2. SYNOPSIS

Name of Company: CHIESI Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier:**	*(for National Authority Use only)*
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Title of Study: Evaluation of the effect of 4 weeks treatment with CHF 4226 pMDI 2 µg dose given once daily in the evening on 24-hour trough FEV_1 in adult and adolescent patients aged 15 years or older with moderate or severe persistent asthma

Investigators: See Appendix 16.1.4 for a complete list of investigators. Professor [redacted] was the coordinating investigator located in [redacted]

Study Centers: A total of 27 sites in Romania, Hungary, Bulgaria, Poland, and the UK participated in this study.

Publication (reference): Not applicable

Studied period (years): Date of first patient enrolled: 26 February 2007 Date of last patient visit: 18 July 2007	**Phase of development:** IIb

Objectives:

The primary objective was to characterize the mean trough (23 to 24 hours after dosing) forced expiratory volume in the first second (FEV_1) following 4 weeks of treatment (Visit 6/Day 28) with CHF 4226 2 µg given q.d. in the evening and to compare it with placebo.

The secondary objectives were:

- to compare the mean trough 23 to 24-hour FEV_1 observed with CHF 4226 2 µg q.d. with the one observed with formoterol 12 µg b.i.d. after 4 weeks of dosing (Day 28)
- to assess the effect on the average (area under the curve [AUC] standardized for time) FEV_1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}) 0 to 3 hour post evening dose administration and the peak FEV_1, FVC, FEF_{25-75} observed with CHF 4226 with the one observed with placebo and formoterol, after the first dose (Day 1), after 1 day (Day 2), 7 days (Day 8), 14 days (Day 15) and at 4 weeks (Day 28) of dosing.
- to assess the effect on mean trough FEV_1, FVC, FEF_{25-75} of CHF 4226 over placebo and to compare it with the one observed with formoterol after 1 day (Day 2), 7 days (Day 8), 14 days (Day 15), at 4 weeks (Day 28) and after 28 days (Day 29) of dosing.

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- to assess the effect on the average FEV_1, FVC, FEF_{25-75} AUC 12 to 24 hours of CHF 4226 over placebo and to compare it with the one observed with formoterol, following last dosing of test treatments on the evening of Day 28.
- To characterize FEV_1, FVC, FEF_{25-75} following the last dose at 1, 2, 3 hours and at 12, 13, 14, 15, 16, 18, 20, 22, 23, and 24 hour timepoints (Days 28 and 29).
- To monitor for safety and tolerability.

Methodology: This was a double-blind, double-dummy, randomized, placebo- and active-controlled, parallel-group clinical study.

The study entailed two periods: a run-in period of 7 days duration (Day -7±2 to Day 1), followed by a randomized, double-blind, double-dummy treatment period of 4 weeks duration. Visits were performed on Day 2, Day 8, Day 15, Day 28 (last dose of treatment) and Day 29.

Number of patients (planned and analyzed):

Planned: 240 patients were planned to be randomized to attain 192 patients (64 in each group) completing the study (assuming a 20% drop-out rate).

Analyzed: 252 patients were actually randomized (83, 84 and 85 in the CHF 4226, formoterol, and placebo groups, respectively) and 243 patients completed the study (80, 80, and 83 in the CHF 4226, formoterol, and placebo groups, respectively).

Diagnosis and main criteria for inclusion: Male and female patients ≥ 15 years of age were enrolled at Day -7±2 (Visit 1) into the run-in period if they had moderate or severe persistent asthma according to the Global Initiative for Asthma (GINA) 2005 "Classification of Asthma Severity by Daily Medication Regimen and Response to Treatment"

Test product, dose and mode of administration, batch number: CHF 4226 pMDI 2µg (given once daily in the evening). Batch number [redacted]

Duration of treatment: 4 weeks

Reference therapy, dose and mode of administration, batch number: Formoterol 12µg (Foradil® Aerolizer®) (given twice daily). Bulk lot number [redacted]

Matched placebo to CHF 4226 pMDI (given once daily in the evening) : Batch number [redacted]

Matched placebo to Foradil® Aerolizer® (given twice daily): Batch number [redacted]

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Criteria for evaluation:

Efficacy

Primary efficacy variable:

- The primary efficacy variable was the mean of 23 and 24-hour trough FEV_1 at Day 28.

Secondary efficacy variables:

- Mean of 23 and 24-hour trough FEV_1, as recorded on Day 2, Day 8, Day 15 and Day 29.
- Mean of 23 and 24-hour trough FVC and FEF_{25-75}, as recorded on Day 2, Day 8, Day 15, Day 28 and Day 29.
- AUC(0,3) standardized by time of FEV_1, FVC and FEF_{25-75} at Day 1, Day 2, Day 8, Day 15 and Day 28.
- Peak FEV_1, FVC and FEF_{25-75} at Day 1, Day 2, Day 8, Day 15 and Day 28.
- AUC(12,24) standardized by time of FEV_1, FVC and FEF_{25-75} at 12 to 24 hours after Day 28 dosing, which data was recorded at Day 29.
- FEV_1, FVC and FEF_{25-75} at all timepoints (1 and 2 hours pre-dose and 1, 2 and 3 hours post-dose on Day 1, Day 2, Day 8, Day 15 and Day 28, and 12, 13, 14, 15, 16, 18, 20, 22, 23 and 24 hours post-dose on Day 29).
- Daytime, Nighttime and Complete day (Daytime and Nighttime) asthma symptoms scores and percentage of days free of symptoms.
- Morning, evening and daily number of puffs of salbutamol rescue medication usage and percentage of days without use of rescue salbutamol.
- Asthma control: Percentage of days asthma is controlled.
- Morning and evening PEF (L/min) measured daily with electronic peak flow meter.

Safety:

Adverse events (AEs), laboratory parameters (potassium [K+] and glucose), electrocardiogram (ECG) results (including QTc and heart rate), physical examinations and vital signs (systolic blood pressure [SBP], and diastolic blood pressure [DBP]).

Statistical methods:

Efficacy: The primary efficacy analysis was the assessment of the superiority of CHF 4226 versus placebo for the primary efficacy variable (the mean of the 23 to 24-hour trough FEV_1 at Day 28).

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The comparison of CHF 4226 versus formoterol was only to be performed if the primary comparison of CHF 4226 versus placebo showed superiority. The analysis was performed using an analysis of covariance (ANCOVA) model with baseline as covariate, treatment as fixed effect and country as a random effect.

The results of the comparisons of secondary efficacy variables were intended for supportive purposes only. Mean of 23 and 24-hour trough FEV_1, mean of 23 and 24-hour trough FVC and FEF_{25-75}, peak FEV_1, FVC and FEF_{25-75}, change from baseline in morning and evening PEF, asthma symptom scores and symptom-free time, and salbutamol rescue medication usage were analyzed using the primary efficacy variable model. AUC(0,3) and AUC(12,24) standardized by time of FEV_1, FVC and FEF_{25-75} were calculated using a trapezoidal rule and were analyzed using an ANCOVA model.

Safety: Non-treatment-emergent adverse events (AEs), treatment-emergent AEs (TEAEs), drug-related TEAEs, severe non-treatment-emergent AEs, severe TEAEs, non-treatment emergent serious adverse events (SAEs), treatment emergent SAEs, and TEAEs leading to study withdrawal were summarized. The proportion of patients presenting with TEAEs, TEAEs leading to withdrawal, TEAEs related to study drug and treatment-emergent SAEs were compared between treatments using a Chi-square test or Fisher's exact test. Physical examination data were presented as shift tables. Potassium and glucose values and SBP and DBP were summarized and ANCOVA was used to analyze the change from baseline at Day 28. ECG categorical results and changes in QT, QTcB, QTcF, and HR were summarized and ANCOVA was used to analyze the change from baseline at Day 28 for QTcB and QTcF. Patients with a FEV_1 decrease > 15% from pre-dose to 3 hours post dose within visits were tabulated.

Summary – Conclusions

Efficacy Results:

A total of 252 patients were randomized and included in the ITT population; 83 to the CHF 4226 group, 84 to the formoterol group, and 85 to the placebo group. Demographic and baseline characteristics were similar among the three treatment groups. Compliance with study treatment was good.

The primary objective of this study was to characterise the mean trough 23 to 24-hour FEV_1 following 4 weeks of treatment with CHF 4226 2 µg given q.d. in the evening compared with placebo in moderate to severe asthmatic patients on inhaled corticosteroids. Since CHF 4226 has previously been demonstrated to provide bronchodilation over a 24-hour period, this assessment was chosen to confirm the bronchodilating effect at the end of the dosing period.

The primary efficacy analysis did not demonstrate that CHF 4226 2 µg administered once daily in

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the evening was statistically significant superior to placebo on trough FEV_1 after 4 weeks of treatment (LS mean difference = 0.057 L). In comparison, a statistically significant difference of 0.157 L in trough FEV_1 between formoterol 12 µg given twice daily and placebo in favor of formoterol was observed.

Trough FVC and FEF_{25-75} results were consistent with those seen for FEV_1.

The effect of CHF 4226 2 µg once daily on peak FEV_1 and FEV_1 AUC(0,3) was significantly greater than placebo throughout the treatment period. The LS mean treatment difference between CHF 4226 and placebo for peak FEV_1 after 4 weeks of treatment was 0.241 L ($p < 0.001$) and for FEV_1 AUC(0,3) was 0.222 L ($p < 0.001$). The effects of CHF 4226 2 µg administered once daily and formoterol 12 µg given twice daily were comparable with a LS mean treatment difference of 0.073 L in peak FEV_1 and 0.090 L in FEV_1 AUC(0,3) (p-value not significant).

Improvements in mean morning PEF at each defined week were greater for CHF 4226 and formoterol than for placebo. The change from baseline at endpoint for mean morning PEF showed significantly greater improvements for the CHF 4226 and formoterol groups than for the placebo group ($p=0.031$ and $p=0.002$, respectively). Compared to morning PEF, changes from baseline in evening PEF with CHF 4226 were smaller, especially after 2 weeks of treatment, while those for formoterol were greater. The difference between CHF 4226 and placebo for the change from baseline for evening PEF was not significant. Improvements with formoterol in evening PEF were significantly greater than placebo ($p=0.004$) and CHF 4226 ($p=0.010$).

Improvements in asthma symptom scores, symptom-free days, days with asthma control, and days with rescue salbutamol use were seen in all three treatment groups but no significant differences were observed between treatments.

The absence of a significant effect on clinical outcomes for both active treatments relative to placebo might be due to the short duration of the study and to the fact that patients had few symptoms at baseline.

Safety Results:

There were no significant differences in the safety profile between treatment groups.

Adverse events were reported in 16 patients (19.3%) in the CHF 4226 group, 19 patients (22.6%) in the formoterol group and 12 patients (14.1%) in the placebo group. The types of TEAEs were similar between treatment groups. Overall, tachycardia, nasopharyngitis, headache and dyspnea were the only TEAEs reported by more than one patient in any individual treatment group. In the CHF 4226 group, the most common TEAEs were nasopharyngitis and tachycardia, each reported by 3 patients (3.6%) and headache reported by 2 patients (2.4%). Tachycardia was also reported in 3 patients (3.6%) in the formoterol group and 1 patient (1.2%) in the placebo group.

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The incidence of related AEs was similar between CHF 4226 and formoterol (8.4% and 6.0%, respectively). No individual TEAE was considered to be treatment-related in more than one patient in any treatment group.

One fatal event (sudden death) was observed with formoterol. Two patients (1 in the formoterol group and 1 in the placebo group) presented with a SAE; none was reported with CHF 4226.

The proportion of patients experiencing TEAEs that led to withdrawal was low and similar in the three treatment groups (1 patient in the CHF 4226 group, 3 patients in the formoterol group and 2 patients in the placebo group).

The proportion of patients experiencing AEs was comparable between the CHF4226 and formoterol treatment groups and slightly higher than for the placebo group. The incidence of AEs related to study drug was significantly higher in the CHF 4226 group as compared to placebo but was comparable with formoterol.

There was no appreciable effect of treatment on laboratory parameters (potassium and glucose) or vital signs (systolic and diastolic blood pressure). Two patients, 1 in the CHF 4226 group and 1 in the placebo group, experienced clinically significant decreases in potassium values.

Similarly no evidence was observed for an effect of treatment on QTc. A small proportion of patients experienced tachycardia and palpitations in both active treatment groups as well as in the placebo group although no substantial increases in heart rate were observed in any treatment group.

Conclusion:

In conclusion, this study did not show sustained bronchodilation at the end of the dosing period (as evaluated by trough FEV_1) with CHF 4226 at a dose of 2 µg administered once daily in the evening after 4 weeks of treatment in adult and adolescent patients with moderate or severe persistent asthma. CHF 4226 2 µg showed improvements in peak and averaged FEV_1 AUC(0,3) and home morning PEF. CHF 4226 as used in this study was well-tolerated, and no safety issues associated with CHF 4226 treatment were identified.

Date of report: 02 March 2010