Disclaimer: This study was originally sponsored by ALTANA Pharma AG 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 inhaled ciclesonide (640 µg/d) and fluticasone propionate (1000 µg/d) in patients with moderate and severe persistent asthma

Investigator(s) and study center(s): A total of 74 main investigators participated in this international study at 74 centers located in Belgium, France, United Kingdom, Italy, the Netherlands, Spain, and Switzerland.

Coordinating investigator: [redacted] Hôpital COCHIN, Paris, France

Publication (reference): Not applicable

Studied period: 06-Nov-2004 to 23-Nov-2005

Clinical phase: IIIb

Objectives:

The aim of the present study was to evaluate and compare ciclesonide 320 µg, administered twice daily in the morning and evening (CIC640, ex actuator) versus fluticasone propionate 500 µg, administered twice daily in the morning and evening (FP1000, ex valve) in patients with moderate to severe, well controlled persistent asthma with regard to:

- frequency of candidiasis of the oropharynx and/or dysphonia;
- side effects of ICS as recorded by use of the ICQ (inhalative corticosteroids questionnaire);
- asthma control assessed by lung function, asthma symptoms and use of rescue medication;
- additional safety and tolerability aspects of ciclesonide.

Methodology:

The study was conducted using a randomized, double-blind, double-dummy, parallel-group design. Patients were randomized to one of two treatments groups (CIC640 or FP1000) in a 1:1 randomization scheme. The study consisted of a 2-week baseline period (Visits B0 and B2), and a treatment period of 24 weeks (Visits T0 [identical to the last baseline visit], T4, T8, T12, T16, T20 and T24). A follow-up period subsequent to the treatment period was included, if necessary.

During the baseline period, eligible patients continued treatment with their currently inhaled steroid dosage (BDP [beclomethasone dipropionate] ≥1000 µg/d or equivalent) and their inhaled LABA (long-acting beta-agonist) dose in free combination. During the treatment period the patients received a daily dosage of 640 µg ciclesonide administered twice daily (in the morning and in the evening) or a daily dosage of 1000 µg fluticasone propionate administered twice daily (in the morning and in the evening). The use of the LABA had to be continued during the treatment period in the same daily dosage and through the same type of inhaler as used before. Throughout the study period, salbutamol was used as rescue medication.

At each scheduled visit during the study period the patients completed an ICQ (Inhaled Corticosteroids Questionnaire). A self-administered AQLQ(S) (Standardized Asthma Quality-of-Life Questionnaire) was filled out by the patients at Visits B2/T0, T8, T16, and T24 or premature study termination.

Spirometry (FEV_1 [forced expiratory volume in one second], FVC [forced vital capacity], PEF [peak expiratory flow]) was performed at Visits B0, B2/T0, and T24/T_{end}. Home morning and evening PEF, asthma symptom scores, and use of rescue medication were recorded in patient diaries throughout the study period.

Adverse events were documented at each study visit. During each visit an oropharyngeal inspection was performed and the number of patients with LOAEs (local oropharyngeal AEs) was assessed. In addition, the number of skin bruises (>5 cm) on the volar side of the forearms was noted at each visit. Vital signs (BP [blood pressure], HR [heart rate]), physical examinations with ECG (electrocardiogram), and clinical laboratory tests including morning serum cortisol investigations were performed at study start (Visit B0) and at the end of the treatment period (Visit T24 or T_{end} in case of premature study termination). Morning serum cortisol and vital signs were also assessed at Visit T12.

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

According to the sample size calculation five hundred randomized patients were needed.

Analyzed sets:

	Enrolled	Safety set	Full analysis set	Valid cases set
CIC640		259	259	224
FP1000		244	244	202
Total	614	503	503	426

CIC640 = CIC 320 µg bid, FP1000 = FP 500 µg bid
Data source: Tables 15.1.1.2

Diagnosis and main criteria for inclusion:

At Visit B0 (all had to apply):

General criteria:

- written informed consent;

- male or female outpatient aged 18 to 75 years inclusive;
- history of bronchial asthma as defined by ATS (American Thoracic Society) criteria for at least 6 months;
- good health with the exception of asthma.

Asthma treatment[1]:

- pre-treatment with CFC (chlorofluorocarbon)-BDP ≥1000 µg/d or equivalent[2] and a LABA either in free or fixed combination[3]. The dose of this pre-treatment had to be kept constant for at least 8 weeks directly prior to Visit B0.

Lung function:

- FEV_1 ≥80% of predicted measured at least 4h after the last use of short-acting beta-agonists and at least 12 h after the last use of oral and inhaled LABAs and other anti-asthma medications listed in Section 9.4.7, and;

Asthma symptoms (based on investigator assessment and on patient's reporting):

- symptoms less than once a week, and;
- nocturnal symptoms no more than twice a month, and only;
- occasional use of inhaled short-acting ß-agonists.

Randomization Criteria (at T0):

- FEV_1 ≥80% of predicted measured at least 4h after the last use of short-acting beta-agonists and at least 12 h after the last use of a LABA, and;
- sum of night- and daytime asthma symptom score from diary ≤4 during the baseline period, and;
- reversibility of ΔFEV_1 ≥12% and ΔFEV_1 of at least 200 mL of the initial value after inhalation of 200 – 400 µg salbutamol.

If no reversibility could be shown within the baseline period historical data for reversibility (ΔFEV_1 ≥12% and ΔFEV_1 at least 200 mL) duly recorded within the last 5 years, were accepted.
Alternatively, reversibility could be shown by a diurnal PEF fluctuation of ≥15% on at least 3 d during a consecutive 7 d period duly recorded within the last 5 years prior to Visit B0.

[1] This treatment was to be continued during the baseline period. All other anti-asthma medication had to be stopped at Visit B0.
[2] Pre-treatment with ≥1000 µg/d CFC-BDP referred to the following equivalents: ≥400 µg/d HFA (hydrofluoralkane)-BDP (HFA-MDIs [metered dose inhalers] manufactured by or under license of 3M, e.g. QVAR®); ≥1000 µg/d BDP (for all other HFA-MDIs and DPIs [dry powder inhalers]); ≥800 µg/d budesonide (DPIs, CFC-MDIs and HFA-MDIs); ≥400 µg/d flunisolide (for HFA-MDIs manufactured by Forest Laboratories); ≥1000 µg/d flunisolide (for CFC-MDIs); ≥400 µg/d mometasone furoate; ≥500 µg/d fluticasone propionate (CFC MDIs, HFA MDIs and DPIs).
[3] Patients who were treated with a fixed combination of an inhaled steroid and a LABA were to be switched to a free combination at Visit B0 by using the same drugs and same daily dosages through the same type of inhaler as used before.

Test product, dose, mode of administration, batch no.:

Ciclesonide HFA-MDI, 640 µg/d (ex actuator), twice daily, oral inhalation, 4BGA005 and 4BGA006.

Reference product, dose, mode of administration, batch no.:

Fluticasone propionate HFA-MDI, 1000 µg/d (ex valve), twice daily, oral inhalation, X43, X68.

Duration of treatment: 24 weeks

Criteria for evaluation:

Primary variable:

- the proportion of patients with treatment-emergent LOAE (local oropharyngeal adverse events, defined as candidiasis of the oropharynx and/or dysphonia).

Key-secondary variables:

- the ICQ overall score (T_{last} vs. T0);
- the proportion of patients with treatment-emergent LOAE until Visits T24, T20, T16, T12, T8, and T4 vs. T0. Only the first occurrence of LOAE within the respective interval (eg Visit T0 to Visit T12) was considered.

Secondary safety variables:

- the ICQ overall score (T_{end} vs. T0) and ICQ domain scores ($T_{last/end}$ vs. T0);
- the ICQ overall and domain scores (T4, T8, T12, T16, T20, T24 vs. T0);
- number of treatment-emergent LOAEs (T4, T8, T12, T16, T20, T24 vs. T0). All occurrences of LOAE within the respective interval were considered;
- treatment exposure [days];
- adverse events;
- laboratory work-up;
- serum morning cortisol;
- vital signs (blood pressure and heart rate);
- ECG;
- skin bruising;
- physical examination.

Secondary efficacy variables:

- FEV_1 [L], FVC [L], PEF from spirometry (measured) (T24, $T_{last/end}$ vs. T0);
- FEV_1, FVC, PEF % of predicted [%] from spirometry (predicted) (T24, Tlast/end vs. T0);

- home morning and evening PEF from diary (absolute [L/min] and % of predicted [%]) ($W_{last/end}$, W1 to W24 vs. W0, and for the first week daily comparisons to W0);
- diurnal PEF fluctuation [%] ($W_{last/end}$, W1 to W24 vs. W0, and for the first week daily comparisons to W0);
- asthma symptom scores (daytime, nighttime, sum of daytime and nighttime) ($W_{last/end}$, W1 to W24 vs. W0, and for the first week daily comparisons to W0);
- use of rescue medication [puffs/d] ($W_{last/end}$, W1 to W24 vs. W0, for the first week daily comparisons to W0);
- proportion of patients with an asthma exacerbation;
- time to the first asthma exacerbation [d];
- percentage of asthma symptom-free days [%] ($I_{last/end}$ vs. I0);
- percentage of rescue-medication-free days [%] ($I_{last/end}$ vs. I0);
- percentage of days on which a patient perceived asthma control [%] ($I_{last/end}$ vs. I0);
- percentage of nocturnal awakening-free days [%] ($I_{last/end}$ vs. I0);
- AQLQ(S) domain and overall scores ($T_{last/end}$, T24, T16, T8 vs. T0).

Statistical methods:

CIC640 was tested for superiority over FP1000 for the primary variable proportion of patients with treatment-emergent LOAEs. If superiority of CIC640 over FP1000 was confirmed for the primary variable, superiority of CIC640 over FP1000 was tested with respect to the key-secondary variable ICQ overall score. If superiority was shown, CIC640 was tested for superiority over FP1000 with regard to the key-secondary variable proportion of patients with treatment-emergent LOAEs until Visits T24, T20, T16, T12, T8, and T4 in a step-down procedure.

The analyses of the primary and key-secondary variables described above were the only confirmatory results of statistical testing. Results for the remaining secondary variables were to be interpreted in an exploratory manner.

For the superiority tests, the ITT analysis was stipulated as the primary analysis. For non-inferiority tests, the PP analysis was primary. For all statistically analyzed variables, both the PP and ITT analyses were performed and reported. The overall level of significance was set to 5%, two-sided (type I error of $\alpha = 0.05$), which in case of one-sided hypotheses corresponded to 2.5%, one-sided.

The primary variable proportion of patients with treatment-emergent LOAEs and the key-secondary variable proportion of patients with treatment-emergent LOAEs until Visits T24, T20, T16, T12, T8, and T4 were analyzed using the Wilson score method. The two-sided 95%-confidence interval of the difference between CIC640 and FP1000 was calculated according to the Wilson score method, based on survival rates and their standard errors estimated according to Kaplan-Meier, in order to take censored observations into account.

Superiority of CIC640 was concluded if the upper limit of the two-sided 95%-confidence interval of the difference in proportions was below zero. The between-treatment difference for the key-secondary variable ICQ overall score was analyzed by means of an analysis of covariance (ANCOVA) including baseline value (value at randomization Visit T0) and age as covariates, and treatment, sex and center pool as factors.

The ANCOVA model described above was also used for analysis of the difference in FEV_1, FVC, clinic PEF (spirometry), home morning and evening PEF (diary), and the domain scores from ICQ and AQLQ(S). For the lung function variables and AQLQ(S) in addition to superiority tests, non-inferiority tests were performed using the non-inferiority acceptance limits of -200 mL for FEV_1 and FVC, -25 L/min for PEF (spirometry and diary), and -0.5 scores for AQLQ(S).

Non-parametric within- and between-group comparisons of the diary variables diurnal PEF fluctuation, asthma symptom scores, use of rescue medication, percentage of asthma symptom-, rescue medication-, and nocturnal awakening-free days, and percentage of days on which a patient perceived asthma control, were done using the modification of Wilcoxon's signed-rank test according to Pratt and the Mann-Whitney U-test, respectively.

The secondary variables were analyzed in a purely exploratory manner.

Generally, if not stated otherwise, the following sample characteristics were calculated for continuous and quasi-continuous variables: n, arithmetic mean, SD (standard deviation), median, minimum, maximum, and the 68% range, if appropriate. For dichotomous and categorical variables, the absolute and relative frequencies were calculated.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

For the majority of demographic characteristics, there were no noteworthy differences between the treatment groups of the FAS. Within each treatment group slightly more female than male patients were included.

Demographic and other baseline characteristics (FAS)

		CIC640 (N = 259)	FP1000 (N = 244)
Age [years]	Median (range)	46 (18, 75)	47 (18, 73)
Sex [n (%)][a]	Female	136 (52.5)	125 (51.2)
	Male	123 (47.5)	119 (48.8)
Duration of asthma [months]	Median (range)	148 (6, 785)	163 (8, 794)
Smoking status [n (%)][a]	Non-smokers	175 (67.6)	153 (62.7)
	Current/ex-smokers	84 (32.4)	91 (37.3)
ICS pretreatment (µg/day) up to Visit B0 expressed as BDP equivalent	Mean ± SD	1376.4 ± 556.0	1385.0 ± 537.2
FEV_1 at T0 [L][b]	Mean ± SD	2.932 ± 0.819	2.944 ± 0.727
FEV_1 at T0 [% of predicted][b]	Mean ± SD	93.5 ± 10.9	94.4 ± 12.1

[a] Percentages are based on the number of patients in a treatment group.
[b] Values are based on the number of patients with data available.
CIC640 = CIC 320 µg bid, FAS = full analysis set, FP1000 = FP 500 µg bid, n = number of patients with data available, N = number of patients, SD = standard deviation
Data source: Tables 15.1.2.1, 15.1.2.2, 15.1.3.5, 15.2.1.1

LOAE and ICQ results

The evaluation of oropharyngeal adverse events was the primary focus of this study. The number of treatment-emergent events of dysphonia was comparable for the two groups (CIC640: 17 cases in 16 patients [6.2%], FP1000: 16 cases in 15 patients [6.1%]), whereas the number of events of candidiasis of the oropharynx was notably smaller in the CIC640 (9 cases in 8 patients [3.1%]) than in the FP1000 group (22 cases in 19 patients [7.8%]). As a result, the overall number of treatment-emergent LOAEs was lower in the CIC640 treatment group (26 LOAEs in 21 patients [8.1%]) than in the FP1000 group (38 LOAEs in 31 patients [12.7%]).

However, in the first analysis of the confirmatory testing procedure, superiority of CIC640 over FP1000 was not shown for the primary variable 'proportion of patients with LOAEs'. The confirmatory testing strategy therefore ended with the first test and all further analyses are to be interpreted in an exploratory manner. Exploratively, superiority of CIC640 over FP1000 was shown for the proportion of patients with at least one treatment-emergent event of candidiasis of the oropharynx, since the upper limit of the 95% CI did not exceed zero (95% CI for difference CIC640 - FP1000: -0.0954, -0.0102, ITT analysis). With regard to the proportion of patients with at least one event of treatment-emergent dysphonia, superiority of

CIC640 over FP1000 was not demonstrated (95% CI for difference CIC640 - FP1000: -0.0452, 0.0435, ITT analysis). The PP analysis yielded similar results.

The results from the analyses of the key-secondary variable proportion of patients with LOAEs from T0 until Visits T24, T20, T16, T12, T8, and T4, and of the secondary variable time to the first LOAE were similar to those reported above. With regard to the key-secondary variable ICQ overall score, superiority of CIC640 over FP1000 was shown ($p = 0.0060$, one-sided, ITT analysis). The results for the changes in ICQ domain scores and the overall score until each treatment visit support these results.

Asthma control and quality of life results

Generally, for patients in both treatment groups asthma control was well maintained. The percentage of days with asthma control, and the percentages of rescue medication-free days, asthma symptom-free days, and nocturnal awakening-free days were high at study start and increased or remained stable in both treatment groups until the end of treatment (median >92% for all variables). Generally, no statistically significant difference between treatment with CIC640 and FP1000 was shown.

Likewise, asthma symptom scores and use of rescue medication under CIC640 and FP1000 remained stable throughout the treatment period. For both treatment groups, the median asthma symptom score sum, daytime and nighttime symptom scores, and the median use of rescue medication were zero at study start and at the end of the treatment period (ITT and PP analysis). No statistically significant between-treatment difference was present for asthma symptom scores and use of rescue medication.

The number of patients with asthma exacerbations was comparable for the two treatment groups (CIC640: 6 patients [2.3%], FP1000: 7 patients [2.9%]). There was no statistically significant difference between treatment with CIC640 and FP1000 with regard to the time to onset of an asthma exacerbation (ITT and PP analysis).

No clinically relevant within-treatment changes were observed for the spirometry variables FEV_1 and FVC in the CIC640 and FP1000 treatment groups. Clinic PEF increased in patients treated with FP1000, while it remained almost stable in the CIC640 treatment group (ITT and PP analysis). Non-inferiority of CIC640 to FP1000 was demonstrated for both FEV_1 and FVC (all $p < 0.0001$, one-sided), but not for clinic PEF.

Home morning and evening PEF remained unchanged, ie without clinically relevant change, in the CIC640 and the FP1000 treatment groups. Non-inferiority of CIC640 to FP1000 was demonstrated for morning and evening PEF (all p-values ≤ 0.0001, one-sided, PP and ITT analysis).

Small improvements in PEF fluctuation during the treatment period were observed for patients in the CIC640 and FP1000 treatment groups (HL point estimate, CIC640: -1.036, FP1000: -0.768, ITT analysis), but there was no statistically significant between-treatment difference.

An increase in the AQLQ(S) overall score was observed for patients treated with CIC640 (LSMean: 0.14), but not for patients treated with FP1000 (LSMean: 0.01, ITT analysis).

Treatment with CIC640 was superior to treatment with FP1000 with regard to the changes in the overall score (p = 0.0144, one-sided, ITT analysis). The results for the analysis of the individual AQLQ(S) domain scores generally corresponded to those for the overall score. Superiority of CIC640 over FP1000 was shown with regard to the changes in the domain scores activity and symptoms (ITT analysis).

Safety results

Treatment-emergent AEs were reported for 131 patients (50.6%) treated with CIC640 and for 134 patients (54.9%) treated with FP1000. The following table gives an overview of treatment-emergent AEs and SAEs.

Treatment-emergent AEs (SAF)

	CIC640 (N = 259)	FP1000 (N = 244)	Total (N = 503)
Number of patients (%)[a] with:			
AEs	131 (50.6)	134 (54.9)	265 (52.7)
SAEs: all	7 (2.7)	7 (2.9)	14 (2.8)
deaths	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested by the investigator	30 (11.6)	45 (18.4)	75 (14.9)
AEs leading to discontinuation	9 (3.5)	10 (4.1)	19 (3.8)

[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.
CIC640 = ciclesonide 320 µg bid, FP1000 = fluticasone propionate 500 µg bid, N = number of patients in each treatment group.
Data source: Table 15.3.1.3, Listing 16.2.7.10

As LOAEs and asthma exacerbations were reported as AEs and evaluated as primary safety or secondary efficacy variable, respectively, they are reported in the safety as well as in the results section.

The most frequently reported treatment-emergent AEs in each treatment group were related to the SOC infections and infestations followed by the SOC respiratory, thoracic and mediastinal disorders. In the SOC infections and infestations nasopharyngitis, oral candidiasis and upper respiratory tract infection (URTI) was most often reported (nasopharyngitis: CIC640: 4.6% of the patients, FP1000: 5.7%; oral candidiasis CIC640: 3.1% of patients, FP1000: 7.4%; URTI: CIC640: 3.5% of patients, FP1000: 2.5%). On the PT level asthma was the most frequently documented AE and was reported under CIC640 for 6.6% of patients, and under FP1000 for 10.2% of patients.

For most of the patients in both treatment groups the AEs were mild or moderate in intensity. The number of patients with severe AEs was slightly higher in the FP1000 treatment group (5.7%) than in the CIC640 (3.9%) group. However, in both treatment groups all AEs with severe intensity occurred as single events only, except for asthma (two patients) in the FP1000 group.

The investigators assessed a likely relationship to the study medication for 11.6% of patients with AEs in the CIC640 treatment group, and for 18.0% of patients with AEs in the FP1000 group. The sponsor considered the AEs in 10.4% of the patients under CIC640, and in 13.5% of the patients under FP1000 as likely related to study medication. The investigator assessed one AE in one patient from the FP1000 treatment group as definitely related to the study medication (nasopharyngitis in patient 80189). The sponsor did not rate any AE as definitely related to the study drug.

There were no deaths during the study.

Eighteen SAEs were reported during the treatment period (11 SAEs in seven patients [2.7%] in the CIC640 group, and seven SAEs in seven patients [2.9%] in the FP1000 group). Four of the SAEs (anaphylactic reaction, colon cancer and ovarian neoplasm, and coronary artery disease) in the CIC640 treatment group led to premature study withdrawal of three patients. In the FP1000 treatment group two SAEs (depression and syncope) led to the withdrawal of two patients. All SAEs in both treatment groups were assessed as unlikely related or unrelated to study medication.

The study was discontinued due to AEs by nine patients (3.5%) treated with CIC640, and by 10 patients (4.1%) treated with FP1000. In the CIC640 treatment group, the investigator considered three AEs leading to withdrawal of one patient as likely related to study medication (insomnia, hypertension, pruritus generalised). Four AEs leading to study discontinuation of four patients in the FP1000 treatment group (breath odour, asthma, oral candidiasis, insomnia) were assessed as likely related to study medication by the investigator. One additional AE leading to withdrawal in the FP1000 group (nasopharyngitis) was considered definitely related to the study medication by the investigator.

No trend towards a clinically relevant change in any hematology or biochemistry variable was apparent in either treatment group. The relatively large numbers of potassium values outside the laboratory reference or alert range that were found in both treatment groups were based on technical problems, ie hemolytic blood samples.

Morning serum cortisol values decreased in patients treated with FP1000. Statistical significance was seen in the SAFETY analysis for the difference between treatment with CIC640 and FP1000 ($p = 0.0328$, two-sided). In the restricted (RESTR[4]) analysis morning serum cortisol remained unchanged during the treatment period in both treatment groups and no statistically significant between-treatment difference was observed.

Two patients presented with positive pregnancy tests at visit T24. For one patient under FP1000 (CRF ID 80047) the blind code was broken due to pregnancy and the patient was considered a protocol violator. The second patient was not unblinded prematurely and was therefore not considered a major protocol violator.

For six patients under CIC640 and three patients under FP1000 violations of ALTANA Pharma alert values for blood pressure or heart rate were observed, which led to AE

[4] The restricted safety analysis (RESTR) was based on valid values only.

documentation (except for one patient with an alert value at baseline). The AEs were considered unrelated or unlikely related to study medication by both the investigator and the sponsor.

Conclusions

Besides a generally comparable efficacy, the results of this study indicate that ciclesonide has a better safety profile than fluticasone with regard to candidiasis of the oropharynx and ICS-specific side effects as assessed by the ICQ.

Date of report: **21-Sep-2006**