Disclaimer: This study was originally sponsored by Takeda 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.

2 Synopsis

Title of the study:

Effect of ciclesonide (320 µg/day) vs. fluticasone propionate (375 µg/day) vs. placebo on short-term linear growth rate and HPA-axis function in prepubertal children with mild asthma

Investigator(s) and study center(s):

[redacted] Odense University Hospital, Kolding Sygehus, 6000 Kolding, Denmark

Coordinating investigator(s): Not applicable

Publication (reference): Not applicable

Studied period: 29-Aug-2005 (first patient in) to 01-Dec-2005 (last patient out)

Clinical phase: Phase IIIa

Objectives:

- To compare the effects of ciclesonide (320 µg/d), FP (fluticasone propionate, 375 µg/d), and placebo on short-term linear growth rate and HPA (hypothalamic-pituitary-adrenal) axis function in prepubertal children with mild persistent asthma.
- To collect further data on safety and tolerability.

Methodology:

This was a double-blind, double-dummy, placebo-controlled, randomized, three-period crossover study with a baseline period of 2 weeks and three treatment periods of 2 weeks each. The treatment periods were separated by two washout periods of 2 weeks each.

At the beginning of the first treatment period (Visit T0), patients were randomly assigned to one of the six treatment sequences. Patients were treated during the respective treatment periods with either:

- ciclesonide 320 µg/d (*ex actuator*), administered as one puff in the morning and one puff in the evening (160 µg twice daily) *versus*
- FP 375 µg/d (*ex valve*), administered as two puffs in the morning and one puff in the evening (250 µg am / 125 µg pm *ex valve*, corresponding to 220 µg am / 110 µg pm *ex actuator*) *versus*
- placebo

All study drugs were inhaled by using a HFA 134-a (hydrofluoralkane) MDI (metered dose inhaler) with spacer (AeroChamber Plus™). Patients were allowed to continue with their rescue medication (ie a short-acting or long-acting inhaled beta-agonist) according to their individual needs.

Lung function (FEV_1) was measured by spirometry at all visits. Patients recorded their asthma symptoms and use of rescue medication in a diary on a daily basis throughout the study. Knemometry of the right lower leg was performed during all visits using a Valk knemometer. Urine free cortisol data was obtained from 12-h overnight urine samples, collected at the end of each treatment period (Visits T1, T3, T5). AEs (adverse events) and concomitant medications were documented by the investigator. Standard laboratory investigations, physical examinations, and vital signs were performed at Visits B0 and $T5/T_{end}$.

After the end of the treatment period, patients were treated according to their individual medical needs and AEs that were ongoing at the termination visit were followed up.

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

Of the 28 enrolled patients, all were randomized. The Safety Set and the Full Analysis Set consisted of 28 patients. One patient in the Full Analysis Set was a protocol violator, leaving 27 patients in the Valid Cases Set.

	Number of patients[a]		
	CIC	FP	pbo
ITT analysis of knemometry	28	28	28
PP analysis of knemometry	26	27	25

[a] Number of patients with data available at baseline and endpoint.

CIC = ciclesonide 160 µg twice daily (*ex actuator*), FP = fluticasone propionate 250 µg in the morning /125 µg in the evening (*ex valve*), ITT = intention-to-treat, pbo = placebo, PP = per-protocol.

Diagnosis and main criteria for inclusion:

Patients who met the following criteria were considered for inclusion into the study:

- written informed consent by the patient's parent(s) or legal guardian(s) and by the patient, if capable;
- male or female outpatients aged 6 to 12 years;
- prepubertal stage, defined as
  - girls: breasts ≤ Tanner stage I (1969);
  - boys: testicular volume ≤ 2 ml measured with a Prader orchidometer;
- good health with the exception of asthma;
- history of asthma, as defined by ATS (American Thoracic Society) criteria, for at least 6 months;
- prior to inclusion (ie for at least 3 weeks prior to Visit B0) only use of rescue medication (meaning use of short-acting beta-agonists or long acting inhaled beta-agonists as needed, the latter for a maximum of 3 times per week);
- FEV_1 ≥80% predicted (measured at least 6 h after the inhalation of a short-acting beta-agonist or 10 h after inhalation of a long-acting inhaled beta-agonist);

- stable clinical state (no asthma exacerbation or relevant respiratory tract infection within 4 weeks directly prior to Visit B0);
- ability to use the MDI (metered dose inhaler) with spacer correctly and reliably.

Test product: Ciclesonide HFA (hydrofluoroalkane) -MDI

Dose: Ciclesonide 320 µg/d (*ex actuator*), administered as one puff in the morning and one puff in the evening (ciclesonide 160 µg twice daily)

Mode of administration: Oral inhalation

Batch No.: 4BGA006

Duration of treatment: 2 weeks

Reference product (ciclesonide): Placebo HFA-MDI

Dose: Administered as one puff in the morning and one puff in the evening

Mode of administration: Oral inhalation

Batch No.: 0BGA003

Duration of treatment: 2 weeks

Reference product: Fluticasone propionate HFA-MDI

Dose: FP 375 µg/d (*ex valve*), administered as two puffs in the morning and one puff in the evening (FP 250 µg am / 125 µg pm *ex valve*, corresponding to FP 220 µg am / 110 µg pm *ex actuator*)

Mode of administration: Oral inhalation

Batch No.: 8248

Duration of treatment: 2 weeks

Reference product (fluticasone propionate): Placebo HFA-MDI

Dose: Administered as two puffs in the morning and one puff in the evening

Mode of administration: Oral inhalation

Batch No.: FBG004

Duration of treatment: 2 weeks

Criteria for evaluation:

Variable of primary interest (safety)
Growth rate of the right lower leg as measured by knemometry [mm/wk].

Secondary variables (safety)
12-h overnight urine volume [L/12h], 12-h overnight urine cortisol [nmol/L], 12-h overnight urine creatinine [mmol/L], 12-h overnight cortisol adjusted for creatinine [nmol/mmol], weight and height[1], AEs, blood biochemistry, hematology, blood pressure, heart rate, physical examination.

Secondary variables (efficacy)
FEV_1 [L], FEV_1 [% predicted], daytime and nighttime asthma symptom scores, use of rescue medication, number of patients with lack of efficacy (asthma exacerbation).

Statistical methods:

The variable of primary interest growth rate of the right lower leg as measured by knemometry and variables regarding urine cortisol were evaluated by using an ANCOVA model. Pairwise between-treatment comparisons at the two-sided 5% level were performed according to the following scheme: ciclesonide *versus* FP, ciclesonide *versus* placebo, and FP *versus* placebo. The ITT analysis was of primary interest for this test of difference, but both the ITT and PP analyses were performed and reported.[2]

SUMMARY - CONCLUSIONS

Demographic data and baseline characteristics of patients in the Full Analysis Set were comparable for all treatment sequences; no substantial differences to the Valid Cases Set were observed.

Efficacy

- In this study, assessment of efficacy was not of primary interest and efficacy measurements (FEV_1, asthma symptom score, and use of rescue medication) were performed to ensure that asthma was well controlled during the study period.
- No clinically relevant changes in asthma control occurred during the course of the study. There were no patients with an asthma exacerbation.

Safety

- The primary variable growth rate by knemometry was higher for ciclesonide than for FP treatment; the between-treatment difference was statistically significant. There was no statistically significant difference between ciclesonide treatment and placebo. The growth rate during FP treatment was statistically significantly lower than the growth rate during the placebo period. The results of the robustness analysis (see Table below), excluding invalid data, confirmed the results of the primary analysis.

[1] The variables weight and height were only investigated within patients' demographics.

[2] Note: no statistical analysis was performed for 12-h overnight urine volume, 12-h overnight urine creatinine, asthma symptom scores, rescue medication use, lack of efficacy.

Growth rate [mm/wk]: robustness analysis of between-treatment differences, endpoint analysis (ITT, PP)

	Test			Ref			Difference Test - Ref[a]		
		n	LSMean ± SE		n	LSMean ± SE	LSMean ± SE	95% CI	p-value[b]
ITT	CIC	28	0.30 ± 0.07	FP	27	0.08 ± 0.07	0.23 ± 0.09	0.05, 0.40	0.0137
	CIC	28	0.30 ± 0.07	pbo	27	0.43 ± 0.07	-0.13 ± 0.09	-0.31, 0.05	0.1484
	FP	27	0.08 ± 0.07	pbo	27	0.43 ± 0.07	-0.35 ± 0.09	-0.53, -0.18	0.0002
PP	CIC	26	0.28 ± 0.07	FP	27	0.08 ± 0.06	0.20 ± 0.08	0.03, 0.37	0.0218
	CIC	26	0.28 ± 0.07	pbo	24	0.46 ± 0.07	-0.18 ± 0.09	-0.36, -0.01	0.0438
	FP	27	0.08 ± 0.06	pbo	24	0.46 ± 0.07	-0.38 ± 0.09	-0.55, -0.21	0.0001

[a] Based on ANCOVA model.

[b] Two-sided p-value, significance level 5%.

CI = confidence interval, CIC = ciclesonide 160 µg twice daily (*ex actuator*), FP = fluticasone propionate 250 µg in the morning /125 µg in the evening (*ex valve*), LS = least squares, n = number of patients with data available at baseline and endpoint, pbo = placebo, SE = standard error of the LSMean.

- Analyses of the secondary variable 12-h overnight urine cortisol adjusted for creatinine showed no statistically significant difference between ciclesonide and FP treatment. Compared to placebo, no statistically significant suppression of cortisol levels was observed during ciclesonide or FP treatment.
- Analyses of the secondary variable 12-h overnight urine free cortisol not adjusted for creatinine, revealed a statistically significant difference between ciclesonide and FP treatment, but not between ciclesonide treatment and placebo, or FP treatment and placebo.
- Overall, 18 patients experienced 32 AEs during the treatment periods: 7 patients experienced 10 AEs during ciclesonide treatment, 7 patients experienced 7 AEs during FP treatment, and 11 patients experienced 15 AEs during the placebo period.

Frequency of treatment-emergent AEs (SAF)

	Number (%)[a] of patients			
Number of patients (%)[a] with:	CIC (N = 28)	FP (N = 27)	Placebo (N = 28)	Total (N = 28)
AEs	7(25.0)	7(25.9)	11(39.3)	18(64.3)
SAEs: all	0	0	0	0
deaths	0	0	0	0
AEs with causality suggested[b]	0	0	0	0
Discontinuation due to AEs	0	0	0	0

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

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

CIC = ciclesonide 160 µg twice daily (*ex actuator*), FP = fluticasone propionate 250 µg in the morning /125 µg in the evening (*ex valve*), N = number of patients in each treatment group, SAF = safety set.

- The most frequently reported AE 'nasopharyngitis' belonged to the SOC (system organ class) 'infections and infestations' (ciclesonide: 7.1%, FP: 7.4%, placebo: 21.4% of patients).
- Most patients experienced treatment-emergent AEs of mild or moderate intensity. AEs of severe intensity occurred in one patient (3.6%) during ciclesonide treatment ('headache'), in two patients (7.4%) during FP treatment (one 'upper abdominal pain', one 'influenza like illness'), and in two patients (7.1%) during the placebo period (one 'nasopharyngitis', one 'cough').
- The investigator assessed two AEs as not related (both during placebo treatment), all other AEs as unlikely related to study medication.
- No deaths, SAEs, or AEs leading to discontinuation were reported for this study.
- For blood biochemistry and hematology laboratory values, no relevant changes from baseline to above the sponsor-defined alert range were observed. There were no AEs related to laboratory measurements in this study.
- Blood pressure and heart rate, measured at the beginning of the study and at the end of the treatment period, did not reveal any relevant influence of the study medication.
- Abnormal findings from physical examinations were unchanged or improved at the termination visit.

Conclusions:

The present study demonstrated that ciclesonide 320 µg/d (*ex actuator*), administered in a twice-daily dosing regimen, was safe and well tolerated in prepubertal children with mild persistent asthma. No clinically relevant changes in asthma control occurred during the course of the study.

When compared with placebo, growth rate under ciclesonide treatment was not significantly different, whereas during FP treatment a statistically significant and clinically relevant decrease in growth rate was shown. Treatment with ciclesonide 320 µg/d (*ex actuator*) had significantly less impact on short-term lower leg growth rate (measured by knemometry) than treatment with FP 375 µg/d (*ex valve*).

Compared with placebo, cortisol levels numerically increased during treatment with ciclesonide but decreased during FP treatment. However, these changes were not statistically significant. FP treatment led to a statistically significant decrease in cortisol compared with ciclesonide.

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