2 Synopsis

Title of the study:

Efficacy of ciclesonide and of a fixed combination with fluticasone propionate and salmeterol versus placebo on long-term asthma control.

Investigators:

A total of 98 main investigators participated in this international multi-center study. For a list of all investigators please refer to Appendix 16.1.4.

Coordinating investigators:

[redacted] McMaster University in Hamilton, Ontario, Canada
[redacted] University of Odense, Kolping, Denmark
[redacted] University Hospital of Groningen, The Netherlands

Publication (reference):

Not applicable

Studied period:

13-Nov-2003 to 28-Oct-2005

Clinical phase:

IIIb

Objectives:

- The aim of the present study was to compare the efficacy of 160 µg ciclesonide in the evening (CIC160, ex actuator) and of a combination of 100 µg fluticasone propionate and 50 µg salmeterol bid (FP200S100, ex valve) vs. placebo (PLAC) on long-term asthma control in patients with mild persistent asthma;
- in addition, the study was to provide further information on the safety and tolerability of long-term treatment with ciclesonide.

Methodology:

The study was conducted using a randomized, double-blind, double-dummy, placebo-controlled, parallel-group design. Patients were randomized to one of three treatments groups (CIC160 or FP200S100 or PLAC) in a 1:1:1 randomization scheme. The study consisted of a two-week baseline period (Visits B0, B1 [optional]), and a treatment period of 52 weeks (visits T0, T1, T2, T4, T6, T8, T10 and T12). A follow-up period subsequent to the treatment period was included, if necessary.

During the baseline period, all patients were treated with rescue medication only. During the treatment period the patients received a daily dosage of 160 µg ciclesonide administered in the evening or a fixed combination of 100 µg fluticasone propionate and 50 µg salmeterol administered twice daily (in the morning and in the evening) or placebo. Throughout the study period, salbutamol was used as rescue medication.

Spirometry (FEV_1 [forced expiratory volume in one second], FVC [forced vital capacity]) was measured at the start of the study (Visit B0) and at each subsequent visit. Throughout the study, patients recorded their morning and evening PEF (peak expiratory flow) using an electronic PEF meter, and documented their daily use of rescue medication as well as their asthma symptoms in the integrated electronic diary. Adverse events were documented at each study visit. Routine laboratory investigations were performed at study start (Visit B0 [Visit B1 if applicable]), at Visit T6 and at the end of the treatment period (Visit T12 or T_{end} in case of premature study termination). Blood sampling to determine eosinophils was performed at study start (Visit B0) and during the treatment period at Visits T2 to T12 [T_{end}]). Pregnancy tests were done at each study visit. Measurements of vital signs were performed at Visits B0, T6 and T12 (T_{end}), and physical examinations were done at the start (B0) and the end of the study (Visit T12 or T_{end}). Completion of a standardized asthma quality of life questionnaire (AQLQ[S]) was mandatory at randomization (T0) and at Visits T4, T8 and T12 or T_{end}.

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

	CIC 160	FP200S100	PLAC	Total
Enrolled				n = 1432
Randomized	n = 212	n = 223	n = 222	n = 657
FAS	n = 210	n = 222	n = 220	n = 652
VCS	n = 187	n = 186	n = 191	n = 564

Diagnosis and main criteria for inclusion:

- mild bronchial asthma;
- written informed consent obtained;
- aged ≥12 to 75 years inclusive;

- had a clinical diagnosis of mild persistent asthma, ie asthma symptoms (eg wheezing, cough, breathlessness) at least once a week, but not every day, during the last 2 months prior to Visit B0;
- were pretreated with SABAs (short-acting beta-agonists) only during the last 2 months prior to Visit B0;
- had FEV_1 ≥80% of predicted measured at least 4h after the last use of rescue medication;
- were currently, with the exception of asthma, in good health;
- reversibility of ΔFEV_1 ≥12% (or at least 200 mL) initial after inhalation of 200 -400 µg salbutamol at Visit B0, or
  diurnal PEF fluctuation of at least 15% during at least 3 days within the last 7 days of the baseline period.
  If this could not be demonstrated, the following historical data, documented within 1 year before B0, were accepted too:
  - reversibility of ΔFEV_1 ≥12% (or at least 200 mL), or
  - PC_{20} FEV_1 (methacholine ≤8 mg/mL), or
  - decrease in FEV_1 ≥15% after exercise;
- use of rescue medication not every day during the baseline period;
- total daytime asthma symptom score >2 and <10 during the last 14 days prior to T0;
- no nocturnal asthma symptoms or nighttime asthma symptom score 1 or 2 during maximal 2 nights of the last 14 days prior to T0.

Test product:

Ciclesonide 160 µg

Dose:

Ciclesonide 80 µg/puff ex actuator (corresponding to 100 µg/puff ex valve)

Mode of administration:

Ciclesonide 80 µg/puff: two puffs once daily in the evening (T0 - T12), administered using an MDI for oral inhalation.

Batch No.:

Ciclesonide 80 µg/puff: 2BGA004, 2BGA005, 2BGA006

Duration of treatment:

52 weeks

Reference product:

Fluticasone propionate 200 µg and salmeterol 100 µg

Dose:

Fluticasone propionate 50 µg/salmeterol 25 µg per puff ex valve

Mode of administration:

Fluticasone propionate 50 µg/salmeterol 25 µg per puff: Two puffs twice daily in the morning and in the evening, administered using an MDI for oral inhalation.

Batch No.:

Fluticasone propionate 50 µg/salmeterol 25 µg per puff: No. 031, No. 056, No. 0070, No. 0078A + 0080

Criteria for evaluation:

Efficacy evaluation (primary):

- time to onset of the first severe asthma exacerbation [d].

Efficacy evaluation (co-primary):

- percentage of poorly controlled asthma days [%].

Efficacy evaluation (key-secondary):

- percentage of asthma symptom-free days [%] (analysis of the entire treatment period).

Efficacy evaluation (secondary):

- FEV1 [L], FVC [L] from spirometry (measured) (Tlast/end, T12, T10, T8, T6, T4, T2, T1 vs. T0);
- FEV1 % of predicted [%], FVC % of predicted [%] from spirometry (predicted) (T0 to T12);
- morning PEF, evening PEF from diary (absolute [L/min]) (Wlast/end, W1 to W52 vs. W0);
- morning PEF, evening PEF from diary (% of predicted [%]) (W0 to W52);
- diurnal PEF fluctuation [%] calculated from diary values (Wlast/end, W1 to W52 vs. W0);

- asthma symptom score sum (0, 1,…,8) (Wlast/end, W1 to W52 vs. W0);
- daytime and nighttime asthma symptom score (0, 1,…,4) (Wlast/end, W1 to W52 vs. W0);
- use of rescue medication [puffs/d] (Wlast/end, W1 to W52 vs. W0);
- percentage of asthma symptom-free days [%] (Intlast/end vs. Int0);
- percentage of rescue-medication-free days [%] (analysis of the entire treatment period, Intlast/end vs. Int0);
- percentage of days a patient perceived asthma control [%] (analysis of the entire treatment period, Intlast/end vs. Int0);
- percentage of nocturnal awakening-free days [%] (analysis of the entire treatment period, Intlast/end vs. Int0);
- AQLQ(S) domain and overall scores (Tlast/end, T12, T8, T4 vs. T0);
- net benefit in quality of life (T12, T8, T4 vs. T0);
- blood eosinophils.

Safety evaluation (secondary):

- treatment exposure [d];
- adverse events (AEs);
- laboratory work-up;
- vital signs (blood pressure and heart rate);
- physical examination;
- number of patients with local AEs.

Statistical methods:

CIC160 was tested for superiority over PLAC for the primary variable time to the first severe asthma exacerbation (proof of efficacy). If this was confirmed, superiority of CIC160 over PLAC was tested with respect to the co-primary variable percentage of poorly controlled asthma days.

If superiority was shown, the comparison of the combination FP200S100 vs. PLAC, concerning the primary and co-primary variables, was done analogously to that of CIC160 vs. PLAC.

If and only if superiority of both CIC160 and the combination FP200S100 over PLAC with respect to the primary and co-primary variable was demonstrated (proof of assay sensitivity), CIC160 was tested for non-inferiority to FP200S100 with regard to the primary and co-primary variables. Due to the lack of established non-inferiority limits for both the time to the

first severe asthma exacerbation and percentage of poorly controlled asthma days, the assessment of non-inferiority of CIC160 to FP200S100 was to be based on medical judgment.

If and only if non-inferiority of CIC160 to FP200S100 with respect to the primary and co-primary variables was shown, the key-secondary variable percentage of asthma symptom-free days was tested in the confirmatory testing procedure analogously to the procedures used for the primary and co-primary variables, ie superiority of both CIC160 and FP200S100 over PLAC with regard to the percentage of asthma symptom-free days was a prerequisite for the non-inferiority test of CIC160 vs. FP200S100. Non-inferiority of CIC160 to FP200S100 was to be assessed by medical judgement.

The above described analyses of the primary, co-primary and key-secondary variables 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 time to first asthma exacerbation was analyzed using the log-rank test. Between-treatment differences for the co-primary variable percentage of poorly controlled asthma days and the key-secondary variable percentage of asthma symptom-free days were analyzed by means of the Mann-Whitney U-test.

In addition, a Cox proportional hazards regression was applied to perform survival analyses on time to a severe asthma exacerbation, with treatment, age, sex, country pool and smoking status as factors and covariates.

The number of severe asthma exacerbations was investigated using a Poisson regression model. Logistic regression analyses were performed to investigate whether a patient had experienced at least one severe asthma exacerbation as a function of the factors and covariates listed above.

The Mann-Whitney U-test was used to analyze non-parametrically the number of severe asthma exacerbations, in addition to the Poisson regression (see above). Furthermore, the annualized number of severe asthma exacerbations was analyzed using this test. The number of days with a severe asthma exacerbation, observed and annualized, was also analyzed with the Mann-Whitney U-Test. In addition to the logistic regression, the number of patients having experienced at least one severe asthma exacerbation was analyzed using Fisher's exact test.

The lung function variables FEV_1, FVC, and PEF from diary, and AQLQ(S) were evaluated using an analysis of covariance (ANCOVA) including baseline value (value at randomization visit T0) and age as covariates, and treatment, sex and country pool as factors.

In addition to hypothesis testing, means and two-sided 95%-confidence intervals were presented for the within- and between-treatment differences.

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

Non-parametric between-group comparisons of blood eosinophils and of the diary variables diurnal PEF fluctuation, asthma symptom scores, use of rescue medication, percentage of poorly controlled asthma days, percentage of asthma symptom-, rescue medication-, and nocturnal awakening-free days, and of the percentage of days on which a patient perceived asthma control were performed using the Mann-Whitney U-test.

Adverse events, blood pressure, heart rate, physical examination, and laboratory values were evaluated by means of descriptive statistics. Differences between treatments in the number of patients with local oropharyngeal adverse events were analyzed using Fisher's exact test.

A sample size of 210 randomized patients per treatment arm was sufficient to ensure a power of 90% in detecting a difference in the probability of not experiencing a severe asthma exacerbation of 0.80 (active treatment) and 0.65 (placebo) at the end of the treatment period.

SUMMARY - CONCLUSIONS

Summary:

Demographic and other baseline characteristics:

Of the 1432 patients enrolled, 652 patients (45.5%) were included in the FAS: 210 patients in the CIC160 treatment group, 222 patients in the FP200S100 treatment group, and 220 patients in the PLAC group. In the FAS, the median age of the patients was about 30 years in all treatment groups. In each of the groups slightly more female (between 56% and 59%) than male patients (between 41% and 44%) were included. All patients included in the study had a history of asthma. The median duration of asthma before study start ranged from 62 to 68 months in the three treatment groups.

Efficacy results

In the first test of the confirmatory testing procedure, superiority of CIC160 vs. PLAC was not shown for the primary efficacy variable time to the first severe asthma exacerbation. The confirmatory testing strategy therefore ended with the first test and all further analyses were performed in an exploratory manner. Descriptively, superiority of FP200S100 over PLAC was shown with regard to the primary variable time to the first severe asthma exacerbation ($p = 0.0002$, two-sided [log-rank test], ITT analysis). The PP analysis yielded similar results.

In purely exploratory manner, the results of the Cox proportional hazards analyses showed a 19% reduction in the risk to experience a first severe asthma exacerbation in patients treated with CIC160 in relation to patients treated with PLAC, compared to a reduction of 52% for patients treated with the combination therapy in relation to patients treated with PLAC.

The percentage of poorly controlled asthma days was stipulated as the co-primary variable. During the whole treatment period, the median percentage of poorly controlled asthma days was 1.7 for the PLAC group, 0.8 for the CIC160 group, and 0.6 for the FP200S100 group. Superiority of both CIC160 and FP200S100 treatment vs. PLAC was demonstrated exploratively with regard to the percentage of poorly controlled asthma days ($p = 0.0016$ and $p < 0.0001$, respectively, ITT analysis). No statistically significant difference between treatment with CIC160 and FP200S100 was shown. The PP analysis confirmed the results from the ITT analysis.

The median overall percentage of asthma symptom-free days, serving as key-secondary variable, was higher with CIC160 (91.5%) and FP200S100 treatment (93.6%) than with PLAC (85.2%, ITT analysis). Superiority of CIC160 vs. PLAC and of FP200S100 vs. PLAC was demonstrated in an exploratory manner (all p-values ≤ 0.0001), and no statistically significant between-treatment difference for CIC160 vs. FP200S100 was observed (ITT and PP analysis).

All three treatment groups showed statistically significant within-treatment decreases in asthma symptom score sum, daytime asthma symptom score, and use of rescue medication (ITT and PP analysis). For each of the three mentioned variables, superiority of both CIC160 and FP200S100 treatment vs. PLAC was shown in an explorative manner. No statistically significant between-treatment difference was observed for the CIC160 to FP200S100 comparison with regard to asthma symptom scores and use of rescue medication (ITT and PP analysis).

Superiority of CIC160 and FP200S100 treatment vs. PLAC was shown for the overall percentage of rescue medication-free days, nocturnal awakening-free days and days with asthma control (PP and ITT analyses). Only with regard to the overall percentage of rescue medication-free days, the comparison of CIC160 vs. FP200S100 treatment revealed a between-treatment difference in favor of FP200S100 (point estimate: -1.18), reaching statistical significance in the ITT analysis ($p = 0.0297$, two-sided) that was not confirmed in

the PP analysis. The results for the analyses of the changes in the percentage of rescue medication-free days, nocturnal awakening-free days, and days with asthma control from baseline (Int0) to the end of treatment ($Int_{last/end}$) were generally comparable to those of the overall percentage. However, superiority of CIC160 treatment vs. PLAC was not demonstrated for the last value or endpoint analysis of the percentage of nocturnal awakening-free days. No statistically significant between treatment differences were shown for CIC160 compared to FP200S100 (ITT and PP analysis).

In the PLAC group, FEV_1 decreased statistically significantly from baseline to the end of treatment (ITT analysis), while no statistically significant change was observed for FVC. No within-treatment changes were observed in the CIC160 treatment group for the spirometry variables FEV_1 and FVC, while the values increased statistically significantly with FP200S100 treatment (ITT and PP analysis). For both FEV_1 and FVC, superiority vs. PLAC was demonstrated for FP200S100, but not for CIC160 (ITT and PP analysis).

The results for morning and evening PEF from diary and PEF fluctuation were in line with the results obtained for the spirometry variables. Statistically significant improvements during the treatment period were only observed for patients in the FP200S100 treatment group, and only treatment with FP200S100 was superior vs. PLAC for PEF from diary and PEF fluctuation (ITT and PP analysis).

Statistically significant increases in the AQLQ(S) overall score were observed for CIC160 and for FP200S100 treatment. Both treatments were superior vs. PLAC with regard to the changes in the overall score (ITT and PP analysis). The between-treatment analysis showed non-inferiority of CIC160 vs. FP200S100 for the AQLQ(S) overall score (lower limit 95% CI: -0.04, ITT analysis). The results for the analysis of the individual AQLQ(S) domain scores generally corresponded to those for the overall score. A net benefit in AQLQ(S) was shown for more patients treated with CIC160 (26.7%) than for patients treated with FP200S100 (17.9%) or PLAC (3.8%, ITT analysis). The PP analysis reflected the ITT analysis.

No statistically significant differences from baseline to $T_{last/end}$ were determined for the CIC160 and FP200S100 treatment groups with regard to blood eosinophils. The within-treatment differences were statistically significant in the PLAC treatment group (ITT and PP analysis).

Safety results

Adverse events

Treatment-emergent AEs were reported for 162 patients (73.6%) treated with PLAC, 154 patients (73.3%) treated with CIC160, and 142 patients (64.0%) treated with FP200S100.

The most frequently reported treatment-emergent AEs in each treatment group were related to the system organ class infections and infestations and included nasopharyngitis and

pharyngitis. Nasopharyngitis was most often reported for patients treated with CIC160 (PLAC: 14.5% of patients, CIC160: 18.1%, FP200S100: 13.1%), while pharyngitis was most frequently documented for patients under PLAC (PLAC: 10.5% of patients, FP200S100: 6.3%, CIC160: 7.6%). All cases of severe asthma exacerbations were documented as AEs in this study. Thus, on the preferred term level asthma was the most frequently documented AE. The frequency of local oropharyngeal AEs was low in all three treatment groups.

For most of the patients in all treatment groups the AEs were mild or moderate in intensity and were not attributed a causal relationship to study medication by the investigator or the sponsor.

The investigator assessed a likely relationship to the study medication for 6.4% of patients with AEs in the PLAC treatment group, for 5.7% of the patients with AEs in the CIC160 group, and for 6.3% of patients with AEs in the FP200S100 treatment group. The sponsor considered the AEs in 2.3% of the patients under PLAC, in 2.4% of the patients under CIC160, and in 4.1% of the patients under FP200S100 as likely related to study medication. Both investigator and sponsor did not rate any AE as definitely related to the study drug.

There were no deaths during the study.

Twenty-three SAEs were reported during the treatment period. In the PLAC group nine SAEs occurred in seven patients (3.2%), and in the CIC160 treatment group, 10 SAEs occurred in nine patients (4.3%). In the FP200S100 group, four SAEs were recorded in four patients (1.8%). All SAEs in all three treatment groups were assessed as unlikely related or unrelated to study medication.

The study was discontinued due to AEs by 38 patients (17.3%) treated with PLAC, 23 patients (11.0%) treated with CIC160, and by 12 patients (5.4%) treated with FP200S100. Asthma was the most common AE leading to study discontinuation in each of the three groups (PLAC: 33 patients [15.0%], CIC160: 21 patients [10.0%], FP200S100: 9 patients [4.1%]). Since the events of severe asthma exacerbation were documented as AEs in this study and the patients were to be excluded from further study participation after a second severe asthma exacerbation, most of the AEs leading to study discontinuation were not based on intolerability to the treatments, but were related to the underlying disease.

In the PLAC treatment group, the investigator considered five cases of asthma leading to withdrawal of five patients as likely related to study medication. Eight AEs leading to study discontinuation of six patients in the CIC160 treatment group (seven cases of asthma and one case of dyspnea exacerbated) were assessed as likely related to study medication by the investigator. In the FP200S100 group five AEs causing withdrawal of five patients (two cases of asthma, one case each of dysphonia, throat irritation, and drug hypersensitivity) were considered likely related to study treatment by the investigator. The sponsor assessed only the cases of dysphonia, throat irritation, and drug hypersensitivity in the FP200S100 group as likely related to study medication.

Clinical laboratory

No general trend towards a clinically relevant change in any hematology or biochemistry variable was apparent in any treatment group.

Physical examination and vital signs

For two patients under PLAC, five patients under CIC160, and one patient under FP200S100 alert heart rate findings were documented. For five of the patients (1 from the PLAC, 3 from the CIC160, and 1 from the FP200S100 group) AEs related to the alert heart rate findings, were documented. The AE of the patient under FP200S100 (heart rate increased) was rated likely related to study medication by the investigator, but unlikely related by the sponsor. The other AEs related to alert heart rate findings were considered unrelated or unlikely related to study medication by both the investigator and the sponsor.

Seven patients presented with positive pregnancy tests during the treatment period. For six of the seven patients the blind code was broken and the patients were withdrawn from study participation. Based on the AE blighted ovum one patient was considered not pregnant but discontinued the study due to the AE.

Conclusions:

Regarding the time to the first severe asthma exacerbation, superiority vs. PLAC was not shown for CIC160 in the evening but was descriptively shown for FP200S100 bid. However, with regard to the percentage of poorly controlled asthma days as well as the percentage of asthma symptom-free days, CIC160 and FP200S100 were both superior vs. PLAC without showing statistically significant differences between the two treatments.

Treatment with CIC160 did not reveal new or unknown safety issues.

Date of report: 12-Feb-2007