1 Title Page Clinical Study Report No. 197/2007 Version (1.0)

Title: Efficacy and Safety – Study by ALTANA on Ciclesonide in Pre-school Asthma Patients (BALLOON)		Version date:	20-Mar-2008
		INN:	Ciclesonide
		Program/Project No.:	BY9010
		Compound No.:	B9207-015
		Batch No.: CIC 40 µg: 1BGA006 and 1BGA007, CIC 80 µg: 2BGA006 and 2BGA007, CIC 160 µg: 4BGA006 and 4BGA008, placebo: 0BGA003 and 0BGA004.	
Study Protocol No.:	**BY9010-M1-207**	Development phase:	III
EudraCT No:	2005-001242-17	Indication studied:	Asthma
Study initiation date:	14-Nov-2005	Date of early termination:	not applicable
Study completion date:	23-Nov-2006	Summary of modifications:	not applicable
Name and country of investigators: 77 centers in Brazil, Germany, Hungary, India, the Netherlands, Poland, South Africa, Spain and Switzerland Coordinating investigator:			
Name of sponsor's responsible medical officer:			
Person(s) responsible for study report:			
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 RDM/CK at Nycomed GmbH, 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 Nycomed GmbH, 78467 Konstanz, Germany.			

2 Synopsis

Title of the study: Efficacy and Safety – Study by ALTANA on Ciclesonide in Pre-school Asthma Patients (BALLOON)

Investigator(s) and study center(s): A total of 77 centers in Brazil, Germany, Hungary, India, the Netherlands, Poland, South Africa, Spain and Switzerland participated in the study.

Coordinating investigator:

Publication (reference): Not applicable

Studied period: 14-Nov-2005 (first patient in) to 23-Nov-2006 (last patient out)

Clinical phase: Phase III

Objectives: The objective of this study was to assess the efficacy of CIC (ciclesonide) 40 µg, 80 µg, and 160 µg per day compared with placebo in pre-school asthma patients 2 to 6 years old.

The primary efficacy variable was the time to first LOI (lack of improvement) or EXA (severe asthma exacerbation), whichever occurred first. Other efficacy parameters were asthma symptoms, use of rescue medication, asthma control, and lung function (in patients 4 to 6 years old, able to perform reliable lung function tests).

Furthermore, this study was to provide data on safety and tolerability of CIC in pre-school children.

Methodology:

The study was designed as a randomized, double-blind, parallel-group, placebo-controlled, multi-national and multi-center study with four treatment arms. The study consisted of a variable baseline period of 2 to 4 weeks (Visits B0, B1, B2, and optional Visits B3 and B4) and a treatment period of 24 weeks (Visits T0, T2, T4, T8, T12, T16, T20, and T24). A follow-up visit was included, if necessary.

At baseline Visit B0, patients were to stop their current asthma treatment. They received a MDI (metered dose inhaler) containing placebo as baseline medication (given od pm) and the spacer AeroChamber-Plus™. Two to three year old children were additionally equipped with a facemask, if they were not able to use the MDI correctly and reliably with a spacer alone.

The rescue medication salbutamol was also provided at Visit B0 and was used as needed throughout the study.

After the baseline period, eligible patients were randomly assigned to one of the four treatment arms at T0. Stratification of the patients ensured an equal distribution of patients in the age range 2 to 3 year and 4 to 6 year old. For the treatment period patients received an MDI containing either CIC 40 µg, CIC 80 µg, CIC 160 µg, or placebo, given od pm. In case of a LOI during the treatment period, the support medication montelukast was added to the study medication.

Spirometry was performed at all visits (including a reversibility test at Visit B2) in those patients 4 to 6 years old who were able to perform reliable lung function measurements. Lung function had to be measured at least 4 h after the last use of rescue medication. Home morning and evening PEF (peak expiratory flow, if applicable), asthma symptom scores and use of rescue medication were recorded by caregivers in patient diaries throughout the study period. Adverse events were documented at each visit. An oropharyngeal inspection was carried out, if an oropharyngeal AE (adverse event) was suspected. The caregiver's quality of life was assessed by PACQLQ (paediatric caregiver's quality of life questionnaire) completion[1] at Visits B2 (or optional B3 or B4), T8, T16 and T24. At sites where a stadiometer was available body height by stadiometry was measured at Visits T0, T12 and T24. Routine laboratory investigations (including determination of blood cortisol levels) were done at Visits B2 (or optional B3 or B4), and T24. If applicable, a Phadiatop test was performed at Visit B0. Measurements of vital signs and physical examination were performed at Visits B0, T0, T12 and T24. For the determination of urine cortisol levels, patients collected urine on the morning of Visits B2 (or optional B3 or B4), T12 and T24.

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

According to the sample size calculation, 250 randomized patients per treatment group were needed.

Analyzed sets

	Enrolled	Safety set	Full analysis set	Valid cases set
CIC40		248	248	236
CIC80		245	245	232
CIC160		253	253	243
Placebo		246	246	236
Total	1164	992	992	947

CIC40 = ciclesonide 40 µg od pm, CIC80 = ciclesonide 80 µg od pm, CIC160 = ciclesonide 160 µg od pm.
Please note that patient numbers are indicated 'as randomized'.
Patient 80841 was randomized to placebo but received ciclesonide 80 µg od pm instead.
Data source: Table 15.1.1.2.

[1] Except for India.

Diagnosis and main criteria for inclusion:

At Visit B0

- written informed consent by the patient's parents or legal guardians;
- male or female outpatients;
- age 2 to 6 years;
- good health with the exception of asthma;
- documented diagnosis of asthma for ≥ 6 months with persistent or repeated wheezing, and one or more major risk factors, eg history of allergies, history of eczema, family history of asthma,

  and/or two or more minor risk factors, eg eosinophilia, dyspnoea without having a cold, allergic rhinitis. Only in case risk factors could not be determined, a positive Phadiatop test (determined at B0) was accepted;
- stable clinical state (no asthma exacerbation or respiratory tract infection within the last 30 d prior to B0);
- current asthma treatment: either use of rescue medication (as needed) only, or pre-treatment with ≤ 250 µg fluticasone propionate/d (or equivalent), or pre-treatment with ≤ 125 µg fluticasone propionate/d (or equivalent) in combination with a LABA or with another non-steroidal controller medication, or pre-treatment with other non-steroidal controller medication, at a constant dosage for at least 30 d prior to Visit B0.

Randomization criteria at Visit T0:

- a total daily asthma symptom score of ≥ 1 on at least 4 of the last 7 d prior to Visit T0, or use of > 1 puff of rescue medication on each of at least 4 of the last 7 d prior to Visit T0, (based on the patient's diary; the last 7 d prior to Visit T0 had to be filled out completely);
- ability to use the MDI with spacer correctly and reliably (in patients 2 to 3 years old: spacer with facemask).

Test product, dose, mode of administration, batch no.: Ciclesonide HFA-MDI, 40 µg/puff, 80 µg/puff, or 160 µg/puff ciclesonide (ex actuator), once daily pm, oral inhalation administered with the spacer AeroChamber Plus™ (in children 2 to 3 years old additionally with facemask), batch nos.: 1BGA006 and 1BGA007 (CIC40), 2BGA006 and 2BGA007 (CIC80), 4BGA006 and 4BGA008 (CIC160).

Reference product, dose, mode of administration, batch no.: Placebo HFA-MDI, 1 puff, once daily pm, oral inhalation administered with the spacer AeroChamber Plus™ (in children 2 to 3 years old additionally with facemask), batch nos.: 0BGA003 and 0BGA004.

Duration of treatment: 24 weeks

Criteria for evaluation:

Primary variable:

- time to first LOI or EXA (whichever occurred first).

Key secondary efficacy variable:

- percentage of asthma-controlled days.

Secondary efficacy variables:

- rate of patients with LOI or EXA;
- rate of patients with LOI;
- rate of patients with EXA;
- time to first LOI;
- time to first EXA;
- asthma symptom score (total, daytime, and nighttime);
- use of rescue medication;
- asthma control (days without symptoms and use rescue medication);
- caregiver's quality of life data (PACQLQ);
- morning and evening PEF and PEF fluctuation ;
- lung function variables (FEV_1 [forced expiratory volume in one second], PEF, $FEF_{25-75\%}$ [mean forced expiratory flow during the middle half of the FVC]) measured at the investigational sites.

Secondary safety variables:

- adverse events;
- physical examination;
- vital signs;
- standard laboratory variables;
- serum cortisol and urine cortisol in first morning urine;
- body height as determined by stadiometry (at selected sites).

Statistical methods:

The primary variable time to LOI/EXA was analyzed by means of the Tarone trend test and subsequently with the logrank test in a pairwise manner within an *a priori* ordered testing procedure. First, progressively increasing survival functions of CIC160, CIC80, CIC40 and placebo were tested for differences. At least superiority of CIC160 over placebo was concluded in case of rejecting the null hypothesis of equal survival functions. Subsequently, if the null hypothesis was rejected, CIC80 and CIC40 were tested for superiority over placebo,

respectively by means of the logrank test. Each test was performed at the 2.5% level, one-sided.

For evaluation of superiority the ITT analysis was the primary one, while the PP analysis was used for robustness purposes. A Cox proportional hazards regression analysis was applied to analyze the primary efficacy variable as robustness analysis in addition to the logrank test.

Within-treatment differences for the key-secondary variable percentage of asthma-controlled days were analyzed with the Pratt's Modified Wilcoxon's Signed-rank Test. Between-treatment differences for the key-secondary variable were analyzed with the Mann-Whitney U-test.

The analyses of the primary and the key-secondary variables were the only analyses performed in a confirmatory manner. Results from statistical testing of secondary variables were interpreted in an exploratory manner.

Due to substantial differences between the Asian and the non-Asian patients with regard to asthma severity and the diagnosis of asthma at baseline, posthoc analyses focused on the subgroup of 4 to 6 year old non-Asian patients. EXA rates and lung function variables were analyzed for the overall population and the subgroup of 4 to 6 year old non-Asians over the entire study period (ie including also data after the first LOI in the efficacy analysis).

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Demographic and other baseline characteristics by treatment

		CIC40 (N = 248)	CIC80 (N = 245)	CIC160 (N = 253)	Placebo (N = 246)
Age [y]	Median (range)	4.0 (2.0,6.0)	4.0 (2.0,6.0)	4.0 (2.0,6.0)	4.0 (2.0,6.0)
Sex [n (%)][a]					
	Male	164 (66.1)	160 (65.3)	137 (54.2)	160 (65.0)
	Female	84 (33.9)	85 (34.7)	116 (45.8)	86 (35.0)
Race [n (%)][a]					
	White	159 (64.1)	148 (60.4)	149 (58.9)	159 (64.6)
	Black	7 (2.8)	11 (4.5)	14 (5.5)	8 (3.3)
	Asian	44 (17.7)	44 (18.0)	45 (17.8)	43 (17.5)
	Other	38 (15.3)	42 (17.1)	45 (17.8)	36 (14.6)
Asthma duration [months]					
	Median (range)	21.6 (3.8, 81.1)	22.5 (5.9, 79.8)	23.5 (5.9, 77.1)	21.3 (4.2, 70.2)
Mean ICS dose at B0 [µg/d][b]					
	Mean ± SD	353.0 ± 141.6	339.7 ± 143.0	335.8 ± 142.2	332.0 ± 136.9
Asthma severity [n (%)][a]					
	Intermittent	4 (1.6)	0 (0.0)	3 (1.2)	2 (0.8)
	Mild	29 (11.7)	20 (8.2)	29 (11.5)	21 (8.5)
	Moderate	70 (28.2)	77 (31.4)	65 (25.7)	73 (29.7)
	Severe	143 (57.7)	145 (59.2)	153 (60.5)	150 (61.0)
	No data	2 (0.8)	3 (1.2)	3 (1.2)	0 (0.0)

Please note that data are shown for the FAS.

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

[b] Inhaled steroid doses up to B0 were expressed as CFC-BDP equivalent 'ex valve', statistics refer to patients pretreated with inhaled steroids up to 2 days prior to B0.

CIC40 = ciclesonide 40 µg od pm, CIC80 = ciclesonide 80 µg od pm , CIC160 = ciclesonide 160 µg od pm, ICS = inhaled corticosteroids, N = number of patients, n = number of patients with data available, SD = standard deviation.

Data source: Table 15.1.2.1, 15.1.2.8, 15.1.2.10, 15.1.3.8.

Efficacy results:

The time to the first LOI or EXA, whichever occurred first, was stipulated as the primary variable of efficacy in this study. Confirmatory testing did not show superiority of ciclesonide over placebo for the primary variable (p = 0.6105, one-sided, ITT analysis). In consequence, the null hypothesis was not rejected and the confirmatory testing procedure ended. All further tests were interpreted in an exploratory manner. No statistically significant differences were observed for the individual comparisons of CIC160, CIC80 or CIC40 to placebo.

The percentage of asthma controlled days was defined as key-secondary variable. In the overall population the percentage of asthma controlled days increased in all treatment groups. No statistically significant difference was shown between treatment with ciclesonide and placebo.

A pronounced placebo effect was also seen for further secondary efficacy variables such as symptoms and use of rescue medication and ciclesonide was not statistically superior to

placebo in the overall population. The observed pronounced placebo response for the total asthma symptom scores and the use of rescue medication also affected the results obtained for the asthma control variables and LOI, as these variables are closely related.

Subgroup analyses revealed race and asthma severity as relevant factors affecting the primary variable, with age being less relevant. Baseline characteristics suggested that the Asian population was less frequently pretreated with ICS and had used lower ICS doses. Whereas a tendency to severe asthma was observed in the non-Asian population in every treatment group, the Asian population was non-homogeneous regarding the variable asthma severity. Asthma risk factors which were used as inclusion criteron to support the asthma diagnosis were analyzed by treatment and race and the results showed pronounced differences in the frequencies of risk factors between Asian and non-Asian subjects..

With regard to the primary variable time to first LOI/EXA, exploratory analysis in the subgroup of 4 to 6 year old non-Asian patients showed a higher probability of not experiencing LOI/EXA in the ciclesonide treatment groups compared to placebo. Superiority was shown for CIC80 over placebo ($p = 0.0035$, ITT analysis, Table 15.2.1.5).

With regard to secondary efficacy variables, generally a pronounced placebo effect was also observed in this subgroup and no clinically meaningful differences between ciclesonide and placebo were shown, with the exception of lung function variables (FEV_1, PEF and $FEF_{25-75\%}$), for which the between-treatment comparisons revealed superiority of CIC160 and CIC40 over placebo in all three spirometry variables.

Concerning montelukast treatment, more than 43% of the patients in the ciclesonide and placebo treatment groups received the leukotriene receptor antagonist as support medication during the treatment period. The results of the analyses of the time period with additional montelukast treatment will be described in a separate follow-up report.

Safety results:

Overall, treatment-emergent AEs were reported for 169 patients (68.1%) in the CIC40 group, for 163 patients (66.3%) in the CIC80 group, for 180 patients (71.1%) in the CIC160 group and for 174 patients (71.0%) in the placebo group.

Treatment-emergent AEs (safety set)

Numbers of patients (%)[a] with	n (%)[a] CIC40 (N = 248)	CIC80 (N = 246)	CIC160 (N = 253)	Placebo (N = 245)	Total (N = 992)
AEs	169 (68.1)	163 (66.3)	180 (71.1)	174 (71.0)	686 (69.2)
SAEs	7 (2.8)	11 (4.5)	5 (2.0)	9 (3.7)	32 (3.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested by the investigator	6 (2.4)	0 (0.0)	3 (1.2)	2 (0.8)	11 (1.1)
AEs leading to discontinuation	14 (5.6)	20 (8.1)	16 (6.3)	25 (10.2)	75 (7.6)

[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.
CIC40 = ciclesonide 40 µg od pm, CIC80 = ciclesonide 80 µg od pm , CIC160 = ciclesonide 160 µg od pm,
N = number of patients in each treatment group, n = number of patients with events.
Data source: Table 15.3.1.19, Listing 16.2.6.13.

The most frequently reported treatment-emergent AEs in each treatment group were classified as infections and infestations, followed by respiratory, thoracic and mediastinal disorders. On the PT (preferred term) level upper respiratory tract infection was most often reported (CIC40: 21.0%, CIC80: 19.9%, CIC160: 21.7% and placebo: 21.6%). Other frequently documented AEs included nasopharyngitis (CIC40: 8.1%, CIC80: 13.0%, CIC160: 10.3% and placebo: 9.8%) and asthma (CIC40: 7.3%, CIC80: 10.2%, CIC160: 10.7% and placebo: 15.1%). In particular, the incidence of the AE asthma was higher among the patients of the placebo group compared to the other treatment groups.

For most of the patients in all treatment groups the AEs were mild or moderate in intensity and only a small fraction of patients experienced severe AEs. The percentage of patients with severe AEs was lower in the CIC160 group as compared to the other treatment groups (CIC40: 6.0%, CIC80: 7.7%, CIC160: 3.6% and placebo: 6.1%).

None of the AEs was assessed to be definitely related to study medication. The vast majority of the AEs were assessed as unrelated or unlikely related. The investigators recorded a likely relationship to the study medication for 2.4% of patients under CIC40, for 0.0% of patients under CIC80, for 1.2% of patients under CIC160 and for 0.8% of patients under placebo therapy. The majority of AEs considered as likely related corresponded to (oral) candidiasis, increased blood cortisol levels and dysphonia.

There were no deaths during the study.

A total of 39 SAEs (serious adverse events) were reported during the treatment period (8 SAEs in 7 patients [2.8%] in the CIC40 group, 12 SAEs in 11 patients [4.5%] in the CIC80 group, 8 SAEs in 5 patients [2.0%] in the CIC160 group and 11 SAEs in 9 patients [3.7%] in the placebo group). On the SOC (system organ class) level, the most frequently reported SAEs belonged to the categories respiratory, thoracic and mediastinal disorders, and infections and infestations. On the PT level, the SAE asthma was most frequently

documented. In the CIC80 and placebo groups a higher percentage of patients experienced the SAE asthma as compared to the CIC40 and CIC160 groups. All SAEs were assessed as unlikely related or unrelated to study medication. Most of the SAEs led to study discontinuation (CIC40: 4 patients [1.6%], CIC80: 7 patients [2.8%], CIC160: 1 patient [0.4%], placebo: 7 patients [2.9%]).

A total of 85 AEs in 75 patients (7.6%) led to premature study discontinuation. Withdrawal rates in the CIC80 and placebo groups were higher than in the CIC40 and CIC160 groups (CIC40: 5.6%, CIC80: 8.1%, CIC160: 6.3% and placebo: 10.2%).

Overall, asthma was the most frequent AE resulting in study discontinuation. In the groups CIC40 and placebo the investigator assessed 3 AEs each as unlikely related to study medication, whereas in the groups CIC80 and CIC160 all AEs leading to withdrawal were assessed as being not related to study drug.

No trend towards a clinically relevant change in any hematology or biochemistry variable was apparent in any treatment group. One patient under treatment with placebo discontinued the study due to the laboratory AE ‘white blood cell count increased’. Investigations of blood pressure, heart rate and physical examination did not reveal any relevant influence of the study medication.

Stadiometry measurements, which were performed to assess the effect of study medication on body height growth, revealed a statistically significant increase in body height in all treatment groups from baseline to last visit. No statistically significant differences were observed when comparing changes in growth rate between treatment groups.

In the between-treatment analysis for serum and urine cortisol, no statistically significant differences were detected for any of the analyzed treatment groups. Two patients treated with CIC40 developed the AE ‘increased blood cortisol levels’, which was assessed in both cases as likely related to the use of study medication. However the opposite effect (ie a decrease) would be expected for the intake of corticosteroids.

Subgroup analysis of 2 to 3 and 4 to 6 year old patients revealed no safety concerns specific to either of these age groups.

Conclusions:

Date of report: 20-Mar-2008