2. 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 200/2 µg per actuation	**Page:**	

Title of Study: A single-centre, randomised, double-blind, double dummy, placebo and active-controlled, 3-way cross-over study to evaluate the 24 hour FEV_1 profile of a single dose of the CHF 5188 pMDI (400/4µg once daily) (Fixed combination Budesonide/Carmoterol 200/2µg) in adult patients with moderate or severe persistent asthma.

Investigators: Professor [redacted]

Study Centre(s): [redacted]

Publication (reference): No publications at time of reporting

Studied Period:	**Phase of development: II**
1 October 2008 to 5 January 2009	

Objectives: The primary objective of the study was to demonstrate that CHF5188, given once daily in the morning to moderate or severe asthmatic patients, maintains the bronchodilator effect over the 24 hour dosing interval.

The secondary objectives were:

- To compare the efficacy of CHF5188 with that of Symbicort® (budesonide/formoterol) 200/6 µg given twice daily (TDD 400/12 µg)
- To monitor safety and tolerability

Methodology *(Study Design):* This was a Phase II, single centre, randomised, double-blind, double-dummy, placebo- and active-controlled (Symbicort® 400/12µg), 3-way crossover, single dose study in asthmatic patients.

A total of 4 clinic visits were performed during the study: a screening visit (V1), followed by a run-in period of 3 to 14 days, and 3 study visits (V2, V3, V4) separated by a 5 to 7 days wash-out period.

- Visit 1 (V1): screening visit;

- Visit 2 (V2): randomisation visit, 1st treatment period;
- Visit 3 (V3): 2nd treatment period;
- Visit 4 (V4): 3rd treatment period.

At each treatment period, the patient received one of the following three treatments:

- Treatment A: CHF 5188 400/4 µg once daily;
- Treatment B: budesonide/formoterol (Symbicort®), 200/6 µg twice daily;
- Treatment C: placebo.

The screening visit established the eligibility of patients for inclusion in the study (routine haematology and blood chemistry, serum pregnancy testing, if applicable, medical history, physical examination, 12-lead electrocardiogram (ECG), spirometry and inclusion/exclusion criteria).

At V2, V3 and V4 pre- and post-dose vital signs, pre-dose spirometry (T-1h and T-10min) and post-dose 24 hour spirometry (T1h, T2h, T3h, T6h, T10h, T12h, T14h, T16h, T22h, T23h and T24h) were evaluated.

Adverse events (AEs) and serious AEs (SAEs) were monitored

Number of patients *(planned and analysed)*: Assuming a drop-out and/or non-evaluable patient rate of 20% and in order to have 34 completed patients, the total number of planned randomised patients was 42. A total of 38 patients were randomised to one of the six possible treatment sequences at the first randomised period (Visit 2). The intent-to-treat (ITT) population consisted of 38 randomised patients who received at least one dose of study medication and had at least one post-baseline efficacy evaluations for a given treatment period. One patient had their data excluded from the per-protocol (PP) population as they were taking an oral corticosteroid for a treatment emergent AE of lower respiratory tract infection.

Diagnosis and main criteria for inclusion: Outpatients with moderate or severe asthma, not optimally controlled and receiving a stable dose of corticosteroid, attending the hospital clinic were considered for inclusion. To be eligible for the study, patients must have had forced expiratory volume in the first second (FEV_1) ≥50% and ≤90% of predicted patient's normal value and not less than 0.9L in absolute value. The patients must have had a positive response to salbutamol, defined as an increase of at least 12% and of at least 200 mL in the FEV_1 measurements within 30 minutes from intake, to be included in the study.

Test product, dose and mode of administration, batch number:

CHF 5188: budesonide/carmoterol (200/2 µg) – Inhaled

Batch Number: [redacted] **Expiry date:** [redacted]

Duration of treatment: Once daily, single day dosing, 2 puffs, total daily dose 400/4 µg

Reference therapy, dose and mode of administration, batch number:

Symbicort® Turbuhaler®: Budesonide/formoterol, 200/6 µg - Inhaled

Batch Number: [redacted]**; Expiry date:** [redacted]

Duration of treatment: Twice daily, single day dosing, total daily dose 400/12 µg

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Criteria for evaluation:

Efficacy: The primary efficacy variable was the trough FEV_1 (mean 23h-24h FEV_1)

Secondary variables were FEV_1 AUC_{0-24}, AUC_{0-12}, AUC_{12-24} all standardised by time; FVC and FEF_{25-75} AUC_{0-24}, AUC_{0-12}, AUC_{12-24} all standardised by time; Trough FVC and FEF_{25-75}; peak FEV_1, FVC and FEF_{25-75}; FEV_1, FVC and FEF_{25-75} absolute and percent changes from pre-dose at each time point; differences between active treatments and placebo in FEV_1, FVC and FEF_{25-75} absolute changes from baseline; FEV_1, FVC and FEF_{25-75} absolute and percent FEV_1, FVC and FEF_{25-75} change from pre-dose to trough and peak values.

Safety: Safety was assessed by monitoring adverse events (AEs), adverse drug reactions (ADRs), vital signs (heart rate and blood pressure) and ECG.

Statistical methods: Descriptive statistics were presented for all the efficacy and safety variables, for the ITT and safety populations respectively.

Mixed model, including treatment and period as fixed effects, patient as random effect and pre-dose value as covariate were used to compare treatment groups when analysing continuous outcomes. The least squares (LS) means for treatment effects and the relative 95% CIs were presented.

The assessment of superiority was evaluated by calculating the bilateral 95% CI and the p-value for the difference between the LS means for CHF 5188 and placebo from the mixed model. CHF 5188 was to be claimed as superior to placebo if the difference was statistically significant (p-value ≤ 0.05). No adjustment for multiple comparisons was done for the primary efficacy variable as comparisons between CHF 5188 and Symbicort®, and for Symbicort® and placebo were considered as secondary comparisons.

Based on the above described mixed model, bilateral 95% CIs and p-values for the differences between the LS means for CHF 5188 and Symbicort®, and for Symbicort® and placebo were calculated.

Summary – Conclusions:

Efficacy Results:

CHF5188 was superior to placebo for the primary efficacy variable trough FEV_1. (LS mean difference: 0.26 L; 95% CI: 0.17-0.35 L, p<0.001; ITT population). This finding was supported by the results for the secondary efficacy variables as shown in the table below for the ITT population. The effect of CHF5188 400/4µg given once daily was also comparable to Symbicort® 200/6µg given twice daily.

Parameter	LS Mean Treatment Difference (CHF5188-Placebo) [95% CI]; p-value	LS Mean Treatment Difference (CHF5188-Symbicort®) [95% CI]; p-value
FEV_1		
Trough	0.26 L [0.17-0.35]; p<0.001	0.05 L [-0.02, 0.12]; p=0.170
Peak	0.39 L [0.31-0.48]; p<0.001	0.16 L [0.09, 0.22]; p<0.001
AUC_{0-12}	0.47 L [0.39-0.56]; p<0.001	0.25 L [0.16, 0.34]; p<0.001
AUC_{12-24}	0.37 L [0.28-0.46]; p<0.001	0.05 L [-0.01, 0.11]; p=0.115
AUC_{0-24}	0.42 L [0.34-0.50]; p<0.001	0.15 L [0.08, 0.22]; p<0.001
FVC		
Trough	0.17 L [0.04-0.30]; p=0.013	0.03 L [-0.08, 0.15]; p=0.572
Peak	0.26 L [0.12-0.40]; p<0.001	0.07 L [-0.11, 0.25];p=0.448
AUC_{0-12}	0.32 L [0.20-0.44]; p<0.001	0.12 L [-0.00, 0.24]; p=0.057
AUC_{12-24}	0.25 L [0.14-0.36]; p<0.001	0.02 L [-0.08, 0.13]; p=0.641
AUC_{0-24}	0.29 L [0.17-0.40]; p<0.001	0.07 L [-0.04, 0.18]; p=0.198
FEF_{25-75}		
Trough	0.31 L/sec [0.17-0.44]; p<0.001	0.07 L/sec [-0.06, 0.20]; p0.314
Peak	0.62 L/sec [0.47-0.77]; p<0.001	0.23 L/sec [0.12, 0.34]; p<0.001
AUC_{0-12}	0.63 L/sec [0.49-0.77]; p<0.001	0.33 L/sec [0.20, 0.46]; p<0.001
AUC_{12-24}	0.44 L/sec [0.32-0.56]; p<0.001	0.04 L/sec [-0.05, 0.14] p=0.367
AUC_{0-24}	0.54 L/sec [0.42-0.65]; p<0.001	0.17 L/sec [0.08, 0.26]; p<0.001

The change from pre-dose FEV_1, FVC and FEF_{25-75} was greater after treatment with CHF5188 than after placebo at all time points during the dosing interval. The change from pre-dose FVC, pre-dose FEV_1 and pre-dose FEF_{25-75} was generally greater after treatment with CHF5188 than with Symbicort® at all time points during the dosing interval. The results of the sensitivity analysis (FEV_1 AUC_{0-12}, AUC_{12-24}, AUC_{0-24}) to evaluate the influence of rescue medications taken during the visit, were entirely consistent with that of the overall study result.

Safety Results: Treatment emergent AEs were reported in 8 patients (21.1%) after treatment with CHF5188, in 5 patients (13.2%) after treatment with Symbicort® and in 10 patients (27.0%) after placebo. Adverse drug reactions were reported in 6 patients (15.8%) after treatment with CHF5188, in 5 patients (13.2%) after treatment with Symbicort® and in 3 patients (8.1%) after placebo. There were no SAEs and only one severe AE, which occurred in a patient after the treatment period with placebo. The only withdrawal due to an AE was in a patient after treatment with CHF5188. The most common ADR was headache, occurring in 5 patients (13.2%) after treatment with CHF5188, in 4 patients (10.5%) after treatment with Symbicort® and in 3 patients (8.1%) after placebo. There were no notable differences in vital signs or ECG between treatment groups.

Conclusion:

CHF5188 400/4µg given once daily maintained a bronchodilator effect over the 24 hour dosing interval when given as a single dose in the morning to moderate or severe asthmatic patients. The effect of CHF5188 on lung function parameters was superior to placebo and comparable to Symbicort® 200/6µg administered twice-a-day. A single dose of CHF5188 400/4µg was well tolerated.

Date of report: 15 July 2009