2 Synopsis

Title of the study:
Comparison of ciclesonide (80 µg or 160 µg once daily in the evening) and fluticasone propionate (100 µg twice daily in the morning and evening) in pediatric asthma patients

Investigator(s) and study center(s): 50 investigational centers located in Brasilia, Germany, Hungary, Poland, Portugal, and South Africa

Coordinating investigator(s):
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Publication (reference): Not applicable

Studied period: 25-Oct-2004 (first patient in) to 18-Nov-2005 (last patient out)

Clinical phase: Phase III

Objectives:
The primary objective of this study was to evaluate and compare the efficacy of ciclesonide HFA134-a MDI (80 µg or 160 µg od pm) with that of FP HFA134-a MDI (100 µg bid) in children with persistent asthma. In addition, the efficacy of ciclesonide 80 µg/day and 160 µg/day were compared to further study the dose response in children. Finally, additional data on the safety of ciclesonide in children were gathered.

Methodology:
The present study has a double-blind, double-dummy, randomized, three-arm parallel group design. It consisted of a baseline period of two to four weeks (Visits B1, B2, and B3, B4 if applicable), a 12-week treatment period, and a follow-up if required. At Visit T0 eligible patients were randomized to treatment with ciclesonide 80 µg od pm, or ciclesonide 160 µg od pm, or FP 100 µg bid (at a 1:1:1 ratio). Additional on site visits were performed after four weeks (T4), eight weeks (T8), and twelve weeks (T12). Patients used salbutamol as rescue medication throughout the study (baseline and treatment period). All study medication MDIs were used without a spacer.

Lung function (FEV_1, PEF) was measured at all visits. Throuhgout the study patients recorded their morning and evening PEF, use of rescue medication, and asthma-related symptoms in a paper diary. AEs and concomittant medication were documented by the investigator throughout the study. At Visits T0 and $T12/T_{end}$ a MCh (methacholine) challenge test was

performed in a subset of patients. QoL (quality of life) was assessed by PAQLQ(S) (Paediatric Asthma Quality of Life Questionnaire [Standardized]) and PACQLQ (Paediatric Caregiver's Asthma Quality of Life Questionnaire) at baseline Visit B2 (B3, B4 if applicable), T4, and T12/T_{end}. At Visits B0 (or T0) 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) planned and analyzed:

A sample size of n = 198 PP (per protocol) 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.

Analyzed sets:

	Enrolled	Randomized	SAF & FAS	VCS
CIC 80 µg od		252	252	236
CIC 160 µg od		242	242	224
FP 100 µg bid		250	250	234
Total	904	744	744	694

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

Diagnosis and main 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 outpatient aged 6 to 11 years;
- history of persistent bronchial asthma as defined by ATS (American Thoracic Society) criteria for at least six months;
- ability to perform reproducible lung function tests;
- ability to show optimal use of the MDI and inhalation technique (without spacer);
- either treated with rescue medication as needed, or treated with ICS (not exceeding 200 µg FP/d or equivalent) or other controller drugs, respectively, at a constant dose within the last 30 d prior to B0;
- FEV_1 (% of predicted value) measured at least 4 h after the inhalation of a short acting β_2-agonist (eg salbutamol) and at least 24 h after intake of inhaled long acting β_2-agonists, leukotriene antagonists, lipoxygenase inhibitors, inhaled anticholinergics, xanthines, tiotropium bromide, or oral bronchodilators:
  - 50 to 90% for patients using rescue medication only;
  - 80 to 100% for patients using ICS;
  - 50 to 100% for patients using non-ICS controller drugs such as cromones, theophylline, leukotriene antagonists, lipoxygenase inhibitors, or ketotifen.

Randomization criteria (at Visit T0)

- 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 from MDI without spacer;
- either total daily asthma symptom score of one or higher on at least six of the last ten consecutive days or use of a total of eight or more puffs of rescue medication within the last ten consecutive days.

Patients who used more than eight puffs/d on three consecutive days within the last ten days were excluded.

Note: The doses of salbutamol used to demonstrate reversibility were not documented in the diary and were not counted as use of rescue medication.

Test product, dose, mode of administration, bacth no.: Ciclesonide HFA-MDI, 80 µg/d (ex actuator), once daily, oral inhalation, 1BGA005, 1BGA006

Test product, dose, mode of administration, bacth no.: Ciclesonide HFA-MDI, 160 µg/d (ex actuator), once daily, oral inhalation, 2BGA005, 2BGA006

Reference product, dose, mode of administration, batch no.: FP HFA-MDI, 200 µg/d (ex actuator), twice daily, oral inhalation, X28, X96

Duration of treatment: 12 weeks

Criteria for evaluation:

Efficacy

Only the results from statistical testing of the primary variable and the key-secondary variables were confirmatory. Results from statistical testing of secondary variables were interpreted in an exploratory manner.

Primary variable

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

Key-secondary variables

- Morning PEF [L/min] (W_{end} compared to W0)
- $PD_{20}FEV_1$ [cumulative dose µg][1] (T_{last} compared to T0 in a subset of patients)

Secondary variables

- FEV_1 [% of predicted] and [L]

[1] Results for $PD_{20}FEV_1$ were presented in doubling doses.

- PEF [L/min] and [% of predicted]
- MCh responders [%]
- morning PEF [L/min] and [% of predicted]
- evening PEF [L/min] and [% of predicted]
- diurnal PEF fluctuation [%]
- daytime asthma symptom score
- nighttime asthma symptom score
- asthma symptom score
- use of rescue medication [puffs/d]
- percentage of asthma symptom free-days [%]
- percentage of rescue medication free-days [%]
- percentage of days a patient percieved asthma control [%]
- percentage of asthma controlled days based on asthma symptoms, use of rescue medication, and morning PEF [%]
- percentage of asthma controlled days based on asthma symptoms, use of rescue medication, morning PEF, and PEF fluctuation [%]
- percentage of days without nocturnal awakening [%]

Safety

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

Statistical methods:

With regard to the primary variable FEV_1, the comparison between treatments was based on the difference of T_{end} (PP analysis) and the baseline value at randomization (Visit T0). For the key-secondary variable morning PEF it was based on the difference of W_{end} and W0 (PP analysis), for $PD_{20}FEV_1$ it was based on the difference of T_{last} to T0 (ITT analysis).

The variables were tested confirmatory in the following order:

(1) non-inferiority of ciclesonide 160 µg to FP 100 µg bid with regard to difference in FEV_1,

(2) non-inferiority of ciclesonide 160 µg to FP 100 µg bid with regard to difference in morning PEF

(3) non-inferiority of ciclesonide 80 µg to FP 100 µg bid with regard to difference in FEV_1

(4) non-inferiority of ciclesonide 80 µg to FP 100 µg bid with regard to difference in morning PEF

(5) superiority of ciclesonice 160 µg od to ciclesonide 80 µg od with regard to $PD_{20}FEV_1$

(6) superiority of ciclesonice 160 µg od to ciclesonide 80 µg od with regard to difference in FEV_1

(7) superiority of ciclesonice 160 µg od to FP 100 µg bid with regard to difference in FEV_1, and

(8) superiority of ciclesonice 80 µg od to FP 100 µg bid with regard to difference in FEV_1.

These variables were analyzed with 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. For $PD_{20}FEV_1$ the factors and covariates $PD_{20}FEV_1$ value at Visit T0 ,age, treatment, center, and sex were included. No interaction term was included in this model, which was used to test both within- and between-treatment differences.

The non-inferiority acceptance limits were –0.100 L for FEV_1 and -12.5 L/min for PEF.

Analysis of secondary variables was exploratory. Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Demographic data and baseline characteristics of patients in the VCS were essentially comparable with those described for the FAS. The treatment groups were well balanced with regard to age, weight, and height. The majority of patients had severe persistent asthma.

Demographic and other baseline characteristics by treatment (FAS)

		FAS		
		CIC 80 µg od (N = 252)	**CIC 160 µg od (N = 242)**	**FP 100 µg bid (N = 250)**
Age [years]	Median (range)	9 (6, 11)	9 (6, 11)	9 (6, 11)
Sex [n (%)][a]	Male	164 (65.1)	158 (65.3)	164 (65.6)
	Female	88 (34.9)	84 (34.7)	86 (34.4)
Race [n (%)][a]	Asian	0 (0.0)	1 (0.4)	0 (0.0)
	Black	13 (5.2)	8 (3.3)	9 (3.6)
	White	182 (72.2)	179 (74.0)	179 (71.6)
	Other	57 (22.6)	54 (22.3)	62 (24.8)
ICS pretreatment [n (%)][a]	Not ICS pre-treated	128 (50.8)	116 (47.9)	134 (53.6)
	ICS pre-treated	124 (49.2)	126 (52.1)	116 (46.4)
FEV_1 at T0 [L]	Mean ± SD	1.510 ± 0.374	1.583 ± 0.412	1.523 ± 0.346
[% of predicted]	Mean ± SD	77.1 ± 9.3	77.6 ± 10.3	77.1 ± 9.9
FEV_1 rev. [% of predicted]	Mean ± SD	17.3 ± 6.8	17.7 ± 7.3	17.9 ± 7.5

[a] Percentages are based on the number of patients in a treatment group.
bid = twice daily, CIC = ciclesonide, FAS = full analysis set, FP = fluticasone propionate, ICS = inhaled corticosteroid, N = number of patients in a treatment group, n = number of patients with data available, od = once daily, rev. = reversibility, SD = standard deviation, T0 = randomization visit.
Data source: Table 15.1.2.1, Table 15.1.2.2, Table 15.1.3.1, Table 15.2.1.1, Table 15.2.1.7

Study results

Efficacy results

The primary variable FEV_1 [L] increased statistically significantly (two-sided $p < 0.0001$, PP and ITT) in all treatment groups by 0.220 L in the ciclesonide 80 µg od group, by 0.250 L in the ciclesonide 160 µg od group, and by 0.276 L in the FP 100 µg bid group during treatment (PP). Analysis of between-treatment differences demonstrated non-inferiority of ciclesonide 160 µg od to FP 100 µg bid (non-inferiority margin = -0.100 L, one-sided $p = 0.0030$, PP, confirmed by ITT), thus fulfilling the first step of the hypothesis cascade. In the second step, non-inferiority of ciclesonide 160 µg od to FP 100 µg bid with respect to morning PEF was shown (see below). In a third step, non-inferiority of ciclesonide 80 µg od to FP 100 µg bid with respect to difference in FEV_1 was not shown. All further results of statistical testing were exploratory.

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 80 µg od	214	1.520	77.5	1.542	1.762	0.220 ± 0.022	0.177, 0.264	<0.0001
CIC 160 µg od	212	1.586	78.1	1.542	1.791	0.250 ± 0.022	0.208, 0.292	<0.0001
FP 100 µg bid	224	1.520	77.0	1.542	1.817	0.276 ± 0.21	0.234, 0.317	<0.0001
ITT analysis								
CIC 80 µg od	249	1.510	77.1	1.537	1.760	0.224 ± 0.021	0.182, 0.265	<0.0001
CIC 160 µg od	239	1.579	77.6	1.537	1.797	0.260 ± 0.021	0.218, 0.302	<0.0001
FP 100 µg bid	250	1.523	77.1	1.537	1.813	0.276 ± 0.021	0.236, 0.317	<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 80 µg od	FP 100 µg bid	214	224	-0.055 ± 0.027	-0.108, -0.003	0.0485	0.9801
	CIC 160 µg od	FP 100 µg bid	212	224	-0.026 ± 0.027	-0.079, 0.027	0.0030	0.8289
	CIC 160 µg od	CIC 80 µg od	212	214	0.030 ± 0.027	-0.024, 0.083	n.a.	0.1384
ITT analysis	CIC 80 µg od	FP 100 µg bid	249	250	-0.053 ± 0.027	-0.107, 0.001	0.0426	0.9734
	CIC 160 µg od	FP 100 µg bid	239	250	-0.016 ± 0.028	-0.071, 0.038	0.0013	0.7212
	CIC 160 µg od	CIC 80 µg od	239	249	0.037 ± 0.028	-0.018, 0.091	n.a.	0.0931

[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, n.a. = not applicable, od = once daily, SE = standard error of the LSMean, T0 = randomization visit, T_{end} = last visit (PP analysis), T_{last} = last visit (ITT analysis). Data source: Table 15.2.1.1, Table 15.2.1.2, Table 15.2.1.3, Table 15.2.1.7

The key-secondary variable morning PEF increased statistically significantly (two-sided $p < 0.0001$, PP and ITT) by 23.4 L/min in the in the ciclesonide 80 µg od group, by 29.1 L/min in the ciclesonide 160 µg od group, and by 24.8 L/min in the FP 100 µg bid group (PP). Non-inferiority of ciclesonide 160 µg od to FP 100 µg bid (non-inferiority margin = -12.5 L/min, one-sided $p = 0.0001$, PP, confirmed by ITT) and of ciclesonide 80 µg od to FP 100 µg bid (non-inferiority margin = -12.5 L/min, one-sided $p = 0.0063$, PP, not confirmed by ITT) was demonstrated in the between-treatment analysis.

The key-secondary variable change in $PD_{20}FEV_1$ showed an improvement in airway hyperreactivity in all treatment groups: in the ciclesonide 80 µg od group by 1.804 doubling doses, in the ciclesonide 160 µg od group by 1.250 doubling doses, and in the FP 100 µg bid group by 1.641 doubling doses (ITT within-treatment analysis). There were no statistically significant differences between any of the three treatment groups (ITT and PP between-treatment analysis).

The secondary efficacy variables FEV_1 expressed as % of predicted as well as PEF from spirometry (absolute and % of predicted) increased in all treatment groups statistically significantly (PP and ITT). FEV_1 (% of predicted) increased by 11.3% in the ciclesonide

80 µg od group, by 12.8% in the ciclesonide 160 µg od group, and by 14.2% in the FP 100 µg bid group (ITT). For PEF (absolute values) non-inferiority of ciclesonide 160 µg od to FP 100 µg bid was demonstrated (PP and ITT).

Evening PEF (absolute values) increased statistically significantly in all treatment groups (PP and ITT). Non-inferiority of ciclesonide 160 µg od to FP 100 µg bid was shown (PP and ITT). Asthma symptom scores (asthma symptom score sum, daytime symptom score, nighttime symptom score) decreased statistically significantly in either treatment group (PP and ITT). Non-inferiority of ciclesonide 80 µg od to FP 100 µg bid and of ciclesonide 160 µg od to FP 100 µg bid was shown for symptom score sum and nighttime score. No non-inferiority margin was defined for daytime score. No statistically significant differences were found between treatment groups.

The use of rescue medication decreased statistically significantly in all treatment groups (ITT and PP). No statistically significant differences were found between treatment groups.

The median percentage of days with asthma control (i.e. days with no asthma symptoms, no use of rescue medication, morning PEF >80% predicted, and diurnal PEF fluctuation <15%) increased in all treatment groups to a statistically significant extend (ITT and PP). No statistically significant differences were found between groups.

With respect to time to onset of the first asthma exacerbation, superiority was shown for FP 100 µg bid over ciclesonide 80 µg od and for ciclesonide 160 µg od over ciclesonide 80 µg od (ITT). Patients treated with ciclesonide 160 µg od had a reduced risk of experiencing an asthma exacerbation compared with patients treated with ciclesonide 80 µg od (ITT and PP).

Quality of life (QoL) assessed by Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) improved for all treatments in all categories of the questionnaire (overall score, activities, and emotions) statistically significantly (PP and ITT). Non-inferiority of ciclesonide 80 µg od to FP 100 µg bid and ciclesonide 160 µg od to FP 100 µg bid were shown for all categories (PP and ITT). QoL assessed by Paediatric Asthma Quality of Life Questionnaire (Standardized) (PAQLQ[S]) improved for all treatments in all categories of the questionnaire (overall score, activities, symptoms, and emotions) statistically significantly (PP and ITT). Non-inferiority of ciclesonide 80 µg od to FP 100 µg bid and ciclesonide 160 µg od to FP 100 µg bid were shown for all categories (PP and ITT).

Safety results

In total, 337 patients (45.3%) experienced 557 AEs during the treatment period.

Treatment-emergent AEs (safety set)

	n (%)[a]			
	CIC 80 µg od (N = 252)	CIC 160 µg od (N = 242)	FP 100 µg bid (N = 250)	Total (N = 744)
AEs	117(46.4)	101(41.7)	119(47.6)	337(45.3)
SAEs: all	3(1.2)	3(1.2)	4(1.6)	10(1.3)
deaths	0(0.0)	0(0.0)	0(0.0)	0(0.0)
AEs with causality[b] suggested				
- by the investigator	1(0.4)	2(0.8)	3(1.2)	6(0.8)
AEs leading to discontinuation	13(5.2)	5(2.1)	2(0.8)	20(2.7)
AEs not yet known to be recovered	9(3.6)	9(3.7)	11(4.4)	29(3.9)
Changes in study medication due to AEs	7(2.8)	4(1.7)	2(0.8)	13(1.7)
Changes in conc. medication due to AEs	88(34.9)	72(29.8)	83(33.2)	243(32.7)

[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.
bid = twice daily, conc. = concomitant, CIC = ciclesonide, FP = fluticasone propionate, N = number of patients in each treatment group, n = number of patients with events, od = once daily.
Data source: Table 15.3.1.4, Listing 16.2.7.10

The most frequently reported AEs were classified as infections and infestations. Within this SOC (system organ class), upper respiratory tract infection was the most common AE, reported by 27 patients (10.7%) in the ciclesonide 80 µg od group, by 18 patients (7.4%) in the ciclesonide 160 µg od group, and by 19 patients (7.6%) in the FP 100 µg bid group. The majority of AEs were mild in intensity in all treatment groups. Most of the AEs were assessed as unrelated or unlikely related to the study medication. In the ciclesonide 80 µg od group one patient (0.4%, pharyngeal lesion), in the ciclesonide 160 µg od group two patients (0.8%, petechiae, oral candidiasis), and in the FP 100 µg bid group three patients (1.2%, mouth ulceration, tonsillitis, oral candidiasis) reported treatment-emergent AEs assessed as likely related to the study medication. No AE was assessed as definitely related. Eleven AEs of severe intensity were reported under ciclesonide 80 µg od treatment, four under ciclesonide 160 µg od treatment, and five under the FP 100 µg bid treatment.

No death occurred during this study. Three patients in the ciclesonide 80 µg od group (two cases of asthma, one case of pneumonia), three patients in the ciclesonide 160 µg od group (two cases of asthma, one case of appendicitis), and four patients in the FP 100 µg bid group (two cases of asthma, one case of appendicitis, one case of upper limb fracture) experienced one SAE each. These SAEs were all not related to study medication (investigator's assessment) and all but one patient with PT upper limb fracture in the FP group recovered without sequelae. In total, 13 patients in the ciclesonide 80 µg od group (13 cases of asthma, one case of pneumonia, one case of respiratory viral tract infection), five patients in the ciclesonide 160 µg od group (five cases of asthma, one case of nasopharyngitis), and two patients in the FP 100 µg bid group (asthma) discontinued the study prematurely due to either a single or two concurrent AEs.

As asthma exacerbations were reported as AEs and evaluated as secondary efficacy variable they are included in the safety as well as in the efficacy section.

24h urine free cortisol, adjusted for creatinine, decreased statistically significantly only in the FP group (restricted safety analysis and safety analysis). There were no statistically significant decreases in both ciclesonide treatment groups.

Laboratory investigation, physical examination, and vital signs did not indicate relevant or new safety risks of the study medications.

Conclusions:

Non-inferiority of ciclesonide 160 µg od to FP 100 µg bid was demonstrated with regard to the primary variable FEV_1, the key-secondary variable morning PEF (diary), the secondary variables PEF (spirometry), evening PEF (diary), symptom score sum (diary), nighttime score (diary), and QoL assessed by PACQLQ and PAQLQ(S).

Non-inferiority of ciclesonide 80 µg od to FP 100 µg bid was demonstrated with regard to the key-secondary variable morning PEF (diary), the secondary variables symptom score sum (diary), nighttime score (diary), and QoL assessed by PACQLQ and PAQLQ(S).

During 12 weeks of treatment, ciclesonide 160 µg od was as efficient as FP 100 µg bid in the patient group under investigation. For ciclesonide 80 µg od reduced efficacy compared to FP 100 µ bid was observed for the primary variable FEV_1 and the secondary variable PEF (spirometry), evening PEF (diary). In this study ciclesonide 160 µg od and FP 100 µg bid were superior over ciclesonide 80 µg od with regard to time to onset of the first asthma exacerbation.

Both ciclesonide doses were well tolerated and no unexpected safety results were observed.

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