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: Comparison of the efficacy and safety of 160 µg ciclesonide administered once daily in the evening with or without different spacer types in patients with asthma

Investigator(s) and study center(s): A total of 55 investigators in 55 centers in Canada, France, Germany, Hungary, India and Italy participated in the study.

Coordinating investigator: [redacted] IFG-Institut für Gesundheitsförderung GmbH, Otto-Nuschke-Str. 2, 15562 Rüdersdorf, Germany

Publication (reference): Not applicable

Studied period: 01-Sep-2005 (first patient in) to 18-Jan-2006 (last patient out)

Clinical phase: phase III

Objectives: The aim of the present study was to compare the efficacy of 160 µg ciclesonide once daily in the evening (CIC160) versus 160 µg ciclesonide od pm administered either with spacer AeroChamber Plus® (CIC160P) or with spacer AeroChamberMAX® (CIC160M) on lung function and other variables of asthma control. Additionally, the study was to provide more data on safety and tolerability of ciclesonide.

Methodology:

The study was designed as a randomized, open-label, parallel-group, multi-national, multi-center study with three treatment arms. Patients were randomized to one of the three treatment groups CIC160, CIC160P or CIC160M in a 1:1:1 randomization scheme.

The study consisted of a 1- to 3-week baseline period (Visits B0 and B1; B2 and B3 optional) and a 12-week treatment period (Visits T0, T4, T8, T12).

During the baseline period patients only used salbutamol as rescue medication. During the treatment period the patients received CIC 160 µg od pm administered either without spacer, with spacer AeroChamber Plus® or with spacer AeroChamberMAX® for 12 weeks. Salbutamol was used as rescue medication throughout the study. Spirometry (ie FEV_1, FVC) was performed at all visits. Lung function had to have been measured at least 4 h after the last use of short-acting β-agonists and fixed combinations of short-acting β-agonists and anticholinergics and at least 24 h after the last use of long-acting β-agonists, as applicable. Home morning and evening PEF, asthma symptom scores, use of rescue medication and

compliance to study medication intake were recorded in patient diaries throughout the study period.

Adverse events were documented at each visit. Measurements of vital signs and physical examinations were performed at study start (Visit B0) and at the end of the treatment period. Routine laboratory investigations were also performed at study start (Visit B0), additionally at Visit T0 if the baseline exceeded 2 weeks (excluding the serum pregnancy test) and at the end of the treatment period. Blood samples for morning cortisol measurements were drawn at Visit T0 and at the end of the study (Visit T12).

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

According to the sample size calculation, 450 randomized patients were needed.

Analyzed sets

	n (%)			
	Enrolled	**Safety set**	**Full analysis set**	**Valid cases set**
CIC160		149 (29.9)	149 (29.9)	135 (27.1)
CIC160P		162 (32.5)	162 (32.5)	144 (28.9)
CIC160M		157 (31.5)	157 (31.5)	144 (28.9)
Total	498 (100.0)	468 (94.0)	468 (94.0)	423 (84.9)

Percentages are based on the total number of patients enrolled (ie screened).
CIC160 = ciclesonide 160 µg od pm, CIC160M = ciclesonide 160 µg od pm administered with spacer AeroChamber MAX®, CIC160P = ciclesonide 160 µg od pm administered with spacer AeroChamber Plus®, n = number of patients

Diagnosis and main criteria for inclusion:

- male and female outpatients aged 12 to 75 years inclusive;
- written informed consent;
- history of persistent bronchial asthma (as defined by GINA 2004) for at least 6 months;
- good health with the exception of asthma;
- currently treated with
  - either rescue medication only,
  - or with inhaled steroids with a maximum daily dosage of 250 µg fluticasone propionate (FP) or equivalent;
  - or with other controller drugs, ie leukotriene antagonists, xanthine derivates, inhaled cromones, lipoxygenase inhibitors;
  - or with a fixed or concurrent combination of an inhaled steroid (up to 125 µg/d FP or equivalent) and either a long-acting β-agonist or another asthma controller;

at a constant dose for the last 4 weeks directly prior to baseline.

- **For entering the baseline period FEV_1 had to be in the range of** FEV_1 = 61 to 105% depending on the pretreatment.

Inclusion in the treatment period (randomization criteria):

Patients who met the following criteria were to be considered for randomization (visit T0):

- FEV_1 = 61 to 90% of predicted;
- in case of pretreatment with inhaled steroids up to visit B0: a decrease of FEV_1 by at least 10% initial referred to start of baseline;
- a reversibility of FEV_1 ≥15% initial after inhalation of 200 - 400 µg salbutamol during baseline.

If no reversibility of FEV_1 ≥15% was demonstrated during baseline increased PEF fluctuation or airway responsiveness including historical data were also accepted.

Test product, dose, mode of administration, batch no.: Ciclesonide HFA-MDI, 160 µg/puff (ex actuator), once daily, oral inhalation administered with spacer AeroChamber Plus® or AeroChamber MAX®, 4BGA006.

Reference product, dose, mode of administration, batch no.: Ciclesonide HFA-MDI, 160 µg/puff (ex actuator), once daily, oral inhalation without spacer, 4BGA006.

Duration of treatment: Twelve weeks

Criteria for evaluation:

Primary variable:

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

Secondary efficacy variables:

- FEV_1, FVC, morning and evening PEF (each absolute and in percent predicted); diurnal PEF fluctuation; asthma symptom score; use of rescue medication; number of patients with an asthma exacerbation as well as time to first exacerbation; asthma control.

Variables evaluated for safety and tolerability:

- exposure to study medication; adverse events; laboratory work-up including serum cortisol, serum and urine pregnancy test; vital signs (blood pressure and heart rate); physical examination

Statistical methods:

Non-inferiority of CIC160P to CIC160 and of CIC160M to CIC160 was tested for the primary variable difference in FEV_1 (T_{end} vs. T0). A Bonferroni-Holm adjustment was made to account for the multiple testing of the two comparisons. For evaluation of non-inferiority,

the PP analysis was the primary analysis. The non-inferiority acceptance limit was set to -200 mL for the primary variable difference in FEV_1.

The primary variable was analyzed by an ANCOVA (analysis of covariance) where treatment, sex, center pool, and the stratification variables (current smoking status, ICS pretreatment, inhalation technique, FEV_1 % of predicted at T0) were fixed factors, whereas the baseline value and age were covariates.

SUMMARY – CONCLUSIONS

Demography and baseline characteristics

Demographic and other baseline characteristics by treatment

		FAS			VCS		
		CIC160 (N = 149)	**CIC160P (N = 162)**	**CIC160M (N = 157)**	**CIC160 (N = 135)**	**CIC160P (N = 144)**	**CIC160M (N = 144)**
Age [years]	Median (range)	38 (12, 74)	39 (12, 71)	43 (12, 75)	37 (12, 74)	38 (12, 71)	42 (12, 75)
Sex [n (%)][a]	Male	81 (54.4)	70 (43.2)	66 (42.0)	75 (55.6)	62 (43.1)	62 (43.1)
	Female	68 (45.6)	92 (56.8)	91 (58.0)	60 (44.4)	82 (56.9)	82 (56.9)
FEV_1 at T0 [% of predicted][b]	Mean ± SD	75.9 ± 7.7	75.0 ± 7.0	76.5 ± 7.5	75.6 ± 7.5	75.5 ± 6.9	76.1 ± 7.1
FEV_1 rev.[% increase][c]	Mean ± SD	23.4 ± 9.3	23.0 ± 7.6	22.8 ± 8.7	23.8 ± 9.3	22.8 ± 7.2	22.3 ± 7.1

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

[b] FEV_1 values (% of predicted) are given for the ITT (first three columns) and PP analyses (remaining three columns). T0 values are given for patients with FEV_1 data at T0 and $T_{end/last}$ (paired values). The respective patient numbers were: ITT: CIC160: n = 149, CIC160P: n = 160, CIC160M: n = 157; PP: CIC160: n = 130, CIC160P: n = 139, CIC160M: n = 136.

[c] Among several reversibility measurements (at B0, B1, B2, B3 or historical) the first measurement that fulfilled the randomization criterion was selected for analysis.

CIC160 = ciclesonide 160 µg od pm, CIC160M = ciclesonide 160 µg od pm administered with spacer AeroChamber MAX®, CIC160P = ciclesonide 160 µg od pm administered with spacer AeroChamberPlus®, FAS = full analysis set, n = number of patients with data available, rev. = reversibility, SD = standard deviation, VCS = valid cases set.

Efficacy results

The primary variable difference in FEV_1 (T_{end} versus T0) increased by a comparable amount in all three treatment groups during the study. Confirmatory testing revealed non-inferiority of ciclesonide administered with either spacer type to ciclesonide given without spacer (all p-values <0.0001, one-sided, PP analysis). These results were supported by the ITT analysis. The following table summarizes the results for the primary variable.

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

WITHIN		T0			T_{end}	T_{end} - T0		
	n	Mean	% pred.	LSMean	LSMean	LSMean ± SE	95% CI	p-value[a]
CIC160	130	2.419	75.6	2.365	2.682	0.317 ± 0.073	0.173, 0.460	<0.0001
CIC160P	139	2.356	75.5	2.365	2.701	0.336 ± 0.070	0.198, 0.474	<0.0001
CIC160M	136	2.323	76.1	2.365	2.700	0.335 ± 0.071	0.195, 0.474	<0.0001

BETWEEN					Difference Test - Ref for T_{end} - T0		
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value non-inf.[b]
	CIC160P	CIC160	139	130	0.020 ± 0.047	-0.073, 0.112	<0.0001
	CIC160M	CIC160	136	130	0.018 ± 0.047	-0.075, 0.111	<0.0001

[a] Two-sided p-value for within-treatment differences, significance level 5%.

[b] One-sided p-value for non-inferiority, non-inferiority margin = -200 mL. For the two primary comparisons CIC160P vs. CIC160 and CIC160M vs. CIC160 a Bonferroni-Holm adjustment was made to account for simultaneous testing. The smaller of the two p-values was compared to 1.25%. If the smaller of the two p-values was <1.25%, the other p-value could be compared to 2.5%.

CI = confidence interval, CIC160 = ciclesonide 160 µg od pm, CIC160M = ciclesonide 160 µg od pm administered with spacer AeroChamber MAX®, CIC160P = ciclesonide 160 µg od pm administered with spacer AeroChamber Plus®, FEV_1 = forced expiratory volume in one second, LS = least squares, n = number of patients with data available at T0 and endpoint, SE = standard error of the LSMean, T0 = randomization visit, T_{end} = last visit (PP analysis).

Non-inferiority of CIC160P and CIC160M, respectively, to CIC160 was shown in an exploratory manner for the secondary variables FVC (CIC160P vs. CIC160: p = 0.0001, CIC160M vs. CIC160: p = 0.0002, one-sided, PP analysis), morning and evening PEF, and total asthma symptom scores in the PP analysis. The results of the PP analyses were supported by the ITT analyses. The improvements in the diary variables were, however, numerically more pronounced under CIC160 and CIC160P.

For the variables PEF fluctuation, use of rescue medication, percentage of days with asthma control, nocturnal awakening-, rescue medication- and asthma symptom-free days, no statistically significant between-treatment or clinically relevant differences were observed. No patient of the CIC160 group experienced an asthma exacerbation. Asthma exacerbations were recorded for two (1.2%) and three (1.9%) of the patients on CIC160P and CIC160M, respectively (FAS).

Safety results:

Treatment emergent AEs were reported for 29 patients (19.5%) in the CIC160 treatment group, for 34 patients (21.0%) in the CIC160P group and for 41 patients (26.1%) in the CIC160M treatment group. The number of patients experiencing AEs with a suspected relationship to the study drug, or experiencing SAEs or AEs leading to withdrawal was comparable between the treatment groups. The following table gives an overview of treatment-emergent AEs and SAEs.

Treatment-emergent AEs (safety set)

	n (%)[a]			
	CIC160 (N = 149)	**CIC160P (N = 162)**	**CIC160M (N = 157)**	**Total (N = 468)**
AEs	29 (19.5)	34 (21.0)	41 (26.1)	104 (22.2)
SAEs	2 (1.3)	1 (0.6)	1 (0.6)	4 (0.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested by the investigator	1 (0.7)	1 (0.6)	1 (0.6)	3 (0.6)
AEs leading to discontinuation	2 (1.3)	2 (1.2)	3 (1.9)	7 (1.5)

[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.

CIC160 = ciclesonide 160 µg od pm, CIC160M = ciclesonide 160 µg od pm administered with spacer AeroChamber MAX®, CIC160P = ciclesonide 160 µg od pm administered with spacer AeroChamber Plus®, N = number of patients in each treatment group, n = number of patients with events.

Asthma was among the most frequently reported AEs in all treatment groups (CIC160: 4 patients, 2.7%; CIC160P: 6 patients, 3.7%; CIC160M: 4 patients, 2.5%). Other frequently reported AEs were bronchitis acute in the CIC160 (4 patients, 2.7%) and nasopharyngitis in the CIC160P and CIC160M treatment groups (6 patients each, 3.7% and 3.8%, respectively).

For the majority of patients with AEs in each treatment group, both the investigator and the sponsor assessed the AEs as unrelated or unlikely related to the study medication. None of the AEs was considered to be definitely related to the study medication. In each group only one AE was attributed a likely relationship to the study drug by both the investigator and the sponsor (CIC160: chest discomfort, CIC160P and CIC160M: dysphonia). Additionally, in the CIC160M treatment group, the sponsor considered one AE (cough) to be likely related to the study medication, whereas the investigator assessed the AE as unrelated.

For most patients with AEs in all treatment groups, the AEs were documented as mild or moderate in intensity. The number of patients who experienced AEs of severe intensity was below 2% in all treatment groups

During the study period two SAEs (hypertensive crisis, osteotomy) were reported in two patients (1.3%) on CIC160, four SAEs (two occurrences of cholangitis, pancreatitis chronic, pancreatic carcinoma) in one patient (0.6%) in the CIC160P and one SAE (abortion spontaneous) in one patient (0.6%) in the CIC160M treatment group. All SAEs were assessed as unrelated to the study medication by both the investigator and the sponsor. None of the SAEs led to premature study discontinuation.

None of the AEs leading to study discontinuation were considered likely or definitely related to the study medication.

No general trend towards a clinically relevant change in any hematology or blood chemistry variable was apparent in any treatment group. Blood pressure and heart rate measured at the beginning of the study and the end of the treatment period did not reveal any relevant influence of the study medication.

No statistically significant between-treatment changes in morning serum cortisol were observed in either analysis.

Treatment with ciclesonide with or without spacer devices for 12 weeks was safe and well tolerated. No clinically relevant differences regarding the safety profile were evident between the three treatment groups.

Date of report: **21-May-2007**