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	**Volume:**	
Name of Active Ingredient: Budesonide / carmoterol	**Page:**	

Title of Study: A randomised, double-blind, active-controlled, 3-way cross-over study to evaluate the effect on trough FEV_1 after 4 weeks treatment with CHF 5188 pMDI qd (fixed combination budesonide / carmoterol) in adult patients with moderate or severe persistent asthma

Coordinating Investigator: Dave Singh, MD, Wythenshawe Hospital, Manchester, UK

Study Centre(s): 13 centres in 3 countries; Germany (5 centres), UK (4 centres), Poland (4 centres)

Publication (reference): None

Studied Period:	**Phase of development:**
FPFV: 11 January 2010 LPLV: 22 June 2010	Phase II

Objectives:

Primary objective:

To demonstrate superiority of the fixed combination CHF 5188 pMDI 400/4 µg administered once-a-day in the morning over budesonide extrafine pMDI on trough FEV_1 after 4 weeks of treatment in persistent moderate or severe asthmatic patients partly controlled with ICS or ICS/LABA.

Secondary objectives:

- To compare the efficacy of CHF 5188 pMDI given once-a-day with that of Seretide® Evohaler® pMDI 50/25 µg administered twice-a-day after 4 weeks of treatment
- To assess the occurrence of tolerance by comparing the effect on trough and peak FEV_1 after the first and the last dose of study drug
- To monitor safety and tolerability

Methodology *(Study Design):*

This was an international, multicentre, randomised, double-blind, double-dummy, active-controlled, three-way cross-over, multiple dose Phase II study performed in patients with moderate or severe persistent asthma.

Three treatments were tested: CHF 5188 (budesonide/carmoterol) pMDI 400/4 µg once daily, budesonide extrafine pMDI 200 µg twice daily (budesonide), and Seretide® (fluticasone/salmeterol) Evohaler® pMDI 100/50 µg twice daily.

Patients had a 14 ± 2 day run-in period with budesonide then received consecutively the three randomised treatments of 4 weeks each. A wash-out period of 7 ± 2 days with budesonide was implemented between each treatment.

Number of patients (planned and analysed):

Population	N patients (%)	CHF 5188	Budesonide	Seretide®
Randomised	122 (100.0%)	119	118	119
Safety	122 (100.0%)	119	118	119
Intent-To-Treat	122 (100.0%)	119	118	119
Per Protocol *	121 (99.2%)	117	111	116
Extended Per Protocol	101 (82.8%)	101	101	101

* Definition is applied to any one treatment group

Diagnosis and main criteria for inclusion:

Patients could be enrolled into the run-in period if they met all of the following criteria:

1. Written informed consent obtained;
2. Male or female patients aged ≥ 18 years;
3. Patients with moderate or severe asthma partly controlled with ICS or ICS/LABA at a stable dose for at least 8 weeks prior to inclusion, according to the GINA 2008 “Management Approach Based On Control" recommendations;
4. Patients with Forced Expiratory Volume in the first second (FEV_1) ≥60% and ≤90% of predicted for the patient normal value;
5. Patients with a documented positive response to the reversibility test, defined as an increase of at least 12% and at least 250 mL from pre-dosing values in the measurement of FEV_1 within 30 minutes after the inhalation of 400 µg salbutamol pMDI;

Patients could not participate if they had a COPD diagnosis, were current or ex-smokers (>5 pack-years <1 year of study start), history of serious asthma complications or seasonal variation, a clinically significant ECG abnormality, or clinically significant and uncontrolled concomitant disease, or used any of the following medications within the specified time period: systemic corticosteroids (4 weeks), depot injectable corticosteroids (8 weeks), short-acting β_2-agonists (6 hours), long-acting β_2-agonists (24 hours), short-acting anticholinergics (12 hours), leukotriene modifiers (4 weeks), fixed combinations of an anti-cholinergic and short-acting β_2-agonist (12 hours), oral or nebulised bronchodilators (4 weeks), nebulised corticosteroids (4 weeks), sodium cromoglycate or nedocromil sodium (4 weeks).

Patients were randomised if they fulfilled all inclusion/exclusion criteria, had used only permitted concomitant medication during the run-in and did not have increased asthma symptoms or rescue salbutamol use.

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

CHF 5188 pMDI (fixed combination budesonide/carmoterol), 200/2 µg x 2 puffs qd (Total Daily Dose: 400/4 µg)

Morning: 2 puffs CHF 5188 + 2 puffs placebo Evohaler® pMDI

Evening: 2 puffs placebo pMDI +2 puffs placebo Evohaler® pMDI

Treatment was administered every day for 4 weeks.

Batch No.: CHF 5188: [redacted] Expiry date: [redacted]

Placebo: [redacted], Expiry date: [redacted]

Duration of treatment:

Each patient had a run-in period of 2 weeks following screening and was randomised on Day 1 of the first planned treatment. Patients were to receive three 4-week treatment-periods, each of which was separated by a 1-week wash-out period. Patients were thus on-study for a total of 16 weeks.

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

Budesonide extrafine pMDI 200 µg x 1 puff bid (TDD: 400 µg)

Morning: 1 puff budesonide + 1 puff placebo pMDI + 2 puffs placebo Evohaler® pMDI

Evening: 1 puff of budesonide I + 1 puff placebo pMDI + 2 puffs placebo Evohaler® pMDI

Treatment was administered every day for 4 weeks.

Batch No.: Budesonide: [redacted] Expiry date: [redacted]

Placebo: [redacted], Expiry date: [redacted]

Seretide® Evohaler® pMDI (fixed combination fluticasone/salmeterol 50/25 µg x 2 puffs bid (TDD: 200/100 µg)

Morning: 2 puffs placebo pMDI + 2 puffs Seretide®

Evening: 2 puffs placebo pMDI + 2 puffs Seretide®

Treatment was administered every day for 4 weeks.

Batch No.: Seretide®: [redacted], Expiry date: [redacted]

Placebo: [redacted] Expiry date: [redacted]

Criteria for evaluation:

Efficacy:

Primary efficacy endpoint:

- Trough FEV_1 after Day 28 dose (mean 23h-24h values)

Secondary efficacy endpoints:

- Trough FEV_1 and Forced Vital Capacity (FVC) after Day 1 dose (mean 23h-24h values)
- Trough FVC after Day 28 dose (mean 23-24h values)
- Peak FEV_1 and FVC on Day 1 and Day 28
- FEV_1 $AUC_{0\text{-}24,\ 0\text{-}12,\ 12\text{-}24}$ standardised by time after Day 1 and Day 28 study drug intake
- Asthma symptoms, reliever medication and asthma control

Safety:

- Adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), serious adverse drug reactions (SADRs)
- Vital signs (HR and BP)
- Routine laboratory tests and ECGs

Statistical methods:

Descriptive statistics (mean, SD, median, minimum and maximum for continuous variables and frequency count for categorical variables) were calculated for each variable by treatment group. For within-group analyses, the 95% confidence interval (CI) for mean changes from baseline was calculated.

Sample size

With a two-sided significance level fixed at 5%, a sample size of 90 evaluable patients was needed to ensure 80% power to detect a difference of at least 0.090 L between CHF 5188 and budesonide for the primary efficacy variable (trough FEV_1), with an estimated standard deviation of differences equal to 0.300 L (based on data from previous trials). A 20% drop-out/non-evaluable rate was assumed, and thus 113 randomised patients were planned.

Efficacy analysis

The primary analysis was a comparison between CHF 5188 and budesonide in terms of trough FEV_1 using an ANCOVA model, including pre-dose FEV_1 as a covariate, treatment and period as factors and patients as random effect.

If the difference between treatments was significantly in favour of CHF 5188 ($p<0.05$), then its superiority over budesonide was demonstrated.

Comparisons between CHF 5188 and Seretide®, and between Seretide® and budesonide were secondary, so no adjustment for multiple comparisons was made.

Safety analyses

Incidence of AEs, SAEs, ADRs and SADRs were compared between treatments using the McNemar test.

Summary – Conclusions:

Eight (6.6%) of the 122 randomised patients discontinued prematurely (5 withdrew consent, 2 due to AEs, 1 due to a protocol violation). Twelve patients (9.8%) had major on-study deviations.

Patient demographics and medical history were consistent with patients having moderate to severe asthma. Mean screening (visit 1) value for FEV_1 was 2.41 L ± 0.64 being 72.3% ± 7.4% (range 60.1%-89.9%) of the patient‟s nomal predicted value.

Efficacy Results:

ANCOVA mixed model analyses comparing LS means of the treatment difference for primary and secondary endpoints are described below.

The primary efficacy analysis to test the superiority of CHF 5188 over budesonide in terms of trough FEV_1 at Day 28 did not show CHF 5188 to be superior in any of the efficacy populations (ITT p=0.763; PP p=0.895, extended PP p=0.831). Secondary efficacy analysis showed CHF 5188 was significantly superior to budesonide for trough FEV_1 at Day 1 ($p <0.001$).

Seretide® was significantly superior to budesonide for trough FEV_1 at both Day 1 and Day 28 ($p<0.001$).

CHF 5188 and Seretide® were significantly superior to budesonide for peak FEV_1 at Days 1 and 28 (both $p < 0.001$). Seretide® was significantly superior to both CHF 5188 and budesonide in time averaged FEV_1 over 24 h at Day 1 ($p=0.045$ and $p<0.001$ respectively) and Day 28 ($p=0.005$ and $p<0.001$ respectively). The main difference of Seretide® over CHF 5188 was seen in the AUC_{12-24} period.

A larger but non-significant decrease in mean trough FEV_1 values from Day 1 to Day 28 was seen with CHF 5188 compared to Seretide® whilst the decrease in mean peak FEV_1 values was similar. This reflects a certain degree of broncho-tolerance with the two ICS/LABA combinations which was more pronounced at the end of the dosing interval. Clinical symptoms improved with all three treatments during the 2 weeks after treatment start, maintained during the third and fourth weeks of treatment. Improvement was comparable for CHF 5188 and Seretide®, being approximately twice that of budesonide, with reductions in overall asthma scores (mean reduction of 1.0 ± 2.1 with CHF 5188 versus 0.4 ± 3.2 with budesonide), number of puffs of rescue medication over a 2-week period (0.6 ± 1.3 versus 0.3 ± 1.3 respectively), percent of time requiring rescue medication (18.5% ± 29.4% versus 9.9% ± 29.9% respectively), and asthma control days (17.8% ± 28.2% versus 9.7% ±26.4% respectively).

Safety Results:

Treatment compliance and exposure were high with 93.4% of patients completing the planned 28-day treatments for all three therapies.

AEs were reported in 31.1% of patients during CHF 5188 or Seretide® treatment and 22.0% with budesonide. Treatment with CHF 5188 did not result in significantly more AEs than with budesonide or Seretide® ($p=0.114$ and 1.000 respectively, McNemar test).

Related AEs were reported in 9.2% of CHF 5188-treated patients, 5.9% with budesonide and 9.2% with Seretide®. The profile of related AEs was very similar between all three treatment groups, with only cough being slightly more frequent with CHF 5188.

The most common related AEs reported with CHF 5188 were headache, cough and pharyngolaryngeal pain.

No clinically significant modifications in vital signs, ECG and routine laboratory tests were reported.

No fatal, serious or severe AEs occurred. Two patients discontinued due to AEs (mild asthma exacerbation, possibly related to Seretide®, and unrelated moderate lower respiratory tract infection).

CHF 5188 administered as once daily pMDI (fixed combination budesonide/carmoterol 200/2 µg per actuation) has a similar safety profile as that of Seretide® Evohaler® (Fluticasone/Salmeterol 50/25 µg x 2 puffs bid) and budesonide extrafine pMDI 200 µg x 1 puff bid.

Conclusion:

Although CHF 5188 pMDI (fixed combination budesonide/carmoterol 200/2 µg per actuation) administered once daily at the dose of 400/4 µg per day for 28 days in patients with moderate to severe persistent asthma was well tolerated and proved to be better than budesonide pMDI 200 µg twice-daily on asthma control indicators, its bronchodilator effect was not sufficiently sustained over 24 h to support a once-a-day dosing.

Date of report: 10 March 2011