**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.

# 1 Title Page — Clinical Study Report No. 130/2006

Version (1.0)

| | |
|---|---|
| Title:<br>ADVICE<br>A dose range finding study of formoterol administered once daily in the evening in combination with ciclesonide using the Ultrahaler™ versus monotherapy of each drug in asthmatic patients. | Version date: 22-Jan-2007<br>INN: Ciclesonide; Formoterol fumarate<br>Project No. / List No.: BY9010<br>Compound No.: B9207-015<br>Batch No.:<br>CIC/formoterol 80/4.5 µg: PM/003/05<br>CIC 80 µg: PM/001/05<br>formoterol 4.5 µg: PM/007/05 |
| Study Protocol No.: **BY9010/M1-506** | Development phase: II |
| EudraCT No: 2004-004708-19 | Indication studied: Asthma |
| Study initiation date: 18-Jul-2005 | Date of early termination: not applicable |
| Study completion date: 04-Jan-2006 | Summary of modifications: not applicable |

Name and country of investigators:

26 centers in France, Germany, Hungary, and South Africa participated
Coordinating investigator:

Name of sponsor's responsible medical officer:

ALTANA Pharma AG (RCS/P1), Byk-Gulden-Str. 2, 78467 Konstanz, Germany

Person(s) responsible for the study report:
ALTANA Pharma AG (RCO/R1), Byk-Gulden-Str. 2, 78467 Konstanz, Germany

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 RCO/CT at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

# 2 Synopsis

**Title of the study:**

**A** dose range finding study of formoterol administered once daily in the e**v**ening **i**n combination with **c**icl**e**sonide using the UltrahalerTM versus monotherapy of each drug in asthmatic patients. The **ADVICE**-study.

**Investigator(s) and study center(s):**

International study at 26 centers in Hungary (12 centers), South Africa (7 centers), Germany (5 centers), and France (2 centers).

**Coordinating investigator(s):**

**Publication (reference):** Not applicable.

**Studied period:** 18-Jul-2005 (first patient in, ie first patient visit) to 04-Jan-2006 (last patient out, ie last patient visit).

**Clinical phase:** phase II.

**Objectives:**

The study compared two doses of the fixed combination ciclesonide/formoterol vs its components. All treatments were given od (once daily) in the evening.

The primary objectives of this pilot study were:

- to compare the efficacy of two doses of the fixed combination ciclesonide/formoterol (320/9 µg/d or 320/18 µg/d) vs monotherapy of formoterol (18 µg/d) with regard to the time to first experience of LOE (lack of efficacy);
- to compare the effect size of two doses of the fixed combination ciclesonide/formoterol (320/9 µg/d or 320/18 µg/d) vs monotherapy of ciclesonide (320 µg) and monotherapy of formoterol (18 µg) with regard to 24-h serial measurements of $FEV_1$ as well as pre-dose $FEV_1$ (forced expiratory volume in 1 second).

Additionally, the safety and tolerability was assessed by AEs (adverse events), physical examinations, ECG (electrocardiogram) and vital signs over 8-weeks treatment.

**Methodology:**

The study was conducted as a randomized, double-blind, parallel-group, multi-center study, which comprised a baseline period of 2-3 weeks and a double-blind treatment period of 8 weeks.

Eligible patients entered the baseline period at Visit B0 (enrolment), replaced their individual asthma treatment, with ciclesonide 320 µg in the evening via a DPI (dry powder inhaler, Ultrahaler™). Patients were also provided with salbutamol administered by a MDI (metered dose inhaler) as rescue medication.

Patients who meet the randomization criteria at Visit T0[1] were randomly assigned to one of the following treatments using FACTS (Fisher Automated Clinical Trial Services):

- CIC320/F18 (ciclesonide/formoterol 320/18 µg od) in the evening;
- CIC320/F9 (ciclesonide/formoterol 320/9 µg od) in the evening;
- CIC320 (ciclesonide 320 µg od) in the evening;
- F18 (formoterol 18 µg od) in the evening.

Patients visited the investigational site weekly during the whole treatment period (Visits T1, T2, T3, T4, T5, T6, T7 and T8/Termination). At Visits T0, T2 and T8 serial $FEV_1$ measurements were performed over a 24-h dosing interval starting in the afternoon. At all other visits (including the Early Termination Visit, if applicable) investigations took place in the morning.

Throughout the study (baseline and treatment period), patients documented the morning and evening PEF (peak expiratory flow), the daytime and nighttime asthma symptom scores as well as the number of puffs of rescue medication by using an electronic PEF meter combined with an electronic diary. Patients entered data into the home diary first and then performed the PEF measurements before any use of study medication.

During the study, safety and tolerability were evaluated by means of spontaneously reported AEs, physical examinations (including vital signs and ECG), and assessment of standard laboratory values.

[1] Visit T0 corresponded to the Baseline Visit at which the patient was randomized. If patients did not fulfill the randomization criteria after 2-weeks baseline at Visit B2, lung function tests could be repeated on two further occasions following shortly thereafter (ie at optional Visits B3 and B4).

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

In this pilot study, the sample size was primarily chosen on grounds of feasibility.

| | Enrolled | Safety set (= Full analysis set) | Valid cases set |
|---|---|---|---|
| **Baseline medication (CIC 320 µg)** | 380 | | |
| **CIC320/F18** | | 70 | 61 |
| **CIC320/F9** | | 68 | 57 |
| **CIC320** | | 70 | 63 |
| **F18** | | 68 | 59 |
| **Total** | 380 | 276 | 240 |

Note: During the baseline period all patients received ciclesonide 320 µg once daily.
CIC320 = ciclesonide 320 µg once daily, CIC320/F9 = ciclesonide/formoterol 320/9 µg once daily, CIC320/F18 = ciclesonide/formoterol 320/18 µg once daily, F18 = formoterol 18 µg once daily, N = number of patients in a treatment group.

**Diagnosis and main criteria for inclusion:**

Patients who met the following criteria were considered for inclusion into the study:

Inclusion into the baseline period (at Visit B0):

- written informed consent;
- male or female outpatients;
- aged 18 to 75 years;
- history of bronchial asthma for ≥6 months;
- good health, with the exception of asthma.

Additionally, patients had to have received specified pretreatment (at a constant dosage during ≥4 weeks prior to entry into the study) and meet specified $FEV_1$ criteria (when rescue medication had been withheld for ≥6 h and asthma controller had been withheld for ≥24 h):

- pretreated with 200 to 250 µg/d fluticasone propionate (or equivalent) as monotherapy and the $FEV_1$ had to be >60% to <80% of predicted;
- pretreated with 200 to 250 µg/d fluticasone propionate (or equivalent) in combination (with one of the following: a long-acting $\beta_2$-agonist [in a fixed or free inhaled corticosteroid combination], sustained-release theophylline, a leukotriene antagonist, a lipoxygenase inhibitor, inhaled anticholinergic, an oral ß-agonist, inhaled disodium cromoglycate, inhaled nedocromil) and the $FEV_1$ had to be >60% to ≤85% of predicted.

Inclusion into the treatment period (randomization criteria at Visit T0):

After the baseline period, patients were randomized if they fulfilled the following criteria at Visit T0:

- $FEV_1$ >60% to <80% of predicted (again rescue medication withheld for ≥6 h prior to the measurement);
- reversibility demonstrated by $\Delta FEV_1$ ≥15% initial after inhalation of 200 to 400 µg salbutamol or, if reversibility could not be achieved during baseline,[2] diurnal PEF fluctuation ≥15% during at least 3 d within the last 7 d of baseline period;
- asthma symptoms occurring more than once a week, but not daily during the baseline period prior to Visit T0;
- The LOE criteria with regard to clinical asthma exacerbation, use of rescue medication and nocturnal awakenings not being met during baseline.

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

Ciclesonide/formoterol 320/18 µg (ex actuator), od, oral inhalation, PM/003/05.

Ciclesonide/formoterol 320/9 µg (ex actuator), od, oral inhalation, PM/003/05.

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

Ciclesonide 320 µg (ex actuator), od, oral inhalation, PM/001/05.

Formoterol 18 µg (ex actuator), od, oral inhalation, PM/007/05.

**Duration of treatment:** Baseline period of 2-3 weeks (open-label ciclesonide 320 µg od) and a double-blind treatment period of 8 weeks.

**Criteria for evaluation:**

The **variables of primary interest** were:

- time to onset of the first LOE [d];
- time-averaged $FEV_1$ over a 24-h dosing interval after 2 weeks of treatment vs the reference profile at Visit T0 [L];
- pre-dose $FEV_1$ [L] (more precisely, $FEV_1$ prior to the dose of the 24-h profile, after 2 weeks of treatment compared to $FEV_1$ at the beginning of the 24-h reference profile at Visit T0).

The **secondary variables** included time averaged $FEV_1$ and pre-dose $FEV_1$ after 8 weeks of treatment as well as morning measurements of lung function, daily recordings of morning and evening PEF, symptoms and use of rescue medications as well as variables derived from these data.

[2] Historical data for reversibility, documented within one year before Visit B0, was also considered to be acceptable.

**Statistical methods:**

The variable of primary interest "time to onset of the first LOE" was analyzed by means of the log-rank test. The other variables of primary interest "difference in time-averaged $FEV_1$ after two weeks of treatment compared to baseline" as well as the "difference in pre-dose $FEV_1$ after two weeks of treatment compared to baseline" were analyzed by means of an ANCOVA (analysis of covariance) model with the baseline value at visit T0 and age as covariates and sex, center (pool) and treatment as fixed factors. The ITT analysis was the primary analysis.

All tests were performed at the one-sided 2.5%-level. The variables of primary interest were tested with a priori ordered hypotheses in an exploratory intention. Firstly, superiority of CIC320/F18 vs F18 was tested and subsequently CIC320/F9 vs F18 with regard to the time to onset of the first LOE. In the next step, superiority of CIC320/F18 vs F18 and subsequently CIC320/F9 vs F18 was tested with regard to the difference in pre-dose $FEV_1$. Thereafter, superiority of CIC320/F18 vs CIC320 and subsequently CIC320/F9 vs CIC320 was tested with regard to the difference in time-averaged $FEV_1$.

The corresponding comparisons for the difference in pre-dose $FEV_1$ and difference in time-averaged $FEV_1$ after 8 weeks of treatment were analyzed analogously. Secondary pulmonary function variables were analyzed by means of the same ANCOVA model as defined for the variables of primary interest. Other secondary variables from diaries were analyzed non-parametrically. Descriptive statistics were provided for safety variables.

## SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Overall, the baseline characteristics compared well between the treatment groups of the double-blind treatment period. The median age of the patients ranged from 38.0 to 46.5 years across the treatment groups. Overall, 81.2% patients were Caucasian. Slightly more female than male patients were included, however, the proportion of males varied across the treatment groups (58.6% for CIC320/F18 to 38.2% for F18). $FEV_1$ % of predicted were comparable across all of the double-blind treatment groups. The vast majority of the patients in each group had been pretreated with ICS plus LABA (52.9 to 61.8% patients across the treatment groups) or ICS alone (32.4 to 44.3%). The overall mean duration of the patients' asthma was approximately 170.4 months.

Efficacy results

*Variables of primary interest*

The proportion of patients experiencing a LOE was 11.4% for CIC320/F18, 14.7% for CIC320/F9, 24.3% for CIC320, and 39.7% for F18. The time to onset of first LOE favored CIC320/F18 over F18 (one-sided p <0.0001) and also CIC320/F9 over F18 (one-sided p = 0.0016, log-rank test). Comparisons between the combination regimens with CIC320 alone did not reveal any statistically significant differences.

**Time to first lack of efficacy: between-treatment differences (ITT)**

| | | | | Pat. with LOE | | Difference Test - Ref | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Log-rank test | Cox proportional hazards model | |
| Test | Ref | N Test | N Ref | n (%) Test | n (%) Ref | p-value 1-sided[a] | Hazard ratios [95% CI] | p-value 1-sided[b] |
| CIC320/F18 | F18 | 70 | 68 | 8 (11.4) | 27 (39.7) | <0.0001 | 0.627 [0.479, 0.822] | 0.0004 |
| CIC320/F9 | F18 | 68 | 68 | 10 (14.7) | 27 (39.7) | 0.0016 | 0.579 [0.401, 0.836] | 0.0018 |
| CIC320/F18 | CIC320 | 70 | 70 | 8 (11.4) | 17 (24.3) | 0.0311 | 0.621 [0.406, 0.951] | 0.0141 |
| CIC320/F9 | CIC320 | 68 | 70 | 10 (14.7) | 17 (24.3) | 0.1669 | 0.621 [0.281, 1.371] | 0.1191 |

[a] Two-sample log-rank test for superiority, 1-sided, significance level 2.5%.
[b] Cox proportional harzards model. Analysis with factor / covariates treatment, age, sex and country pool. One-sided p-value for superiority, significance level 2.5%.
CIC320 = ciclesonide 320 µg once daily, CIC320/F9 = ciclesonide/formoterol 320/9 µg once daily, CIC320/F18 = ciclesonide/formoterol 320/18 µg once daily, F18 = formoterol 18 µg once daily, ITT = intention-to-treat, N = number of patients in a treatment group, n = number of patients with lack of efficacy.

When Cox-proportional hazards regression was applied to analyze the time to the onset of the first LOE as a robustness analysis, both doses of the fixed combination ciclesonide/formoterol were superior to formoterol monotherapy, and CIC320/F18 was superior to ciclesonide monotherapy.

The increases in time-averaged $FEV_1$ over baseline after 2 weeks of treatment demonstrated the superiority of CIC320/F18 to CIC320 (0.155 L, one-sided p <0.0001), CIC320/F9 to CIC320 (0.153 L, one-sided p <0.0001), CIC320/F18 to F18 (0.110 L, one-sided p = 0.0014), and CIC320/F9 to F18 (0.108 L, one-sided p = 0.0018). None of the between-treatment comparisons indicated a difference between the various treatment groups for the pre-dose $FEV_1$ after 2 weeks of treatment.

*Secondary Variables*

When the time-averaged $FEV_1$ after 8 weeks of treatment was compared to T0, CIC320/F18 and CIC320/F9 was superior to F18 (0.099 L [p = 0.0107, one-sided] and 0.144 L [p = 0.0005, one-sided], respectively) and also to CIC320 (0.094 L [p = 0.0135, one-sided] and 0.139 L [p = 0.0006, one-sided], respectively). When the pre-dose $FEV_1$ after 8 weeks of treatment was compared to T0, CIC320/F9 was superior to F18 (0.172 L, p = 0.0056, one-sided). The change was numerically higher when CIC320/F18 and F18 were compared (0.112 L). Analysis of the time-averaged excess $FEV_1$ at 8 weeks demonstrated the superiority of CIC320/F18 and CIC320/F9 to CIC320 (0.216 and 0.200 L, respectively; each p <0.0001, one-sided), but not compared to F18.

Over the 8 week double-blind treatment period, superiority was demonstrated for both doses of the fixed combination over both monotherapy components for $peak_{0\text{-}3h}FEV_1$, morning home PEF, and the percentage of days with asthma control (based on asthma symptoms, rescue medication, morning home PEF and diurnal home PEF fluctuation). Both combinations were superior to F18 for morning $FEV_1$ and evening home PEF. CIC320/F9 was superior to F18 for FVC. CIC320/F9 was superior to F18 for nighttime symptoms and CIC320 for rescue medication use.

Safety results

*Baseline period*

In total, 19.2% patients experienced 105 AEs during the baseline period (ie under treatment with open label CIC320 µg). The most frequently reported were classed as nervous system disorders in 6.6% patients (thereof headache in 6.3% patients). AEs that occurred during the baseline period were assessed by the investigators as not related in 16.6% patients, as unlikely related in 1.3% and as likely related in 1.3%. Treatment related AEs were reported for five patients (1.3%): hypersensitivity, dysphonia, pharyngeal lesion, pharyngolaryngeal pain (in separate patients), and headache and dry skin (in another patient). AEs during the baseline period were generally mild (12.9% patients) in intensity. AEs of moderate and severe intensity were reported at a frequency of 5.8% and 0.5% patients, respectively.

**Frequency of baseline AEs (total set)**

| | CIC320 µg (N=380) |
|---|---|
| Number of patients (%)[a] with | |
| AEs | 73 (19.2) |
| SAEs: all | 0 (0.0) |
| deaths | 0 (0.0) |
| AEs with causality[b] suggested | |
| - by the investigator | 5 (1.3) |
| - by the sponsor | 5 (1.3) |
| AEs leading to discontinuation | 6 (1.6) |
| Changes in study medication due to AEs | 4 (1.1) |
| Changes in conc. medication due to AEs | 45 (11.8) |

[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.
CIC320 = ciclesonide 320 µg once daily, N = number of patients in the baseline period.

No deaths or other SAEs occurred during the baseline period. Six patients (1.6%) had AEs that led to study discontinuation (four cases of asthma, hypersensitivity, and aspiration).

*Double-blind treatment period*

The AEs occurring during the double-blind treatment period are summarized below:

**Frequency of AEs: double-blind treatment period (SAF)**

| | CIC320/F18 (N=70) | CIC320/F9 (N=68) | CIC320 (N=70) | F18 (N=68) | Total (N=276) |
|---|---|---|---|---|---|
| **Number of patients (%)[a] with** | | | | | |
| AEs | 30 (42.9) | 29 (42.6) | 34 (48.6) | 37 (54.4) | 130 (47.1) |
| SAEs: all | 3 (4.3) | 0 (0.0) | 0 (0.0) | 1 (1.5) | 4 (1.4) |
| deaths | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| AEs with causality[b] suggested | | | | | |
| - by the investigator | 4 (5.7) | 3 (4.4) | 4 (5.7) | 6 (8.8) | 17 (6.2) |
| - by the sponsor | 2 (2.9) | 2 (2.9) | 2 (2.9) | 5 (7.4) | 11 (4.0) |
| AEs leading to discontinuation | 2 (2.9) | 0 (0.0) | 1 (1.4) | 4 (5.9) | 7 (2.5) |
| AEs not yet known to be recovered | 2 (2.9) | 1 (1.5) | 3 (4.3) | 1 (1.5) | 7 (2.5) |
| Changes in study medication due to AEs | 2 (2.9) | 0 (0.0) | 1 (1.4) | 4 (5.9) | 7 (2.5) |
| Changes in conc. medication due to AEs | 24 (34.3) | 17 (25.0) | 22 (31.4) | 27 (39.7) | 90 (32.6) |

[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.
CIC320 = ciclesonide 320 µg once daily, CIC320/F9 = ciclesonide/formoterol 320/9 µg once daily, CIC320/F18 = ciclesonide/formoterol 320/18 µg once daily, F18 = formoterol 18 µg once daily, N = number of patients in a treatment group. SAF = safety set.

In total, 47.1% patients experienced 248 AEs during the double-blind treatment period: 77 AEs in 42.9% (CIC320/F18), 42 AEs in 42.6% patients (CIC320/F9), 61 AEs in 48.6% patients (CIC320), and 68 AEs in 54.4% patients (F18). The most frequently reported AEs during the double-blind treatment period were classed as infections and infestations

(26.4% patients). The investigator suggested a causal relationship to study medication (at least likely) for 6.2% patients who reported AEs during the double-blind treatment period: 5.7% patients for CIC320/F18, 4.4% patients for CIC320/F9, 5.7% patients for CIC320, and 8.8% patients for F18. One AE during the double-blind treatment period (throat irritation in the CIC320/F9 group) was assessed as definitely related by the investigator. The only at least likely related AEs occurring in more than one patient in a given treatment group were oral candidiasis (three patients [4.4%] for F18) and headache (two patients [2.9%] for CIC320/F18 and CIC320).

No deaths occurred during the double-blind treatment period. Three patients under treatment with CIC320/F18 (asthma, arteriosclerosis, and gastroenteritis) and one patient under treatment with F18 (epiglottitis) experienced an SAE during the double-blind treatment period. All SAEs were assessed as unrelated to study medication by both the investigator and the sponsor. Within 5 to 13 d after onset, the patients recovered from the SAEs without sequelae. Seven patients (2.5%) discontinued the study prematurely due to the occurrence of an AE during the double-blind treatment period: two patients (2.9%) under treatment with CIC320/F18, one patient (1.4%) under treatment with CIC320, and four patients (5.9%) under treatment with F18. With the exception of bronchitis (CIC320/F18), these were all AEs of asthma.

All baseline AEs and the vast majority (>90%) of AEs during the double-blind treatment period were reported as recovered without sequelae.

None of the laboratory abnormalities occurring during the baseline period were assessed as related to treatment by the investigator. One of the laboratory abnormalities occurring during the double-blind treatment period was reported as likely related by the investigator: increased CPK in the F18 group, which resolved without sequelae while the patient remained under study medication until the end of the trial.

**Conclusions:**

**Date of report:** **22-Jan-2007**