2 Synopsis

Title of the study:

Comparison of inhaled ciclesonide (160 µg bid or 320 µg bid) and fluticasone propionate (250 µg bid or 500 µg bid) in pretreated patients with mild to moderate asthma

Investigator(s) and study center(s):

Two centers in Belgium.

Coordinating investigator(s):

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Publication (reference): Not applicable

Studied period: 27-May-2003 (first patient in) to 10-Apr-2006 (last patient out)

Clinical phase: Phase IIIb

Objectives:

The primary objective of this study was to investigate the effect of ciclesonide (320 µg/d and 640 µg/d) vs FP (fluticasone propionate) (500 µg/d and 1000 µg/d) and placebo, respectively, on 24 h time average (mesor) of serum cortisol in asthmatic patients.

Methods:

This was a double-blind, double-dummy, randomized, placebo-controlled, 5 period change-over study with a baseline period of 4 to 6 weeks, five treatment periods of 9 days each separated by washout periods of 4 to 12 weeks each, and a follow-up, if required.

At the start of the **baseline period**, pretreatment was withdrawn and patients received their basic asthma medication (ciclesonide 160 µg od and salmeterol 50 µg bid) for the entire study. Blood sampling for determination of baseline plasma cortisol concentration was conducted, lung function tests followed by AMP and MCh challenges were performed. At the end of the 4 to 6 week baseline period, patients were randomized to one of the ten treatment sequences if FEV_1 was > 60% of predicted. After 7 days of treatment the patients returned and stayed 24 h at the investigational site. Blood sampling for 24 h serum cortisol profile started at 08:00 pm after inhaling the evening dose of study medication and blood was drawn in 2 h intervals up to 08:00 pm the next day. During the same interval, urine was collected for determination of cortisol excretion. At 08:00 am of the consecutive day further blood samples for determination of bone formation markers and standard laboratory were drawn. After nine days of treatment the patients returned for the last visit of the first treatment period and MCh and AMP challenges were performed. The subsequent tratment sequences followed the same scheme. At the start of the baseline period and the end of the treatment period an ECG and a

physical examination were performed, vital signs recorded and a standard laboratory work-up performed. AEs were assessed at all visits.

No. of patients (total) planned and analyzed:

A sample size of n = 30 ITT (intention-to-treat) patients was sufficient to ensure a power of 80% in correctly concluding a difference in means of 49 nmol/L with regard to the primary variable.

All of the 32 enrolled patients were randomized and formed the safety set, which was identical to the full analysis set. Three patients of the full analysis set were protocol violators, therefore the valid cases set consisted of 29 patients. Further, patient 90005 was excluded from safety and efficacy analyses as this patient did not comply with the described scheme of study medication intake.

Diagnosis and main criteria for inclusion:

Outpatients of either sex fulfilling the following criteria were considered for study inclusion:

- obtained written informed consent;
- age of ≥ 18 and ≤ 65 years;
- history of bronchial asthma for at least 6 months;
- current asthma treatment either with ICS (equal or less than CFC-BDP 1000 µg/d or equivalent) or ICS (CFC-BDP 200 µg bid or equivalent) plus LABA;
- FEV_1 > 60% of predicted;
- hyperreactivity to MCh ($PC_{20}FEV_1$ < 8 mg/mL);
- hyperreactivity to AMP ($PC_{20}FEV_1$ < 60 g/mL);
- no asthma exacerbation or relevant respiratory tract infection within the last 8 weeks prior to the study;
- good health with the exception of asthma;
- normal function of the HPA (hypothalamic pituitary adrenal) axis (baseline plasma cortisol concentration at 08:00 am ± 30 min > 5 µg/dl [corresponds to > 138 nmol/L]).

Basic medication, dose, mode of administration, batch no:

- Ciclesonide HFA-MDI, 160 µg/d (ex actuator), once daily, oral inhalation, 2BGA003, 2BGA004, 2BGA005, 2BGA006; and
- Salmeterol HFA-MDI, 100 µg/d (ex actuator), twice daily (salmeterol 50 µg bid), oral inhalation, 2K762, 3G838, 3L879, 4L1040

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

- Ciclesonide HFA-MDI, 320 µg/d (ex actuator), twice daily (ciclesonide 160 µg bid), oral inhalation, 2BGA003, 2BGA004, 2BGA005, 2BGA006; or
- Ciclesonide HFA-MDI, 640 µg/d (ex actuator), twice daily (ciclesonide 320 µg bid), oral inhalation, 4BGA003, 4BGA004, 4BGA005, 4BGA006; or
- Ciclesonide placebo HFA-MDI, twice daily, oral inhalation, 0BGA001, 0BGA002, 0BGA003

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

- FP HFA-MDI, 500 µg/d (ex valve), twice daily (FP 250 µg bid), oral inhalation, 2L028, 3C013, 3G026, 4K062; or
- FP HFA-MDI, 1000 µg/d (ex valve), twice daily (FP 500 µg bid), oral inhalation, 2K131, 3C023, 3G029, 4H057; or
- FP placebo HFA-MDI, twice daily, oral inhalation, FBG002, FBG003

Duration of treatment: Five 9-day treatment periods, separated by washout periods of 4 to 12 weeks; basic medication was taken during the entire study (baseline and treatment period).

Criteria for evaluation:

Primary variable (safety)

24 h serum cortisol mesor [nmol/L].

Co-primary variable (safety)

24 h urine cortisol adjusted for creatinine [nmol/mmol].

Secondary variables (safety)

Exposure to study medication, AEs, standard laboratory, urine cortisol variables, bone formation markers, vital signs, physical examination, and ECG.

Secondary variables (efficacy)

Hyperresponsiveness to AMP and MCh, lung function (FEV_1 and FVC).

Statistical methods:

The primary safety variable 24 h serum cortisol mesor and the co-primary safety variable 24 h urine cortisol adjusted for creatinine were tested in a confirmatory manner for between treatment differences at the one-sided 2.5% level. The saftey analysis was based on all randomized patients, the restricted safety analysis was based on all patients of the safety set

without influenced serum or urine cortisol levels. The variables serum cortisol mesor, urine cortisol, bone formation markers, doubling doses expressed as log-transformed values, and lung function were analyzed by means of an ANCOVA or ANOVA model including the fixed factors 'treatment', 'period', 'sequence', 'sex', 'asthma pretreatment', 'center', the covariate 'baseline value', the random nested factor 'patient within sequence', a dependent variable, and an error term. No interaction term was included. Analysis of secondary variables was exploratory. Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Demographic and baseline characteristics of patients in the full analysis set were comparable to those in the valid cases set. The treatment groups were well balanced. More female than male patients were randomized. The majority of all randomized patients was white, non-smokers, and pretreated with ICS plus LABA. At randomization mean FEV_1 amounted to 85% of predicted and at the first baseline visit all patients were hyperresponsive to both AMP and MCh.

Safety results

As the restricted safety analysis excluded protocol violations with a possible impact on the HPA axis, this analysis was the preferred one to assess the effect on ciclesonide and FP on the HPA axis. In addition, patient 90005 did not comply with the prescribed study medication intake and this patient was excluded from the analyses.

For 24 h serum cortisol samples, superiority of ciclesonide 640 µg/d over FP 1000 µg/d was shown in the restricted safety analysis excluding patient 90005 (one-sided $p = 0.0197$). Further, both ciclesonide doses had less effect on serum cortisol levels than FP when compared to placebo. Both FP dosages were significantly different to placebo.

For 24 h urine cortisol samples, adjusted for creatinine, both analyses excluding patient 90005 showed no statistically significant differences between active treatments. In contrast to ciclesonide, both FP doses showed a significant effect on urine cortisol levels when compared to placebo.

FP 1000 µg/d lowered P1CP and serum osteocalcin levels compared to placebo (two-sided $p = 0.0207$ and $p = 0.0026$, respectively). FP 500 µg/d and both ciclesonide doses had no significant effect on these two variables when compared to placebo.

In total, 22 patients experienced 56 AEs during the treatment period. The number of patients experiencing AEs was comparable for all treatments.

The most frequently reported AEs were classified as infections and infestations: 4 patients for treatment with ciclesonide 320 µg/d, 2 patients for treatment with ciclesonide 640 µg/d, 5 patients for treatment with FP 500 µg/d, 1 patient for treatment with FP 1000 µg/d, and

6 patients for treatment with placebo. Other most frequently reported AEs were classified as respiratory, thoracic and mediastinal disorders: 2 patients for treatment with ciclesonide 320 µg/d, 1 patient for treatment with ciclesonide 640 µg/d, 2 patients for treatment with FP 500 µg/d, 3 patients for treatment with FP 1000 µg/d, and 3 patients for treatment with placebo. The majority of AEs were of mild or moderate intensity in all treatment groups. The majority of AEs were assessed as unrelated to the intake of study medication by the investigator. Under treatment with FP 1000 µg/d two AEs (muscle spasms) were assessed as likely related by the investigator. No AE was assessed as definitely related by the investigator. Two AEs of severe intensity were reported for treatment with ciclesonide 320 µg/d (blood creatinine phosphatase increased and arthralgia) and one per patient in each of the other treatments (alanine aminotransferase increased for treatment with ciclesonide 640 µg/d, rhinitis allergic for treatment with FP 500 µg/d, asthma for treatment with FP 1000 µg/d, and face oedema for placebo). No death occurred during this study. One patient in the placebo group experienced two SAEs (face oedema and laryngeal oedema), which were assessed as not related to the intake of study medication by the investigator and from which the patient recovered without sequelae. No patient discontinued the study prematurely due to AEs.

For blood biochemistry and hematology laboratory values, no changes from baseline above the alert ranges were observed.

Physical examination, BP, HR, and ECG assessed or measured at baseline and endpoint of the study period did not reveal any clinically relevant influence of the different treatments.

Efficacy results

No clinically relevant differences between ciclesonide and FP were noted for the improvement in airway responsiveness to AMP and MCh. Regarding lung function, no relevant differences between treatments were seen.

Conclusions:

This study demonstrated that ciclesonide 320 µg/d and ciclesonide 640 µg/d had less effect on HPA axis compared to FP as assessed by 24 h serum cortisol mesor and urine cortisol.

Date of report: 25-Apr-2007