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 (Glycopyrrolate Bromide 12.5 µg or 25 µg)	**Volume:**	
Name of Active Ingredient: Glycopyrrolate Bromide	**Page:**	

Title of Study:

A multicentre, randomised, double-blind, active-controlled, 4-way cross-over study to evaluate the efficacy and safety of a free combination of 3 doses of glycopyrrolate with fixed combination beclomethasone dipropionate plus formoterol (Foster®) in a metered dose inhaler for the treatment of patients with chronic obstructive pulmonary disease (COPD)

Investigators: 28 recruiting investigators in 6 European countries.

Study Centre(s): 28 recruiting centres: 10 in Germany, 6 in Hungary, 1 in Italy, 4 in Poland, 6 in Russia and 1 in the United Kingdom

Publication (reference):

Studied Period: FPFV:27/MAR/2012 LPLV: 21/SEP/2012	**Phase of development:** Phase II

Objectives:

Primary Objective

The primary objective of the study was to evaluate the efficacy of a free combination of glycopyrrolate bromide (termed Glyco or CHF 5259) at three dose levels with fixed combination beclomethasone dipropionate plus formoterol fumarate (BDP/FF termed Foster® or CHF 1535) in a pressurised metered dose inhaler (pMDI) by comparison with Foster® alone in terms of forced expiratory volume in the 1st second (FEV_1) area under the curve between time 0 and 12 hours (AUC_{0-12h}) normalised by time on Day 7.

Secondary Objective

The study also aimed to evaluate the effect of the free combination Glyco plus Foster® on other lung function parameters and on clinical outcome measures, and to assess the safety and the tolerability of the study treatments.

Methodology *(Study Design):*

This was a Phase II, multicentre, randomised, double-blind, active-controlled, 4 way cross-over, multiple dose study designed to evaluate the efficacy of a free combination of Glyco at three dose levels (25 µg, 50 µg or 100 µg daily) with fixed combination Foster® (BDP/FF 400 µg/24 µg daily) vs. Foster® alone, administered by pMDI over a 7-day treatment period in patients with COPD.

This study comprised a pre-screening visit occurring 2 ± 1 days prior to a screening visit, followed by a 4-week run-in period on Foster® pMDI. The investigational phase lasted approximately seven weeks and comprised four treatment periods (each of 7 days duration). The four treatment regimens were: Foster® + Glyco 25 µg, Foster® + Glyco 50 µg, Foster® + Glyco 100 µg, Foster® alone. Each patient was randomised to one of four treatment sequences arranged in a 4x4 Williams design, and received all four treatments during the study. Each treatment period was separated by a wash-out period of 7 days on Foster® pMDI.

During the treatment periods, safety and efficacy measures were taken at each visit, and patients used a diary card to record the daily use of treatment and rescue medication.

Number of patients *(planned and analysed)*:

Approximately 258 patients were targeted for screening to obtain 142 evaluable patients.

	Intent-to-treat n (%)	**Per Protocol n (%)**	**Safety n (%)**
Total	178 (100)	174 (97.8)	178 (100)
Foster® + Glyco 25 µg	175 (98.3)	162 (91.0)	175 (98.3)
Foster® + Glyco 50 µg	175 (98.3)	164 (92.1)	175 (98.3)
Foster® + Glyco 100 µg	175 (98.3)	161 (90.4)	175 (98.3)
Foster® alone	172 (96.6)	160 (89.9)	172 (96.6)

Source: Table 14.1.1.3

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 [GOLD] guidelines) and a smoking history of at least 10 pack years. Both current and ex-smokers were eligible. Patients had post-bronchodilator FEV_1 (L) between 30% and 60% of the predicted normal value, post-bronchodilator FEV_1/forced vital capacity (FVC, L) <0.7, and an increase in FEV_1 from baseline of at least 60 mL 30 minutes after 80 µg ipratropium.

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

Test Product: free combination of Foster® (BDP 100 µg / FF 6 µg per metered dose) + Glyco (12.5 µg OR 25 µg per metered dose) .

Dose:

- Total daily dose: Foster® two inhalations twice daily (BDP 400 µg / FF 24 µg) + Glyco 12.5 µg one inhalation twice daily (25 µg) + one inhalation of placebo twice daily – **Treatment A**;
- Total daily dose: Foster® two inhalations twice daily (BDP 400 µg / FF 24 µg) + Glyco 25 µg one inhalation twice daily (50 µg) + one inhalation of placebo twice daily – **Treatment B**;
- Total daily dose: Foster® two inhalations twice daily (BDP 400 µg / FF 24 µg) + Glyco 25 µg two inhalations twice daily (100 µg) – **Treatment C**.

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

Batch Numbers:

Foster® (BDP/FF) 100/6 µg: Batch number: [redacted], expiry date: [redacted]

Glyco (Glycopyrrolate Bromide) 12.5 µg: Batch number: [redacted], recheck date: [redacted]

Glyco (Glycopyrrolate Bromide) 25 µg: Batch number: [redacted], recheck date: [redacted]

CHF 1535 Placebo: Batch number: [redacted], recheck date: [redacted]

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

Reference product: Foster® (BDP 100 µg / FF 6 µg)

Dose:

- Total daily dose: Foster® two inhalations twice daily (BDP 400 µg / FF 24 µg) + two inhalations of placebo twice daily – **Treatment D**.

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

Batch Numbers:

Foster® (BDP/FF) 100/6µg: Batch number: [redacted], expiry date: [redacted]

CHF 1535 Placebo: Batch number: [redacted], recheck date: [redacted]

Duration of treatment:

A run-in period of 28 ± 2 days followed by a 7-week treatment phase consisting of four 1-week treatment periods separated by 1-week wash-out periods.

Criteria for evaluation:

Efficacy:

The primary efficacy variable was FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 7.

The secondary efficacy variables comprised lung function- and symptoms-based endpoints as follows:

Lung-function based endpoints:

- Trough FEV_1, FVC and inspiratory capacity (IC) at 12 hours (h) on Day 1 and Day 7 (mean of the two measurements at 12 h and 12.5 h post-dose);
- Trough FEV_1, FVC and IC at 24 h (mean of the two measurements 23.5 h and 24 h after

the Day 7 dose; i.e. on the morning of Day 8);

- FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 1;
- FEV_1 area under the curve between time 0 and 24 hours ($AUC_{0\text{-}24h}$) and between 12 and 24 hours ($AUC_{12\text{-}24h}$) normalised by time on Day 7;
- Peak FEV_1, FVC and IC on Day 1 and Day 7;
- FEV_1, FVC and IC at each time point on Day 1 and Day 7.

Symptoms based endpoints:

- Transition dyspnoea index (TDI) score on Day 8;
- Average use of rescue medication (number of puffs/day) during the treatment period;
- Percentage of rescue use-free days during the treatment period.
- average number of times rescue medication used in a 24-hour period

Safety:

Safety assessments included the following:

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Vital signs (systolic and diastolic blood pressure, heart rate);
- Standard haematology and blood chemistry;
- 12-lead electrocardiogram (ECG).

Statistical methods:

Primary efficacy variable

In order to adjust for multiplicity, the single-step Dunnett procedure was used for the primary comparisons of each dose level of the free combination Glyco + Foster® vs. Foster® alone.

FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 7 was analysed using an analysis of covariance (ANCOVA) model including treatment, period and patient as fixed effects and baseline FEV_1 (mean of the two measurements at 45 minutes and 10 minutes pre-dose on Day 1 in each treatment period) as a covariate. The adjusted mean differences between each dose level of the free combination Glyco + Foster® and Foster alone was calculated with their Dunnett's simultaneous 95% confidence intervals (CIs) and p-values.

At each dose level, superiority of the free combination Glyco + Foster® over Foster® alone was demonstrated if the lower limit of the simultaneous CI for the mean difference was >0.

Pairwise comparisons between the dose levels of the free combination Glyco + Foster® were also performed without adjusting for multiplicity.

Secondary efficacy variables

- Trough FEV_1 at 12 h on Day 1 and Day 7 (mean of the two measurements at 12 h and 12.5 h post-dose), trough FEV_1 at 24 h (mean of the two measurements 23.5 h and 24 h after the Day 7 dose; i.e. on the morning of Day 8), peak FEV_1 on Day 1 and Day 7, FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 1, FEV_1 $AUC_{0\text{-}24h}$ and $AUC_{12\text{-}24h}$ normalised by time on Day 7 were analysed using the same model as for the primary efficacy variable;
- Trough FVC and IC at 12 h on Day 1 and Day 7 (mean of the two measurements at 12 h and 12.5 h post-dose), trough FVC and IC at 24 h (mean of the two measurements at 23.5 h and 24 h post-dose) on Day 7 (i.e. on the morning of Day 8) and peak FVC and IC on Day 1 and Day 7 were analysed using the same model as for the primary efficacy

variable, including baseline FVC or IC (mean of the two measurements at 45 minutes and 10 minutes pre-dose on Day 1 in each treatment period) as appropriate, instead of baseline FEV_1 as a covariate;

- TDI score was analysed using the same model as for the primary efficacy variable, including baseline dyspnoea index (BDI) score in each treatment period as a covariate;
- Average use of rescue medication (number of puffs/day), percentage of rescue use-free days during the treatment period and average number of times rescue medication used in a 24-hour period were analysed using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects;
- Analysis within treatment was performed for all the efficacy variables, except for TDI, average use of rescue medication and percentage of rescue-use free days. The mean change from baseline was calculated with its 95% CI and a paired t-test was performed. The same analysis was performed for change from baseline in FEV_1, FVC and IC at each time point on Day 1 and Day 7.

Safety variables

- The number and the percentage of patients experiencing AEs, ADRs, serious AEs (SAEs) and AEs leading to study withdrawal was summarised by treatment. AEs were also summarised by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA version 15);
- Mean change from baseline in vital signs (pre-dose on Day 1 in each treatment period) was calculated with its 95% CI by treatment;
- Abnormalities in standard haematology and blood chemistry at screening and end of treatment were summarised overall using descriptive statistics;
- Abnormalities in 12-lead ECG and Fridericia's corrected QT interval (QTcF) at screening and end of treatment were summarised overall using descriptive statistics.

Summary – Conclusions:

Efficacy Results:

Primary efficacy analysis

The primary efficacy analysis demonstrated the superiority of the three combinations Foster® + Glyco vs. Foster® alone (p-values always < 0.001) in both the ITT and PP populations, suggesting a clinical benefit of the additive bronchodilator effect of Glyco in COPD patients on background therapy with Foster®. Greater improvement of FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 7 was seen with combinations with higher doses of Glyco (50 µg and 100 µg), indicating a dose-response trend. Indeed, compared to Foster® alone adjusted mean differences were: 87 mL with Foster + Glyco 25 µg, 100 mL with Foster + Glyco 50 µg and 112 mL with Foster + Glyco 100 µg.

Within group analyses showed that change from baseline to post-treatment in FEV_1 $AUC_{0\text{-}12h}$ normalised by time on Day 7 was statistically significant improvement with all treatments.

These results were confirmed in the PP population.

Secondary efficacy analyses

Several secondary efficacy analyses confirmed the superiority of the combinations Foster® + Glyco vs. Foster® alone in terms of pulmonary function and symptoms-based parameters. Furthermore, they confirmed the dose-response trend observed for the primary efficacy variable (Foster® + Glyco 100 µg > Foster® + Glyco 50 µg > Foster® + Glyco 25 µg).

Pulmonary function parameters

Overall, compared to Foster® alone, the three Foster® + Glyco combinations resulted in a statistically significantly greater improvement of all the pulmonary function parameters tested; specifically:

- Trough FEV_1, FVC and IC at 12 h on Day 1 and Day 7 and at pre-dose on Day 8;
- FEV_1 AUC_{0-12h} normalised by time on Day 1;
- FEV_1 AUC_{0-24h} and AUC_{12-24h} normalised by time on Day 7;
- Peak FEV_1, FVC and IC on Day 1 and Day 7, except for peak IC on Day 1, for which Foster® + Glyco 25 µg resulted to be not different from Foster® alone.

With few exceptions, mean changes from baseline in FEV_1, FVC and IC at each time point on Day 1 and Day 7 were a greater improvement or a smaller deterioration with any Foster® + Glyco combination than with Foster® alone.

Overall, Foster® + Glyco combinations with higher doses levels of Glyco (i.e. 50 µg and 100 µg) resulted in a greater improvement of lung function parameters compared to Foster® + Glyco 25 µg.

Within group analyses showed an improvement from baseline to post-treatment in the majority of lung function parameters with all treatments. Statistically significant deteriorations from baseline were observed only with Foster® alone for trough FEV_1, FVC and IC at 12 h on Day 1 and Day 7, and trough IC at pre-dose on Day 8.

Symptoms-based parameters

Foster® + Glyco 100 µg resulted in the greatest improvement in mean TDI (1.3 units), followed by Foster® + Glyco 25 µg, Foster® + Glyco 50 µg and Foster® alone. TDI was statistically significantly higher with Foster® + Glyco 100 µg than with Foster® alone and Foster® + 50 µg.

There were no differences in terms of rescue medication use (average use of rescue medication, percentage of rescue use-free days and average of times of rescue medication use) across treatments.

Overall, the efficacy data showed that the free combination Foster® + Glyco resulted in greater benefit than Foster® alone. Although the greatest improvements in terms of pulmonary function and symptoms-based parameters were seen with Foster® + Glyco 100 µg, the efficacy profile observed with the intermediate dose of Glyco (Foster® + Glyco 50 µg) was still impressive and overall better than the one observed with the lowest dose of Glyco (Foster® + Glyco 25 µg).

Safety Results:

- Treatment-emergent AEs (TEAEs) – Overall, TEAEs were reported less frequently during treatment with any Foster® + Glyco combination (in 7.4%, 5.7% and 8.0% of patients with Foster® + Glyco 25 µg, Foster® + Glyco 50 µg and Foster® + Glyco 100 µg, respectively) than with Foster® alone (in 11.0% of patients). The most frequently reported TEAEs (in > 1 patient with any individual treatment) were: headache, blood bilirubin increased, nasopharyngitis, oral herpes and fatigue. The majority of TEAEs were mild and resolved by the end of the study;
- Treatment-emergent ADRs – Overall, treatment-emergent ADRs were reported less frequently during treatment with any Foster® + Glyco combination (1.7%, 1.1% and 0.6% of patients with Foster® + Glyco 25 µg, Foster® + Glyco 50 µg and Foster + Glyco100 µg, respectively) than with Foster® alone (in 3.5% of patients).

Treatment-emergent ADRs reported during the treatment periods with any Foster®+Glyco combinations comprised: cough, oropharyngeal pain, atrial fibrillation, hyperglycemia, dysphonia, oral candidiasis and throat irritation; blood bilirubin increased, tracheitis, muscle spasms and headache were ADRs reported with Foster® alone. Only the ADR of blood bilirubin increased was reported in > 1 patient (3 patients [1.7%] during treatment with Foster® alone). All ADRs reported during the treatment periods were mild or moderate and the majority resolved by the end of the study.

During the wash-out period, only 3 ADRs were reported in 3 patients (1.7%): oral candidiasis, oropharyngeal pain and hypertension. With the exception of oral candidiasis, all the ADRs reported during the wash-out period resolved;

- Serious TEAEs – Serious TEAEs were reported only in 3 patients undergoing treatment with Foster® + Glyco combinations:
  - Abscess intestinal in 1 patient treated with Foster® + Glyco 25 µg;
  - Bladder transitional cell carcinoma stage II in 1 patient during treatment with Foster® + Glyco 50 µg.
  - Enteritis infectious and acute prerenal failure in 1 patient during treatment with Foster® + Glyco 100 µg.

  All these events led to study discontinuation and were severe, with the exception of the event of bladder transitional cell carcinoma stage II, which was moderate in intensity. All serious TEAEs resolved by the end of the study and none of them were related to the study drug.

  No other TEAEs leading to study discontinuation were reported.

  There were no serious TEAEs reported during the wash-out periods;
- Deaths - No deaths were reported during the study;
- Haematology parameters – Overall, mean changes from baseline to end of study were minimal and the mean values of all haematology parameters were within the normal range. In the majority of patients, all haematology parameters presented normal or non clinically significant (NCS) abnormal values at screening and end of study. Only a small percentage of patients showed shifts from normal values at screening, all of which were NCS;
- Biochemistry parameters – For the majority of biochemistry parameters mean values were within the normal range, and changes from screening to end of study were minimal. Values slightly higher than the upper limit of the normal range were observed for: creatinine, urate, chloride and gamma glutamyl transferase. In the majority of patients, all biochemistry parameters presented normal or NCS values at screening and end of study. Clinically significant (CS) shifts were observed for bilirubin (in 3 patients in the ACBD sequence) and glucose (in 1 patient in the DBCA sequence and 1 patient in the CDAB sequence);
- Vital signs – there were no noticeable changes in vital signs from Day 1 to Day 7;
- ECG – ECG readings were considered either normal or NCS abnormal at screening and end of study in all patients, except for 1 patient randomised to the ACBD sequence for whom the ECG reading was classified as CS abnormal at end of study. QTcF abnormalities at end of the study were mostly observed in patients randomised to the DBCA sequence: increase in QTcF > 60 msec in 2 patients, and absolute QTcF value > 500 msec in 1 patient. However, these QTcF measurements were affected by

confounding factors and therefore did not reflect real values. Only a few patients distributed homogeneously in the sequence groups showed an increase in QTcF > 30 msec related to chronobiological variability.

Conclusion:

Overall, the combination Foster® + Glyco resulted in a greater improvement of lung function and symptoms based parameters than Foster® alone while presenting an acceptable safety profile. A trend toward greater benefits was observed with the Foster® + Glyco combinations with higher doses of Glyco. Compared to Foster® + Glyco 100 µg, the combination Foster® + Glyco 50 µg may be of greater clinical interest as significant improvement of several lung function parameters could still be obtained while administering a lower dose of Glyco.

Date of report: 16 May 2013