3 of the last 10 consecutive days was shown;
- either asthma symptom score of 1 or greater on at least 6 of the last 10 consecutive days or use of a total of 8 or more puffs of rescue medication during the last 10 consecutive days before randomization.

Test product: ciclesonide

Dose: 160 µg od (ex actuator) (ie 160 µg daily dose, equals 200 µg ex valve)

Mode of administration: oral inhalation via spacer

Batch No.: 2BGA003/ 2BGA004

Reference product: FP

Dose: 100 µg bid (ex valve) (ie 200 µg daily dose)

Mode of administration: oral inhalation via spacer

[1] **Note:** Patients hospitalized for practical reasons (eg overnight visits for diagnostic purpose) were included into the study.

Batch No.: D036108/ D040214

Duration of treatment: 12 weeks

Criteria for evaluation:

Efficacy

Primary variable

- FEV_1 [L] (difference between T0 and T_{end})

Key-secondary variables

The key-secondary variables were tested confirmatory in following order: (1) difference in nighttime asthma symptom score, (2) difference in morning PEF from diary, and (3) difference in asthma symptom score sum.

Secondary variables

- FEV_1 [% of predicted]
- PEF [L/min] and [% of predicted]
- morning PEF [% of predicted]
- evening PEF [L/min] and [% of predicted]
- PEF fluctuation [%]
- asthma symptom scores (daytime)
- use of rescue medication [puffs/d]
- percentage of days a patient perceived asthma control based on asthma symptoms and use of rescue medication [%]
- percentage of asthma symptom free days [%]
- percentage of rescue medication free days [%]
- percentage of nocturnal awakening free days [%]
- pre/post comparison of asthma control, symptom-, rescue medication- and nocturnal awakening free days
- time to onset of treatment effect [d]
- number of patients with asthma exacerbation(s)

Safety

- AE assessment
- standard laboratory workup
- physical examination
- vital signs (BP [blood pressure] and HR [heart rate])

Statistical methods:

Spirometric lung function variables as well as morning and evening PEF from diary were analyzed with an ANCOVA (analysis of covariance). The dependent variable was the difference of the values of visits after randomization to the value at Visit T0. Besides the

treatment, the following factors and covariates (all fixed) were included in the model: value at Visit T0, age at inclusion, sex, and center pool. No interaction term was included in this model, which was used to test both within- and between-treatment differences. With regard to the primary variable FEV_1, the comparison between treatments was based on the difference of T_{end} (PP [per protocol] analysis) and the baseline value at randomization (Visit T0). For the key-secondary variables asthma symptom scores (nighttime and sum) and morning PEF from diary it was based on the difference of W_{end} and W0 (PP analysis). The non-inferiority acceptance limits were -0.100 L for FEV_1, +0.15 for nighttime asthma score, +0.30 for asthma score sum, and -15L/min for morning PEF. For spirometry variables an additional repeated measurement model was analyzed to investigate the robustness of the results of the endpoint analysis.

Diurnal PEF fluctuation, asthma symptom scores, use of rescue medication, and asthma control variables were analyzed non-parametrically. Within-group differences were analyzed with Pratt's modification of Wilcoxon's signed rank test; between-treatment comparisons were analyzed with the Mann-Whitney U test.

Descriptive statistics were given for AEs, laboratory variables, and vital signs.

A sample size of n = 198 PP patients in each treatment group was sufficient to ensure a power of 90% in correctly concluding non-inferiority of ciclesonide in comparison to FP with regard to the primary variable.

SUMMARY – CONCLUSIONS

Summary:

In total, 514 patients were randomized; 512 patients took at least one dose of study medication. The latter group formed the SAF (N = 254 for ciclesonide 160 µg od and N = 258 for FP 100 µg bid; identical to the FAS). The VCS included 464 patients (N = 231 for ciclesonide 160 µg od and N = 233 for FP 100 µg bid). The ITT analysis was based on the FAS, whereas the PP analysis was based on the VCS. A total of 46 randomized patients terminated the study prematurely (23 patients in each group).
The treatment groups were well-balanced with regard to age (median 10 years), height, and weight. All patients were Indian. In both treatment groups more male patients (67%, mean FAS) were randomized than female patients (33%, mean FAS). According to GINA 2003 the majority of patients had moderate (29%, mean FAS) to severe (54%, mean FAS) persistent asthma. Only a minority of patients was pretreated with ICS (27%, mean FAS). All patients were non-smokers. Baseline characteristics of lung function (FEV_1 and FEV_1 reversibility) compared well at B0 and T0.

Efficacy results

The primary variable FEV_1 increased statistically significantly ($p < 0.0001$) in both treatment groups by 0.162 L in the ciclesonide 160 µg od group and by 0.187 L in the FP 100 µg bid group during treatment (PP analysis). Analysis of between-treatment differences

demonstrated non-inferiority of the ciclesonide treatment to the FP treatment (non-inferiority margin = –0.100 L, one-sided p = 0.0022, PP, confirmed by ITT).

Change in FEV_1 [L] from T0: within- and between-treatment differences, endpoint analysis

WITHIN		T0			$T_{end/last}$	$T_{end/last}$ - T0		
	n	Mean	% pred.	LSMean	LSMean	LSMean ± SE	95% CI	p-value[a]
PP analysis								
CIC 160 µg od	211	1.389	72.3	1.381	1.543	0.162 ± 0.021	0.121, 0.203	<0.0001
FP 100 µg bid	211	1.372	72.6	1.381	1.568	0.187 ± 0.021	0.147, 0.228	<0.0001
ITT analysis								
CIC 160 µg od	252	1.379	72.1	1.389	1.542	0.153 ± 0.020	0.114, 0.193	<0.0001
FP 100 µg bid	254	1.398	72.4	1.389	1.573	0.184 ± 0.020	0.145, 0.224	<0.0001

BETWEEN					Difference Test - Ref for $T_{end/last}$ - T0			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value non-inf.[b]	p-value sup.[c]
PP analysis	CIC 160 µg od	FP 100 µg bid	211	211	-0.025 ± 0.026	-0.077, 0.026	0.0022	0.8350
ITT analysis	CIC 160 µg od	FP 100 µg bid	252	254	-0.031 ± 0.026	-0.081, 0.019	0.0037	0.8868

[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for non-inferiority, significance level 2.5%, non-inferiority margin = -100 mL.
[c] One-sided p-value for superiority, significance level 2.5%.
bid = twice daily, CI = confidence interval, CIC = ciclesonide, FEV_1 = forced expiratory volume in one second, FP = fluticasone propionate, LS = least squares, n = number of patients with data available at T0 and endpoint, od = once daily, SE = standard error of the LSMean, T0 = randomization visit, T_{end} = last visit (PP analysis), T_{last} = last visit (ITT analysis).

The key-secondary variable nighttime asthma symptom score decreased statistically significantly ($p < 0.0001$) in the ciclesonide 160 µg od group by 0.50 and in the FP 100 µg bid group by 0.57, indicating an improvement. Non-inferiority for ciclesonide to FP was shown, as the upper limit of the 95% CI did not exceed the non-inferiority limit of +0.15 (PP and ITT analysis).

The key-secondary variable morning PEF increased in both treatment groups statistically significantly ($p < 0.0001$) by 31.1 L/min for ciclesonide 160 µg od and by 35.7 L/min for FP 100 µg bid during treatment. Non-inferiority of ciclesonide to FP was demonstrated (non-inferiority margin = –15 L/min, one-sided p = 0.0124, PP; not confirmed by ITT).

The key-secondary variable asthma symptom score sum decreased statistically significantly ($p < 0.0001$) in the ciclesonide 160 µg od group by 1.07 and in the FP 100 µg bid group by 1.21, indicating an improvement. Non-inferiority for ciclesonide to FP with regard to symptom score sum was shown, as the upper limit of the 95% CI did not exceed the non-inferiority limit of +0.30 (PP and ITT analysis).

The predefined confirmatory testing cascade was completed successfully. A repeated measurement analysis model applied for spirometry variables confirmed the results of the primary endpoint analysis.

The secondary efficacy variable FEV_1 expressed as % of predicted as well as PEF from spirometry (absolute and % of predicted) increased in both treatment groups statistically significantly. For PEF (absolute values) non-inferiority of ciclesonide to FP was shown. FEV_1 and PEF expressed as % predicted revealed no statistically significant difference between both treatments according to the two-sided p-values (PP, confirmed by ITT).

Morning PEF (% of predicted) and evening PEF (absolute and % of predicted) from diary increased statistically significantly in both treatment groups (PP and ITT analysis). Regarding all secondary efficacy variables from diary non-inferiority of ciclesonide to FP was provided where a margin was set, while for the remaining variables no statistically significant differences between both treatments were shown. PEF fluctuation decreased statistically significantly in both treatment groups; there were no statistically significant differences between the treatment groups.
Statistically significant decreases were observed for the diary variables daytime asthma symptom score and use of rescue medication in either treatment group. Differences between the treatment groups were in favor of FP for the use of rescue medication (PP, not confirmed by ITT). However, baseline values were higher for FP and both treatments reduced symptoms to zero after 12 weeks of treatment indicating more room for improvement in the FP 100 µg bid group (median).
The median percentage of days with asthma control (defined as symptom and rescue medication free days) as well as the percentage of asthma symptom-, rescue medication-, and nocturnal awakening free-days was high in both treatment groups (> 90%) and did not reveal statistically significant between-treatment differences during the course of the study (PP analysis).
In the pre/post comparison, the percentage of patients perceiving asthma control, asthma symptom free-, rescue medication free-, and nocturnal awakening free days increased in both treatment groups statistically significantly. No statistically significant difference was observed between treatments (PP and ITT analysis).

Nine out of 254 patients (3.5%) of the ciclesonide 160 µg od group and two out of 258 patients (0.8%) of the FP 100 µg bid group experienced an asthma exacerbation. The difference between treatments was statistically significant (ITT, $p = 0.0323$; not confirmed by PP). Eight out of nine LOEs in the ciclesonide 160 µg od group and one out of two LOE cases in the FP 100 µg bid group were concomitantly reported with preceding or parallel infections, mainly URTI, which is known to be a risk factor for asthma exacerbations, particularly in children.

Safety results

During the treatment period 74 (29.1%) patients in the ciclesonide 160 µg od group reported 124 AEs and 74 (28.7%) patients in the FP 100 µg bid group reported 105 AEs.

The most frequently reported AEs belonged to the SOC ‘infections and infestations’. Within this class, upper respiratory tract infection was the most common AE, reported by 35 patients in the ciclesonide 160 µg od group and 28 patients in the FP 100 µg bid group. The majority of AEs were mild in intensity in both treatment groups. Most of the AEs were assessed as ‘unrelated’ to the intake of study medication by the investigator (28.0% of patients [71 out of 74 patients] in the ciclesonide 160 µg od group and 27.9% of the patients [72 out of 74 patients] in the FP 100 µg bid group). Seven AEs of severe intensity were reported under ciclesonide treatment and three under FP treatment.

No death occurred during the study. Three patients in the ciclesonide 160 µg od group and two patients in the FP 100 µg bid group experienced one SAE (serious adverse event) each (ciclesonide 160 µg od group respective PT leukocytosis, eosinophilia, asthma; FP 100 µg bid group respective PT calculus urinary, asthma). They were all ‘unrelated’ to the intake of study medication (investigator’s assessment) and patients recovered from them without sequelae. In total, nine patients in the ciclesonide 160 µg od group (eight cases of PT asthma and one case of PT throat irritation) and four patients in the FP 100 µg bid group (respective PT calculus urinary, dizziness, eye irritation, and asthma) discontinued the study prematurely due to an AE. The AE throat irritation was assessed as ‘unlikely’ related to study medication whereas all other AEs were assessed as ‘unrelated’ by the investigator.

Laboratory investigation, physical examination, and vital signs did not indicate any relevant or new safety risk of both study medications and dosing regimens.

Conclusions:

Date of report: 10-Jul-2006