CLINICAL STUDY SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: CHF 5188 pMDI (pressurised inhalation solution)	**Volume:**	
Name of Active Ingredient: Fixed combination budesonide/carmoterol 200/1 µg per actuation	**Page:**	

Title of study:
Evaluation of cardiac safety, tolerability and efficacy of cumulative doses of CHF 5188 pMDI (fixed combination budesonide/carmoterol 200/1 µg) compared to same cumulative doses of carmoterol pMDI and placebo in asthmatic patients.
A monocentre, randomised, double-blind, 3-way, cross-over clinical study.

Principal Investigator: Professor [redacted]

Study centre: Single centre ([redacted])

Publication (reference): None

Studied period (years):	**Phase of development:** Phase II
First patient enrolled: 01 JUN 2007	
Last patient completed: 25 JUL 2007	

Objectives:

Primary objective
To establish the cardiac safety (corrected QT segment [QTcB] interval) and efficacy (forced expiratory volume in the first second [FEV_1]) of cumulative-doses of CHF 5188.

Secondary objectives
To evaluate the safety and tolerability of CHF 5188 given in cumulative doses.

Methodology:
A monocentre, cumulative-dose, randomised, double-blind, 3 treatments, 3 periods, active- and placebo-controlled, cross-over clinical study.

Number of patients *(planned and analysed)*:

***Planned*:**
Assuming a drop-out and non-evaluable patient rate of 20% and in order to have 18 completed patients at Visit 4, the total number of patients to be randomised was 24.

***Analysed*:**
A total of 38 patients were screened to take part in this study, 14 (36.8%) of whom were not eligible for inclusion and were not randomised. Twenty-four patients (100.0%) were included in the Total, Randomised, ITT and Safety populations. One patient (4.2%) was withdrawn

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from the study after randomisation and was excluded from the PP population. Hence, 23 patients (95.8%) who completed the 3 study periods without any major protocol deviations were included in the PP population.

Diagnosis and main criteria for inclusion:
Patients with a clinical diagnosis of persistent asthma according to the Global Initiative for Asthma (GINA) 2005 "Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment" were recruited if they also met the following inclusion criteria:

- Written informed consent given
- Male or female patients aged ≥ 18 and < 70 years
- Patients already treated with inhaled corticosteroids (ICS) at a stable dose for at least 4 weeks prior to inclusion
- Patients with FEV_1 less or equal to 90% of predicted for the patient normal value and not less than 0.9 L in absolute value
- Patients with a documented positive response to the reversibility test, defined as ΔFEV_1 ≥ 15% and ≥ 200 mL over baseline, 30 minutes after 200 µg salbutamol pressurised metered dose inhaler (pMDI)
- Patients with normal blood pressure (BP) (i.e. supine systolic blood pressure [SBP] ≤ 140mmHg, supine diastolic blood pressure [DBP] ≤ 90mmHg)
- Patients with normal electrocardiogram (ECG) with heart rate (HR) < 100 beats per minute (bpm) and QTcB interval ≤ 450 msec for males and ≤ 470 msec for females
- Patients with a co-operative attitude and ability to be trained to correctly use the pMDI.

Test product, dose and mode of administration, batch number:
CHF 5188 pMDI (Treatment A), a fixed combination of budesonide/carmoterol 200/1 µg per actuation, was administered via inhalation. Batch number: [redacted]. Expiry date: [redacted].

Duration of treatment:
Single cumulative doses. The study comprised of a run-in period of 2 to 7 days and 3 randomised treatment periods separated by wash-out periods of 5 to 7 days. Five cumulative doses were administered to each patient during each of the 3 treatment periods.

Reference therapy, dose and mode of administration, batch number
CHF 4226 pMDI (Treatment B), carmoterol, 1 µg/actuation, was administered via inhalation. Batch number: [redacted]. Expiry date: [redacted].
Placebo pMDI (Treatment C) contained the same excipients as the test product CHF 5188 pMDI and was administered via inhalation. Batch number: [redacted] Expiry date: [redacted].
Each canister of study drug (test product, reference treatment and placebo) contained

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60 inhalations/puffs.

The test product, reference treatment and placebo were administered in 5 cumulative doses (1+ 1 + 2 + 4 + 4 inhalations/puffs, 12 in total) in the morning separated by 30 minutes. The total cumulative dose per visit was 2400/12 µg of budesonide/carmoterol (CHF 5188 pMDI, Treatment A), 12 µg of carmoterol (CHF 4226 pMDI, Treatment B) or placebo.

Criteria for evaluation:

Efficacy

Primary efficacy variable

The primary efficacy variable was the FEV_1 percent change from pre-dose to 240 minutes after the first intake (i.e. 120 minutes after the last cumulative dose).

Secondary efficacy variables

The efficacy profile was completed through the assessment of:

- 8-hour average FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}), i.e. 8-hour area under the curve (AUC) standardised by time
- FEV_1 (L), FVC (L) and FEF_{25-75} (L/s) at all time points (values and changes)
- Peak FEV_1, FVC and FEF_{25-75}.

Safety

Primary safety variable

- Change in QTcB interval from pre-dose to 480 minutes after the first intake (i.e. 360 minutes after the last cumulative dose).

Secondary safety variables

- 8-hour average QTcB and QTcF (i.e. 8-hour AUC standardised by time)
- 8-hour average serum potassium
- 8-hour average serum glucose
- 8-hour average HR
- Serum potassium at all time points
- Serum glucose at all time points
- SBP and DBP in sitting position, at all the time points
- 12-lead ECG (including HR, QTc interval corrected by Bazett's and Fridericia's formula), at all time points
- Fine hand tremor evaluated by means of a 3-point scale (score from 0 to 2)

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- Adverse Events (AEs), and adverse drug reactions (ADRs)
- Laboratory Parameters.

Statistical methods:

Primary efficacy variable

The FEV_1 percent change from pre-dose to 240 minutes after the first intake was analysed using an analysis of covariance (ANCOVA) model, including patient as random effect, period and treatment as factors and pre-dose value as covariate, in order to make a formal comparison between treatment regimens.

Secondary efficacy variables

FEV_1, FVC, FEF_{25-75} values at all time points (i.e. pre-dose, 5, 25, 55, 85, 115, 150, 180, 240, 360, and 480 minutes after the first intake), their relative peaks, and changes from pre-dose to each post-dose time point were summarised by treatment period (A, B, C) by means of descriptive statistics. 95% confidence intervals (CIs) were also calculated for changes from pre-dose. Lung function parameters trends over time were plotted. The analyses of the lung function parameters, i.e. 8-hour average FEV_1, FVC, FEF_{25-75} (8-hour AUC standardised by time) and peak FEV_1, FVC, FEF_{25-75}, were performed using the same ANCOVA model as for the primary efficacy variable. The trapezoidal rule was used to calculate all 8-hour AUCs. The 8-hour AUCs standardised by time were calculated by dividing the AUC values by 8 hours.

Primary safety variable

The primary safety variable was the QTcB interval, defined as the change from pre-dose to 8 hours after the first dose intake. It was analysed using the same ANCOVA model as for the primary efficacy variable in order to make a treatment comparison.

Secondary safety variables

The proportions of patients experiencing AEs, AEs leading to withdrawal, ADRs and serious adverse events (SAEs), and serious ADRs were tabulated for each treatment period (A, B, C) by system organ class and preferred term according to the Medical Dictionary of Regulatory Activities (MedDRA, version 9.1). The AE analysis focused on treatment-emergent AEs (TEAEs), i.e. AEs that occurred after Visit 2 or at Visit 2 after the study drug administration. The incidence of TEAEs was summarized by treatment using descriptive statistics, both in terms of frequency of patients with at least one TEAE and the frequency of TEAEs. Each TEAE was assigned to a treatment according to the start date of the TEAE. It was also specified whether the TEAE occurred on the day of the visit or during the following wash-out

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period.

Laboratory parameters, 12-lead ECG (including HR, QTcB and QTcF intervals), serum potassium, serum glucose, SBP, DBP in sitting position, fine hand tremor at all time points as well as 8-hour average (i.e. 8-hour AUC standardised by time) for QTcB, QTcF, serum potassium, serum glucose and HR were summarised by treatment period (A, B, C) using descriptive statistics. Treatments were compared by means of an ANCOVA model similar to the one used for the efficacy variables. Shift tables from baseline to each visit, with regard to normal range (low, normal, high), were constructed for the relevant safety parameters as well as shift tables crossing category of QTc (QTcB and QTcF) increase by HR increase.

Urine data generated by the Chiesi Farmaceutici pharmacokinetic department to identify carmoterol metabolites were not analysed statistically.

Summary – Conclusions

Four patients were randomised to each of the 6 treatment sequences. Similar baseline characteristics across treatment sequences were observed. Eight male patients (33.3%) and 16 female patients (66.7%) took part in this study. The mean age of patients was 34.7 ± 9.7 years (range: 18.7 to 54.3 years). The mean height, weight and body mass index (BMI) of patients were 169 ± 11 cm (range: 153 to 193 cm), 78.14 ± 19.69 kg (range: 55.70 to 127.40 kg) and 27.32 ± 6.03 kg/m^2, respectively. Twenty-four patients (100.0%) took the correct doses of placebo and 23 patients (95.8%) took the correct doses of CHF 5188 and CHF 4226. No patients with major protocol deviations were observed in this study and minor protocol deviations were only observed in 3 patients (12.5%). Patient [redacted] was withdrawn from the study after receiving placebo and did not receive treatment with CHF 5188 or CHF 4226.

Efficacy results:

In the ITT population, at 240 minutes after first intake, greater mean percent changes in FEV_1 (least square mean [LS mean] ± standard error of the mean [SEM]) were obtained in patients following treatment with CHF 5188 (28.70 ± 2.58%) or CHF 4226 (29.39 ± 2.58%) as compared with placebo (7.48 ± 2.53%). The difference between CHF 5188 and placebo in terms of percent change in FEV_1 from pre-dose to 240 minutes after first intake was highly statistically significant ($p < 0.001$), whereas there was no significant difference between CHF 5188 and CHF 4226. Similar results were observed for each of the lung function parameters assessed: greater increases in FEV_1, FVC and FEF_{25-75} (actual values and percent changes) were observed after treatment with CHF 5188 and CHF 4226 compared with placebo and similar increases were observed in the two active treatments. In general, these

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increases were shown at each post-dose time point, peaked at around 240 minutes after first intake and were still evident 480 minutes after first intake. For each secondary efficacy endpoint, the difference between CHF 5188 and placebo was highly statistically significant ($p < 0.001$), whereas the difference between CHF 5188 and CHF 4226 was not. The LS means (± SEM) observed for the secondary lung function parameters after treatment were as follows:

	CHF 5188 N = 24	CHF 4226 N = 24	Placebo N = 24
8-hour average FEV_1 (L)	2.98 (0.05)	2.97 (0.05)	2.50 (0.05)
Peak FEV_1 (L)	3.10 (0.06)	3.09 (0.06)	2.62 (0.06)
8-hour average FVC (L)	4.07 (0.05)	4.09 (0.05)	3.82 (0.05)
Peak FVC (L)	4.22 (0.05)	4.22 (0.05)	3.95 (0.05)
8-hour average FEF_{25-75} (L/s)	2.38 (0.07)	2.33 (0.07)	1.68 (0.07)
Peak FEF_{25-75} (L/s)	2.61 (0.08)	2.56 (0.08)	1.85 (0.08)

Sources: Section 14.2.2.1, Tables 29 and 30; Section 14.2.2.2, Tables 40 and 41; Section 14.2.2.3, Tables 50 and 51.

Results observed in the PP population were consistent with those in the ITT.

Safety results:

Adverse Events

No deaths or SAEs occurred during the study. One patient (4.2%) was prematurely withdrawn as a consequence of 2 TEAEs: Patient [redacted] experienced moderate upper and lower respiratory tract infections. Overall, 23 patients (95.8%) experienced a total of 83 TEAEs, of whom 21 patients (87.5%) experienced a total of 66 ADRs. The incidence of TEAEs was higher after treatment with CHF 5188 (21 patients, 53 TEAEs) compared with CHF 4226 (13 patients, 20 TEAEs) and placebo (7 patients, 10 TEAEs). The incidence of ADRs was also higher after treatment with CHF 5188 (20 patients, 47 ADRs) compared with CHF 4226 (11 patients, 16 ADRs) and placebo (3 patients, 3 ADRs). The most commonly observed TEAEs by system organ class belonged to nervous system disorders and investigations. More patients experienced at least 1 TEAE belonging to the nervous system disorders class after receiving CHF 5188 (78.3%), when compared with CHF 4226 (13.0%) and placebo (4.2%). More patients experienced at least 1 TEAE in the investigations system organ class after treatment with CHF 5188 (43.5%) or CHF 4226 (39.1%), when compared with placebo (16.7%). The most frequently occurring TEAEs by preferred term were dysgeusia and serum

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potassium decreased. The incidence of dysgeusia was much higher following treatment with CHF 5188 (78.3%) compared with CHF 4226 (8.7%) and placebo (0%). The incidence of serum potassium decreased was higher following treatment with CHF 5188 (39.1%) or CHF 4226 (34.8%) compared with placebo (4.2%). Serum glucose increased occurred slightly more often following treatment with CHF 5188 (13.0%) compared with CHF 4226 (4.3%) and placebo (0%). Sinus tachycardia occurred following treatment with CHF 5188 (13.0%) and tachycardia occurred following treatment with CHF 5188 (4.3%) and CHF 4226 (4.3%). The frequency of serum triglycerides increased was slightly higher after treatment with placebo (12.5%) than after treatment with CHF 5188 (0%) or CHF 4226 (4.3%). The incidence rates of the remaining TEAEs that occurred during the study (by preferred term) were relatively well balanced with regard to the 3 study treatment periods. In total, 4 patients (17.4%) experienced TEAEs of interest (tremor, cough, dysphonia or throat irritation) following CHF 5188 treatment and 1 patient (4.3%) experienced tremor following CHF 4226 treatment. The majority of TEAEs (95.2%) experienced by patients during this study were mild or moderate in intensity. Three patients (13.0%) experienced a total of 4 severe TEAEs after treatment with CHF 5188: dysgeusia (3 patients) and nausea (1 patient). All severe TEAEs observed were ADRs. The majority of TEAEs experienced by patients resolved spontaneously by the end of the study without corrective interventions.

Cardiac Safety

A larger increase in QTcB interval (LS mean ± SEM) at 480 minutes after first intake was observed after patients were treated with CHF 5188 (16.63 ± 3.25 msec) or CHF 4226 (14.42 ± 3.25 msec), than with placebo (4.18 ± 3.18 msec). The difference between CHF 5188 and placebo was statistically significant ($p = 0.003$) whereas the difference between CHF 5188 and CHF 4226 was not. In contrast, negligible decreases in mean QTcF interval were observed at 480 minutes post-dose following treatment with CHF 5188 (-0.33 ± 2.14 msec) and CHF 4226 (-0.41 ± 2.14 msec), as well as with placebo (-4.95 ± 2.10 msec).

Considering the mean changes in QTcB intervals over time the largest increases were observed at 240 minutes after the first intake of CHF 4226 (24.95 ± 3.43 msec) or placebo (7.73 ± 3.38 msec), whereas the largest mean change in QTcB interval after intake of CHF 5188 occurred at 360 minutes (19.82 ± 3.36 msec). These changes were concomitant with the largest increases in HR which were observed at 240 minutes after the first intake of CHF 4226 (14.6 ± 1.6 bpm) and at 360 minutes after the first intake of CHF 5188 (18.4 ± 1.6 bpm). In contrast, the largest mean increase in HR following treatment with placebo was observed at 480 minutes after first intake (8.6 ± 1.8 bpm). Considering the mean changes in QTcF intervals over time, the largest increase was observed at 180 minutes after the first

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intake of both CHF 5188 (11.68 ± 2.44 msec) and CHF 4226 (12.92 ± 2.39 msec), whereas the largest mean change in QTcF interval after intake of placebo (7.28 ± 2.02 msec) was observed at 150 minutes. The 8-hour average QTcB and QTcF intervals were significantly higher following CHF 5188 treatment compared with placebo ($p \leq 0.044$), whereas there were no significant differences between the CHF 5188 and CHF 4226 treatments. The 8-hour average HR was significantly higher following treatment with CHF 5188 in comparison with both placebo and CHF 4226 ($p \leq 0.046$).

The majority of patients had a decrease or an increase in QTcB interval of ≤ 10 msec (CHF 5188: 10 patients [41.7%]; CHF 4226: 5 patients [20.8%]; placebo: 16 patients [66.7%]) and a decrease or an increase in QTcF interval of ≤ 10 msec (CHF 5188: 15 patients [62.5%]; CHF 4226: 20 patients [83.3%]; placebo: 23 patients [95.8%]) after treatment. Five patients (20.8%), 16 patients (66.7%) and 8 patients (33.3%), respectively, had an increase in QTcB interval of between 10 and 30 msec following treatment with CHF 5188, CHF 4226 and placebo, and most of these increases were concomitant with HR increases of ≥ 10 bpm. Seven patients (29.2%), 3 patients (12.5%) and 1 patient (4.2%), respectively, had an increase in QTcF interval of between 10 and 30 msec following treatment with CHF 5188, CHF 4226 and placebo, and these increases mostly occurred concomitantly with HR increases of ≥ 10 bpm. Seven patients (29.2%) and 2 patients (8.3%), respectively, presented with an increase in QTcB interval of between 30 and 60 msec following treatment with CHF 5188 and CHF 4226, together with HR increases of ≥ 10 bpm. One patient (4.2%) presented with an increase in QTcF interval of between 30 and 60 msec following treatment with CHF 5188, concomitantly with a HR increase of ≥ 10 bpm. One patient (4.2%) presented with an increase in QTcB interval of ≥ 60 msec following treatment with CHF 5188, concomitantly with a HR increase of ≥ 10 bpm, but this increase was not outside the normal range for QTcB interval in female patients. The majority of male and female patients had QTcB and QTcF intervals < 450 msec and < 470 msec, respectively, following study drug administration. No significant differences in mean DBP and SBP were observed between treatments from pre-dose to 480 minutes after first intake.

Laboratory findings and other safety assessments

8-hour average serum potassium concentration was significantly lower after CHF 5188 treatment compared with placebo ($p < 0.001$), whereas there was no significant difference between CHF 5188 and CHF 4226. 8-hour average serum glucose concentration was significantly higher after CHF 5188 treatment compared with both placebo and CHF 4226 ($p < 0.001$). In haematology and biochemistry tests conducted at Visits 1 and 4, there were no remarkable differences between treatments with regard to the number of patients who had

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abnormal non-clinically significant and abnormal clinically significant laboratory data. There was also a relatively low incidence of individual clinically significant shifts.

The majority of patients experienced no tremor at all after treatment with placebo. One patient (4.3%) had severe hand tremor at 360 and 480 minutes following CHF 5188 treatment, whereas no patients had severe hand tremor after treatment with CHF 4226 or placebo.

The LS means (± SEM) observed for the secondary safety parameters after treatment were as follows:

	CHF 5188 N = 24	CHF 4226 N = 24	Placebo N = 24
8-hour average serum potassium concentration (mmol/L)	3.69 (0.05)	3.63 (0.05)	3.95 (0.05)
8-hour average serum glucose concentration (mmol/L)	6.83 (0.16)	6.15 (0.16)	5.13 (0.16)
8-hour average QTcB interval (msec)	428.24 (2.08)	428.00 (2.08)	417.85 (2.07)
8-hour average QTcF interval (msec)	416.97 (1.43)	418.03 (1.43)	413.61 (1.42)
8-hour average HR (bpm)	71.46 (1.05)	69.43 (1.06)	64.26 (1.05)

Sources: Section 14.3.2.1, Tables 69, 82, and 94; Section 14.3.2.3, Tables 136 and 150.

Conclusions:

- Treatment with cumulative doses of the combination therapy budesonide/carmoterol 200/1 µg (CHF 5188) was statistically significantly more effective than placebo in improving lung function in terms of standard spirometric tests (FEV_1, FVC and FEF_{25-75}) up to 480 minutes following the first intake of study medication.
- The improvements in lung function observed after cumulative doses of budesonide/carmoterol 200/1 µg (CHF 5188, total dose: 2400/12 µg) were comparable with the results observed after cumulative doses of carmoterol 1 µg alone (CHF 4226, total dose: 12 µg). Both treatments induced clinically relevant improvements in patients' lung function with a rapid onset of action.
- Higher incidence rates of TEAEs and ADRs were observed following cumulative doses of budesonide/carmoterol 200/1 µg (CHF 5188) in comparison with cumulative doses of carmoterol 1 µg alone (CHF 4226) and placebo.
- Dysgeusia and serum potassium decreased were the most frequently occurring TEAEs. Dysgeusia occurred most often after treatment with CHF 5188 (78.3%) compared with

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CHF 4226 (8.7%) and placebo (0%), whereas serum potassium decreased occurred more often after treatment with CHF 5188 (39.1%) or CHF 4226 (34.8%) compared with placebo (4.2%). The high incidence of dysgeusia after treatment with CHF 5188 might be partly explained by the use of a high dose of budesonide and the fact that patients did not rinse their mouths after inhalation of the drug.

- Sinus tachycardia occurred following treatment with CHF 5188 (13.0%) and tachycardia occurred following treatment with CHF 5188 (4.3%) and CHF 4226 (4.3%).
- Four patients (17.4%) experienced TEAEs of interest (tremor, cough, dysphonia or throat irritation) following CHF 5188 treatment and 1 patient (4.3%) experienced tremor following CHF 4226 treatment.
- Treatment with CHF 5188 led to a statistically significant increase in mean QTcB interval at 480 minutes after the first intake of study medication as compared with placebo, whereas there was no statistically significant difference in mean QTcB intervals observed in patients following treatment with CHF 5188 and CHF 4226. Similar results were also observed in the assessments of 8-hour average QTcB and QTcF intervals. In contrast, at 480 minutes post-dose there were no significant differences in mean QTcF intervals following treatment with CHF 5188, CHF 4226 or placebo. In terms of ECG parameters, the cardiac safety of budesonide/carmoterol at cumulative doses of 2400/12 (CHF 5188) and carmoterol at cumulative doses of 12 µg (CHF 4226) were comparable.
- Treatment with budesonide/carmoterol 200/1 µg (CHF 5188) led to a statistically significant decrease in serum potassium concentration as compared with placebo and a statistically significant increase in serum glucose concentration as compared with both placebo and carmoterol 1 µg (CHF 4226).

Date of report: 22 APR 2008