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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 5259 pMDI (Glycopyrronium bromide)	**Volume:**	
Name of Active Ingredient: Glycopyrronium bromide	**Page:**	

Title of Study:

A multinational, multicentre, randomised, double-blind, placebo-controlled, 2-way crossover study to evaluate the efficacy and safety of glycopyrrolate bromide administered via pMDI (CHF 5259), for the treatment of patients with chronic obstructive pulmonary disease

Investigators: 27 recruiting investigators in 4 countries (Poland, Bulgaria, Germany and the United Kingdom)

Study Centres: 27 recruiting centres

Publication (reference): Not Applicable

Studied Period:	**Phase of development:** Phase IIb
FPFV: 27/Jun/2014 LPLV: 06/Feb/2015	

Objectives:

Primary objective

To demonstrate the superiority of CHF 5259 pMDI vs. placebo in terms of change from baseline in pre-dose morning forced expiratory volume in the 1st second (FEV_1) on Day 28.

Key secondary objective

To evaluate the effect of CHF 5259 pMDI in term of the area under the curve between 0 and 12 hours for FEV_1 (FEV_1 AUC_{0-12h}) normalised by time on Day 28.

Secondary objectives

- To evaluate the effect of CHF 5259 pMDI on other lung function parameters, patient's health status (symptom scores) and on clinical outcome measures;
- To assess the safety and tolerability of the study treatment.

Methodology *(Study Design):*

This is a phase IIb, double-blind, randomised, multinational, multicentre, 2-way crossover, placebo-controlled study designed to demonstrate the superiority of CHF 5259 (i.e. glycopyrronium bromide [GB] at 50 µg daily dose) vs. placebo, administered by pMDI over a 4-week treatment period in patients with moderate to very severe COPD.

This study comprised a pre-screening visit (Visit 0 [V0]) occurring no more than 7 days prior to a screening visit (V1), followed by a 2-week open-label run-in period on a background medication of extrafine beclometasone dipropionate (BDP) at a dose equipotent to the patient's previous treatment. Patients took the background medication until the morning of the last day of the last treatment period.

The treatment phase comprised two 4-week treatment periods separated by a 1-week wash-out period. Each treatment period comprised two visits: on Day 1 (i.e. V2 [P1D1] and V4 [P2D1]) and on Day 28 (i.e. V3 [P1D28] and V5 [P2D28]). During the two treatment periods, patients received either a total daily GB dose of 50 µg (test treatment) or placebo (reference treatment). Each patient was randomised to a treatment sequence and received both during the study. In case of patient withdrawal, an Early Termination (ET) visit was performed. A safety follow-up phone call was made one week after the last visit of the last treatment period or one week after the ET visit.

During the run-in period and the treatment phase, efficacy and safety assessments were performed at each visit and patients used a diary card to record daily use of background, study and rescue medication.

Number of patients *(planned and analysed)*:

A total of 98 patients (49 patients per sequence) were planned to be randomised to obtain 78 completed and evaluable patients.

A total of 161 patients were screened, of whom 100 were randomised to one of the two treatment sequences:

- CHF 5259 pMDI/placebo: n=50;
- Placebo/CHF 5259 pMDI: n=50.

	CHF 5259 pMDI	Placebo	Overall
Safety population, n	97[a]	96	100
ITT population, n	98[a]	96	100
PP population, n	93	92	95

[a] Patient [redacted] allocated to the treatment sequence placebo-CHF 5259 pMDI, received a placebo kit in both treatment periods. [redacted] was counted only in the placebo column in the Safety population (i.e. actual treatment) and in both the CHF 5259 pMDI column and the placebo column in the ITT population (i.e. planned treatment).

Diagnosis and main criteria for inclusion:

Eligible patients included male and female adults aged between 40 and 80 years with a diagnosis of COPD (according to Global Initiative for Chronic Obstructive Lung Disease guidelines, revised February 2013) and a smoking history of at least 10 pack years. Both current and ex-smokers (who quit smoking at least 6 months prior to screening visit) were eligible. Patients should have had post-bronchodilator $FEV_1 < 60\%$ of the predicted normal value, post-bronchodilator FEV_1/forced vital capacity (FVC) < 0.7, and a $\Delta FEV_1 \geq 5\%$ after inhalation of 400 µg salbutamol pMDI.

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

Test product: Glycopyrronium bromide (GB, CHF 5259) administered via pMDI.

Dose: 2 puffs, twice daily (bid) of CHF 5259 pMDI at 12.5 µg GB per actuation. Total daily dose: 50 µg GB.

Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Batch number: [redacted]; Expiry date: [redacted]

Duration of treatment:

A run-in period of 2 weeks (±2 days) followed by a treatment phase consisting of two 4-week (±2 days) treatment period separated by 1-week (+2 days) wash-out period.

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

Reference product: Placebo of CHF 5259 administered via pMDI.

Dose: 2 puffs, bid.

Mode of action: Metered dose inhalation of pressurised solution using a standard actuator.

Batch number: [redacted]; Expiry date: [redacted]

Criteria for evaluation:

Efficacy:

The primary efficacy variable was the change from baseline in pre-dose morning FEV_1 on Day 28 (mean of the two measurements at 45 and 10-minute pre-dose).

The key secondary efficacy variable was FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 28.

The other secondary efficacy variables included:

- FEV_1 response (i.e. change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) on Day 28;
- FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 1;
- FEV_1 $AUC_{0\text{-}4h}$ normalised by time on Day 1 and Day 28;
- Change from baseline in trough FEV_1 and FVC at 12 hours on Day 1 and Day 28 (mean of the two measurements at 11.5 and 12-hour post-dose);
- Change from baseline in peak FEV_1 and FVC over 12 hours on Day 1 and Day 28;
- Change from baseline in pre-dose morning inspiratory capacity (IC) on Day 28;
- Change from baseline in 2-hour post-dose IC on Day 1 and Day 28;
- Transition Dyspnoea Index (TDI) score on Day 28;
- Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score and domain scores on Day 28;
- Percentage of days without intake of rescue medication, average use of rescue medication (number of puffs/day) and average number of times rescue medication used per day.

Post-hoc efficacy analyses:

- Change from baseline in peak FEV_1 over 4 hours on Day 1 and Day 28;
- Change from baseline in pre-dose morning FVC on Day 28;
- TDI response (i.e. TDI focal score ≥ 1) on Day 28;
- SGRQ response (i.e. decrease from baseline in SGRQ total score ≥ 4 units) on Day 28.

Safety:

Safety assessments included the following:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Vital signs: systolic and diastolic blood pressure (SBP and DBP);
- 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia's corrected QT interval (QTcF), PR interval (PR) and QRS interval (QRS);
- ECG abnormalities: atrial fibrillation, atrial flutter, ectopic supraventricular rhythm, sinus pauses, non-sustained ventricular tachycardia, 2:1 atrial-ventricular (AV) block, AV Mobitz II, left/right bundle branch block (complete/incomplete), complete heart block;
- Standard haematology and biochemistry.

Statistical methods:

The following populations (defined on a per-period basis, due to the crossover design) were considered for analysis:

- Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after baseline;
- Per-Protocol (PP) population: all patients from the ITT population without any major protocol deviations;
- Safety population: all randomised patients who received at least one dose of the study medication.

All the efficacy variables were analysed in the ITT population. Only the primary efficacy variable, the key secondary efficacy variable and the FEV_1 response (part of the secondary variables) were analysed in the PP population. All safety variables were analysed in the Safety population.

Primary efficacy variable

Change from baseline in pre-dose morning FEV_1 on Day 28 was analysed using an analysis of covariance (ANCOVA) model, including treatment, patient and period as fixed effects and baseline FEV_1 as covariate. The adjusted mean change from baseline for each treatment and the adjusted mean difference between CHF 5259 pMDI and placebo with their 95% confidence intervals (CIs) and p-values were estimated by the model. Superiority was demonstrated by a statistically significant difference between treatments on Day 28 favouring CHF 5259 pMDI.

Key secondary efficacy variable

FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 28 was analysed using an ANCOVA model, including treatment, patient and period as fixed effects and baseline FEV_1 as covariate. The adjusted mean for each treatment and the adjusted mean difference between CHF 5259 pMDI and placebo with their 95% CIs and p-values were estimated by the model.

Other secondary efficacy variables

- FEV_1 response on Day 28 (i.e. change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) was analysed using a conditional logistic regression model with treatment and period as fixed effects, baseline FEV_1 as covariate and patient as strata;
- Percentage of days without intake of rescue medication, average use of rescue medication (number of puffs/day) and average number of times rescue medication used per day were analysed using an analysis of variance (ANOVA) model with treatment, period and patient as fixed effects.

All other secondary efficacy variables were analysed with the same ANCOVA model used for the primary efficacy variable, including the corresponding baseline value as covariate.

Post-hoc efficacy analyses

- Change from baseline in peak FEV_1 over 4 hours on Day 1 and Day 28 and pre-dose morning FVC on Day 28 were analysed using the same model used for the primary efficacy variable, including the corresponding baseline as covariate;
- TDI response (i.e. TDI focal score $\geq$1) on Day 28 and SGRQ response (i.e. decrease from baseline in SGRQ total score $\geq$4) on Day 28 were analysed using a conditional logistic regression with treatment and period as fixed effects, the corresponding baseline as covariate and patient as strata.

Safety variables

The number and percentage of patients with at least one AE and the number of AEs were summarised by System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities by treatment and overall for treatment-emergent AEs (TEAEs), serious AEs, ADRs, serious ADRs, severe AEs and AEs leading to study discontinuation and to death.

Vital signs (SBP and DBP) and their mean changes from baseline (i.e. at pre-dose on Day 1 in each

treatment period) and from pre-dose were summarised by treatment using descriptive statistics.

ECG parameters (HR, QTcF, PR and QRS) and their mean changes from baseline (i.e. at pre-dose on Day 1 in each treatment period) and from pre-dose were summarised by treatment using descriptive statistics. The 95% CIs of the mean were calculated for the actual ECG values and the 90% CIs of the mean were calculated for the changes from baseline and pre-dose.

The number and the percentage of patients with the following QTcF abnormalities were presented by treatment at each scheduled and any unscheduled time points after the first study medication intake:

- QTcF >450 ms, >480 ms and >500 ms (for males);
- QTcF >470 ms and >500 ms (for females);
- Changes from baseline in QTcF >30 ms and >60 ms;
- Only for Day 28: changes from pre-dose at the same visit in QTcF >30 ms and >60 ms.

The following relevant abnormalities recorded by ECG were also summarised by treatment: atrial fibrillation, atrial flutter, ectopic supraventricular rhythm, sinus pauses, non-sustained ventricular tachycardia, 2:1 AV block, AV Mobitz II, left and right bundle branch block (considering both complete and incomplete blocks, presented also separately) and complete heart block.

Standard haematology and biochemistry parameters were presented in shifts tables (from screening to end of treatment) based on normal range according to the following categories: low clinically significant (CS), low non-clinically significant (NCS), normal, high NCS and high CS.

Summary – Results:

Efficacy Results:

Primary efficacy analysis

The primary efficacy analysis (i.e. analysis of the change from baseline in pre-morning FEV_1 on Day 28) demonstrated the superiority of CHF 5259 pMDI vs. placebo in the ITT population, with a difference in adjusted means (95% CI) between treatments of 0.088 L (0.039 L; 0.137 L) ($p<0.001$), and in the PP population, with a difference in adjusted means (95% CI) between treatments of 0.084 L (0.035 L; 0.134 L) ($p=0.001$). These results suggested a clinical benefit for adding GB in COPD patients on background therapy with BDP.

Key secondary efficacy analysis

The key secondary efficacy variable (i.e. FEV_1 AUC_{0-12h} normalised by time on Day 28) was statistically significantly higher with CHF 5259 pMDI than with placebo in the ITT population, with a difference in adjusted means (95% CI) between treatments of 0.121 L (0.079 L; 0.162 L) ($p<0.001$), and in the PP population, with a difference in adjusted means (95% CI) between treatments of 0.111 L (0.070 L; 0.153 L) ($p<0.001$).

Secondary efficacy variables – lung function-based variables

Analyses of lung function-based variables showed a significant improvement with CHF 5259 pMDI compared to placebo for the following secondary efficacy variables:

- FEV_1 response on Day 28 (i.e. change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) in both the ITT and PP populations;
- FEV_1 AUC_{0-12h} normalised by time on Day 1 and FEV_1 AUC_{0-4h} normalised by time on Day 1 and Day 28;
- Change from baseline in trough FEV_1 at 12 hours on Day 1 and Day 28;
- Changes from baseline in peak FEV_1 and FVC over 12 hours and in peak FEV_1 over 4 hours on Day 1 and Day 28;
- Change from baseline in pre-dose morning FVC on Day 28;

- Change from baseline in 2-hour post-dose IC on Day 1 and Day 28.

Secondary efficacy variables – patient's health status and clinical outcome

Analyses of patient's health status and clinical outcome variables showed a significant improvement with CHF 5259 pMDI compared to placebo for the following secondary efficacy variables:

- TDI focal score on Day 28;
- Decreases (i.e. improvement) from baseline in SGRQ total score and symptoms domain scores on Day 28;
- Average use of rescue medication, average number of times rescue medication used per day and percentage of days without intake of rescue medication.

Safety Results:

TEAEs

Overall, 30 (30.0%) patients were reported with 45 TEAEs, with 20 (20.6%) patients experiencing 25 TEAEs during treatment with CHF 5259 pMDI and 17 (17.7%) patients experiencing 21 TEAEs during treatment with placebo. The majority of TEAEs were reported in only 1 patient overall; those reported in > 1 patient were: COPD exacerbation (PT: COPD), nasopharyngitis, cough, hypertension, dyspnoea, oral candidiasis, headache and excoriation. The majority of TEAEs were mild or moderate in intensity and resolved by the end of the study.

No ADRs were reported in this study.

There were 2 serious TEAEs that led to death during the course of the study, both during treatment with CHF 5259 pMDI. One patient was found dead due to unknown causes (PT: death) 4 days after the last intake of CHF 5259 pMDI. Another patient was hospitalised 20 days after the last documented intake of CHF 5259 pMDI and was diagnosed with a [redacted], which led to discontinuation from the study and death 17 and 21 days later, respectively. In addition, there were 3 other serious TEAEs reported in 2 (2.0%) patients: 1 patient had a serious TEAE of COPD exacerbation during treatment with CHF 5259 pMDI and 1 patient had 2 serious TEAEs, 1 of COPD exacerbation and 1 of malignant lung neoplasm, during treatment with placebo.

Six (6.0%) patients were reported with 6 TEAEs leading to study treatment discontinuation: 4 (4.1%) patients due to 4 TEAEs (2 TEAEs of COPD exacerbation, 1 TEAE of [redacted] and 1 TEAE of death) during treatment with CHF 5259 pMDI and 2 (2.1%) patients due to 2 TEAEs of COPD exacerbation during treatment with placebo.

Vital signs

The mean changes from baseline and from pre-dose on Day 1 and Day 28 were minimal and similar with both treatments.

Electrocardiograms

The mean changes from baseline and from pre-dose on Day 1 and Day 28 were minimal and similar with both treatments.

The following abnormalities were reported:

- 1 out of 57 (1.8%) male patient during treatment with placebo had a QTcF value > 450 ms;
- 1 out of 38 (2.6%) female patient had a QTcF value > 470 ms during treatment with CHF 5259 pMDI and during treatment with placebo;
- 4 out of 97 (4.1%) patients had change from baseline > 30 ms during treatment with CHF 5259 pMDI and 1 out of 96 (1.0%) patient had a change from baseline > 30 ms during treatment with placebo.

None of these abnormalities were considered CS.

During treatment with placebo, 1 (1.0%) patient was reported with a mild, non-serious TEAE of ECG

ST segment depression, which was not considered as treatment-related.

Haematology and biochemistry evaluations

Overall, the majority of patients had normal or abnormal NCS low/high values in haematology and biochemistry parameters at screening (V1) and at P2D28 (V5). Only a small percentage of patients had shifts from normal at screening (V1) to NCS low or high values at P2D28 (V5).

Conclusions:

In conclusion, efficacy analyses demonstrated superiority of CHF 5259 pMDI vs. placebo in the change from baseline in pre-dose morning FEV_1 on Day 28 (primary efficacy variable). An overall greater improvement was observed with CHF 5259 pMDI compared to placebo in most of the other lung function parameters, with the improvement seen on Day 1 maintained at Day 28. In addition, a better patient's health status and clinical outcome were observed with CHF 5259 pMDI compared to placebo. No safety concerns were raised with CHF 5259 pMDI compared to placebo.

These results supported the clinical benefits of a 4-week treatment with CHF 5259 pMDI in COPD patients with moderate/severe lung function impairment.

Date of report: 22 September 2015