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: Not applicable	**Volume:**	
Name of Active Ingredient: Glycopyrrolate Bromide combined with BDP+formoterol	**Page:**	

Title of Study: Randomized, double-blind, active controlled, 3-arm parallel group, Multi-national, multi-centre study to evaluate the cardiac safety of two doses of Glycopyrrolate Bromide (25µg and 50µg BID) delivered via HFA pMDI both combined with Foster® 100/6 µg BID delivered via HFA pMDI versus Foster® 100/6 µg BID delivered via HFA pMDI in patients with moderate to severe COPD

Investigators: 37 Principal Investigators in 6 countries

Study Centre(s): The study was conducted in 37 centres in 6 countries (Bulgaria, Germany, Hungary, Poland, Russia and United Kingdom).

Publication (reference): None

Studied Period: FPFV: 18 Apr 2012 LPLV: 27 Sep 2012	**Phase of development:** II

Objectives:

Primary: The primary objective of the study was to assess the effect on change from baseline in average 24h HR at Visit 5 of combination of Foster® HFA pMDI (beclomethasone dipropionate (BDP) + formoterol fumarate (FF) 100/6 µg), 2 inhalations BID, + Glycopyrrolate HFA pMDI (GB) 12.5 µg 2 inhalations BID (therapeutic dose), and Foster® HFA pMDI, 2 inhalations BID, + Glycopyrrolate HFA pMDI 25µg 2 inhalations BID (supratherapeutic dose) compared to Foster® HFA pMDI, 2 inhalations BID in moderate to severe COPD patients.

Secondary: The secondary objectives of the study were:

- To compare the effect of study treatments in terms of other parameters of Cardiovascular Safety (change of ECG parameters and evidence and incidence of arrhythmias);
- To compare the effect of study treatments on pulmonary function parameters (evening trough FEV_1 and trough FVC measured at 12 h post-dose);
- To evaluate the PK profile of GB, BDP, B17MP and FF and to correlate it with cardiac safety parameters;
- To evaluate full PK to permit heart rate-concentration modeling, using mean hourly heart rate as the PD variables.
- To compare the incidence of Adverse Events of all treatment groups.

Methodology (Study Design):

This was a multinational, multicentre, randomised, double blind, active-controlled, 3-arm parallel group study in subjects with moderate to severe COPD.

The study plan included six visits in total at the clinics: a pre-screening visit (Visit 0); a Screening visit (Visit 1, Day -7) planned +2/+7 days after the pre-screening visit; a pre-randomization visit (Visit 2, Day -1) planned at the end of the run-in period 6 days after Visit 1; a randomization overnight visit (Visit 3, Day 1) at 24 hours after the beginning of Visit 2; a treatment visit (Visit 4, Day 7) at 7±1 days after the start of the randomised treatment period; an end of treatment overnight visit (Visit 5, Day 14) at the end of the 14-day randomised treatment period.

Number of patients (planned and analyzed):

	Foster®+Glyco 50µg	Foster®+Glyco 100µg	Foster®+placebo
Planned for safety analysis	53	53	53
Randomised population	65	63	63
Safety population	65	63	63
Per-protocol population	63	57	58
PK population	65	63	63

Diagnosis and main criteria for inclusion:

- Male and female adults aged ≥ 40 years and ≤ 80 years old;
- Male subjects: they and/or their partner had to be willing to use an approved method of contraception from the time of dose administration and until 30 days after the last dose of study;
- Written informed consent obtained by the patient prior to the start of any study-related procedure;
- Outpatient with diagnosis of COPD (defined in GOLD guidelines, up to date 2010) at least in the 6 months before the screening visit, including: a) smoking history of at least 10 pack/years; b) regular use of bronchodilators in the previous 2 months; c) post-bronchodilator FEV_1 ≥ 30% and ≤ 60% of the predicted normal value; d) post-bronchodilator $FEV_1/FVC \leq 0.70$.
- Body Mass Index (BMI) ≥ 18 kg/m^2 and ≤ 35 kg/m^2 and a total body weight ≥ 50 kg (110 Ibs);
- Ability to be trained to the proper use of pMDI inhalers;
- Ability to comply with study procedures.

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

A (Foster®+Glyco 50µg group): Foster® HFA pMDI 100/6: 2 inhalations BID plus GB HFA pMDI 12.5 µg 2 inhalations BID (total daily dose: BDP 400 µg / FF 24 µg / GB 50µg);

B (Foster®+Glyco 100µg group): Foster® HFA pMDI 100/6: 2 inhalations BID plus GB HFA pMDI 25 µg 2 inhalations BID (total daily dose: BDP 400 µg / FF 24 µg / GB 100µg);

Batch numbers:

Foster®: [redacted] (expiry [redacted]); GB 12.5 µg: [redacted] (expiry [redacted]); GB 25 µg: [redacted] ([redacted]).

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

C (Foster®+placebo group)**:** Foster® HFA pMDI 100/6: 2 inhalations BID plus (Foster®) placebo 2 inhalations BID (total daily dose: BDP 400 µg / FF 24 µg).

Batch numbers:

Foster®: [redacted] (expiry [redacted]); Foster® placebo: [redacted] (expiry [redacted]).

Duration of treatment: 14 days

Criteria for evaluation:

Efficacy:

Lung function tests (evening trough FEV_1 and evening trough FVC before the evening dose of study medication, serial spirometry performed at pre-dose and up to 12h 30min post-dose) at Visit 3 and Visit 5.

Safety:

Primary variable: change from baseline in average 24-hour heart rate at visit 5, based on 24-hour digital Holter ECG.

Secondary variables:

- Change from baseline in average 24-hour HR at Visit 3;
- Maximum 24-hour HR: change from baseline at Visit 3 and Visit 5;
- HR, ΔHR at Visit 3 and Visit 5 at each time-point post dose;
- Hourly HR, Δ hourly HR at Visit 3 and Visit 5 in 24 hours time monitoring;

- Maximum hourly HR, Δ maximum hourly HR at Visit 3 and Visit 5;
- QTcF interval, ΔQTcF interval at Visit 3 and Visit 5 at each time-point post dose;
- QTcP interval (population specific), Δ QTcP interval at Visit 3 and Visit 5 at each time-point post-dose;
- Maximum QTcF change from baseline at Visit 3 and Visit 5;
- Maximum QTcP change from baseline at Visit 3 and Visit 5;
- QRS interval, Δ QRS interval at Visit 3 and Visit 5 at each time-point post dose;
- PR interval, ΔPR interval at Visit 3 and Visit 5 at each time-point post dose;
- QT interval, ΔQT interval at Visit 3 and Visit 5 at each time-point post dose;
- Number and percentage of patients with abnormal values of QTcF intervals at each time-point post-morning dose at Visit 3 and Visit 5;
- Number and percentage of patients with significant changes of QTcF intervals from baseline at each time-point post-morning dose at Visit 3 and Visit 5;
- New myocardial infarction statement onset at Visit 5 at 24-hour post-dose in comparison to baseline;
- PVC burden, ΔPVC burden, over 24 hours on Visit 3 and Visit 5;
- PAC burden, ΔPAC burden over 24 hours on Visit 3 and Visit 5;
- Incidence of 24-hour digital ECG Holter findings, including arrhythmias at Visit 3 and Visit 5;
- Adverse Events and Adverse Drug Reactions;
- Vital signs: pulse rate, systolic and diastolic blood pressure;
- Pre-dose chemistry and haematology parameters collected at Visit 3 and Visit 5.

Exploratory endpoint:

- QTcF and HR change from baseline at Glycopyrrolate average C_{max} at Visit 5.

Pharmacodynamics:

Serum potassium and serum glucose: C_{min}, t_{min} and AUC_{0-12h}.

Pharmacokinetics

The following parameters were calculated for BDP, B17MP, FF and GB:

- Visit 3: $AUC_{0-30min}$ (BDP excluded), AUC_{0-t}, AUC_{0-12h}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$;
- Visit 5 (steady state): $AUC_{0-30min,ss}$ (BDP excluded), $AUC_{0-t,ss}$, $AUC_{0-12h,ss}$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $t_{min,ss}$, $C_{av,ss}$, R_{ac} (accumulation rate), $t_{1/2,ss}$.

Statistical methods

The following populations were considered for data analysis: safety population, which included all randomized patients who took at least one dose of the study medication; per-protocol (PP) population, which included all completed patients from the safety population without any major protocol deviations; PK population, which included all patients from the safety population excluding patients without any valid PK measurement or with major protocol deviations significantly affecting PK.

Quantitative variables were summarized by using n (sample size), mean, confidence interval (CI) for the mean, standard deviation (SD), median and range (minimum – maximum). Categorical variables were summarized by using frequency count and percent distribution.

Efficacy:

The comparison between groups of trough FEV_1 and FVC at 12 hours at Day 1 and at Day 14, pre-dose values of FEV_1 and FVC at day 14. and FEV_1 AUC_{0-12h} at Day 1 and at Day 14, was performed by using an analysis of covariance (ANCOVA) model including treatment and country as factors and the baseline value of FEV_1 and FVC as covariates. The number of patients included in the models, the adjusted means for treatments as well as their differences, the relative 95% CIs and p-values were presented.

Safety:

The primary variable (change from baseline in average 24-hour HR at Day 14) was analysed using an ANCOVA model including treatment and country as factors and baseline average 24-hour HR as a covariate. The equivalence between Foster®+Glyco 50µg and Foster®+placebo, and between Foster®+Glyco 100µg and Foster®+placebo, would have been demonstrated if both two-sided 97.5% CIs for the adjusted means differences were entirely within the equivalence margin of ± 5 bpm. As a sensitivity analysis, the primary safety variable was also analysed using the same ANCOVA model including also age, sex and smoking status as additional factors and baseline average 24-hour HR as a covariate.

The change from baseline in average 24-hour HR at Day 1, maximum 24-hour HR at day 1 and day 14, were analysed using an ANCOVA model, as for the primary safety variable.

The changes from baseline of ECG parameters (PR, QRS, QT, QTcF, QTcP and HR) measured at each time point at Day 1 and Day 14 were summarized using mean values with corresponding 90% CIs. The changes from baseline (and the maximum changes) in QTcF and QTcP were analysed at each time point at Day 1 and at Day 14 using an ANCOVA model. Descriptive statistics on the number and proportion of patients with QTcF values > pre-defined cut-offs for males/females or with changes from baseline > 30 msec or 60 msec were presented. QTcF and QTcP time-profile plots at Day 1 and Day 14 were graphically presented.

PVC burden (number of VEs vs. total number of beats) and PAC burden (number of SVEs vs. total number of beats) over 24h and changes from baseline to day 1 and day 14 were summarized using descriptive statistics.

Descriptive statistics for the following Holter variables were presented at baseline, day 1 and day 14: minimum HR, VE total beats, number of non sustained VE runs of 3+ beats ≤ 30 seconds, number of sustained VE runs of 3+ beats > 30 seconds, number of single VE beats, number of paired VE events, SVE total beats, number of SVE runs of 3+ beats ≤ 30 seconds, number of SVE runs of 3+ beats > 30 seconds, number of single SVE beats, number of paired SVE events, maximum RR interval (total pause > 2.5 seconds), and number of ST depression or elevation events ≥ 0.2 MV and duration > 3 minutes.

The following categorical variables were summarized using frequency count and percentage distribution at baseline, Day 1 and Day 14: ventricular proarrhythmia, atrial fibrillation, atrial flutter, 2nd degree AV block Mobitz I, 2nd degree AV block Mobitz II, and 3rd degree AV block.

Adverse Events were coded using the MedDRA dictionary (version 14.0) and summarised by SOC and PT. The number and the proportion of patients with treatment-emergent AEs (TEAEs), SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation and AEs leading to death were summarized by treatment group.

Absolute values and changes from baseline of pre-dose HR, SBP and DBP were summarized using descriptive statistics. The overall incidence of abnormal vital signs was also analyzed.

Absolute values and changes from baseline of haematology and biochemistry were summarized using descriptive statistics. Laboratory values were also classified as Low/Normal/High with respect to the appropriate normal range and shift tables (day 1 vs. day 14) were presented.

Pharmacokinetics/Pharmacodynamics:

Time-profile plots were provided for the following variables: mean serum concentration of potassium and mean change in QT and QTcF intervals, and in HR; the mean value of plasma concentration of B17MP, GB and Formoterol and mean change in QTcF interval; mean value of plasma concentration of B17MP, GB and Formoterol, and HR; mean plasma concentration of B17MP, GB and Formoterol and mean serum concentration of potassium; mean plasma concentration of B17MP, GB and Formoterol and mean serum concentration of glucose. In addition, plots for the mean changes from baseline in QT and QTcF intervals versus the mean serum concentration of potassium were produced, by means of a linear regression model.

PK/PD modelling: relationship between GB plasma concentration and change from baseline in QTcF and in HR:

A log-linear mixed model was used to assess the relationship between the QTcF change from baseline at day 14 and the GB plasma concentration following inhalations of two different doses (50 µg and 100 µg). An estimate of the change from baseline in QTcF and its relative 90% CI were provided at the geometric mean maximum plasma concentration of GB, determined firstly by selecting the C_{max} of each patient and then by averaging the values obtained from all the patients of the treatment group. A scatter plot with the estimated regression line and the relative 90% confidence band for the change from baseline in QTcF versus the natural logarithm of GB plasma concentration was presented. The same analysis was replicated for the change from baseline in HR.

Summary – Conclusions:

Efficacy Results

Mean trough FEV_1 and FVC increased from baseline to both day 1 and day 14 in all treatment groups. The mean increases in through FEV_1 and FVC at 12 hours were slightly higher in the two combination groups than in the Foster® group.

FEV_1:

At day 1, evening through FEV_1 at 12 hours was significantly higher in the Foster®+Glyco 100µg group than in the Foster®+placebo group.

Even if a difference between the Foster® + Glyco 50 µg vs Foster® + Placebo was found, this difference did not reach statistical significance. At day 14, evening through FEV_1 at 12 hours was significantly higher in the Foster®+Glyco 50µg group than in the Foster®+placebo group. The difference between the Foster®+Glyco 100µg group and the Foster®+placebo group was not statistically significant. There were no statistically significant differences between the Foster®+Glyco 50µg group and the Foster®+Glyco 100µg group at both day 1 and day 14.

The mean pre-dose FEV_1 increased from baseline to day 14 in all treatment groups. The extent of the mean increase from baseline was comparable in the three treatment groups and no statistically significant differences in the comparisons between groups were found.

The mean FEV_1 $AUC_{0\text{-}12h}$ at day 14 was significantly higher in the Foster®+Glyco 50µg group than in the Foster®+placebo group. There were no other statistically significant differences between groups in FEV_1 $AUC_{0\text{-}12h}$ at both day 1 and day 14.

The mean peak FEV_1 was significantly higher in the Foster®+Glyco 100µg group than in the Foster®+placebo group at day 1, and was significantly higher in the Foster®+Glyco 50µg group than in the Foster®+placebo group at day 14. There were no other statistically significant differences between groups at both day 1 and day 14.

FVC:

At day 1, evening through FVC at 12 hours was significantly higher in the Foster®+Glyco 100µg group than in the Foster®+placebo group, and was significantly lower in the Foster®+Glyco 50µg group than in the Foster®+Glyco 100µg group. The difference between the Foster®+Glyco 50µg group and the Foster®+placebo group was not statistically significant. There were no statistically significant differences in any comparisons at day 14.

The mean pre-dose FVC increased from baseline to day 14 in all treatment groups. The extent of the mean increase from baseline was comparable in the three treatment groups and there were no statistically significant differences in the comparisons between groups.

Pharmacokinetic Results:

The PK profile of BDP, B17MP and formoterol was comparable in the three treatment groups and was consistent with that observed in previous pharmacokinetics studies with Foster®.

BDP peaked in a few minutes after inhalation and disappeared rapidly from plasma being undetectable just at 30 minutes after inhalation, due to its rapid conversion into the active metabolite B17MP. An apparent accumulation of BDP was detected after repeated administration of all treatments. However this finding can be considered of limited value due to the high variability of DBP exposure.

Rapid formation (median tmax 15 minutes) and absence of accumulation at steady state was observed for B17MP.

Formoterol was rapidly absorbed after inhalation, and its systemic exposure was slightly increased after repeated administration (mean Rac ranged between 1.96 and 2.46).

The systemic exposure of GB increased dose proportionally both after single and repeated administration and a limited accumulation was observed after repeated doses of Foster®+Glyco 50µg and Foster®+Glyco 100µg (mean Rac 3.39 and 2.94, respectively). Terminal elimination half-life of GB was prolonged after repeated administration.

Safety Results:

Primary safety variable (change from baseline in average 24-hour heart rate at visit 5):

The results of the primary safety variable in the safety population are summarized in the table below:

		Foster® 400/24 µg + Glyco 50 µg (N=65)	**Foster® 400/24 µg + Glyco 100 µg (N=63)**	**Foster® 400/24 µg (N=63)**
Baseline	Mean (SD)	79.47 (9.38) n=64	77.73 (9.42) n=63	77.79 (10.03) n=63
Day 14	Mean (SD)	78.19 (9.83) n=64	75.38 (9.87) n=61	74.22 (11.38) n=59
	Mean (SD) change Day 14 - baseline	-1.33 (7.79) n=63	-2.34 (6.05) n=61	-3.39 (7.39) n=59
	Analysis between groups			
	Adjusted mean (95% CI)	-1.772 (-3.813 to 0.268)	-3.236 (-5.351 to -1.122)	-4.202 (-6.301 to -2.103)
	Adjusted mean difference vs. Foster®+placebo (97.5% CI) P value	2.430 (-0.407 to 5.226) 0.054	0.966 (-1.886 to 3.818) 0.445	-
	Adjusted mean difference vs. Foster®+Glyco 100µg (95% CI) P value	1.464 (-0.991 to 3.919) 0.241	-	-

N = number of patients in the Safety population; n = number of patients with non-missing data; SD = standard deviation; CI = confidence interval

The mean 24-hour heart rate slightly decreased from baseline to day 14 in all treatment groups. The ANCOVA model showed that the 97.5% CI of the difference in adjusted means between the Foster®+Glyco 50µg group and the Foster®+placebo group (-0.407 to 5.226) was not entirely within the equivalence margins of ± 5 bpm. Nevertheless, a difference outside the CI margin of 0.2 bpm is clinically meaningless, thus clinically speaking the two groups have to be considered equivalent. In the comparison between the Foster®+Glyco 100µg group and the Foster®+placebo group, the 97.5% CI of the difference in adjusted means (-1.886 to 3.818) was entirely within ± 5 bpm, thus indicating that these two groups were equivalent, as well as it was the case in the comparison of the two combination groups. The same results were observed in the analysis of equivalence in the PP population. The results of the sensitivity analysis in which age, sex and smoking status were added as factors in the model (in addition to treatment and country), were consistent with those observed in the primary analysis.

Secondary safety variables:

Heart rate:

Change from baseline in average 24-hours heart rate at day 1:

The mean 24-hour heart rate decreased from baseline to day 1 in all treatment groups. The extent of the mean decrease was comparable in the three treatment groups and the comparisons between groups did not show any statistically significant difference.

Hourly profile of heart rate

The 24-hour profile of the mean changes from baseline to any post-dose time point in heart rate was comparable in the three treatment groups at both day 1 and day 14.

Maximum 24-hour heart rate

The maximum 24-hour heart rate decreased from baseline to both day 1 and day 14 in the Foster®+Glyco 100µg group, compared to no substantial changes in the other two groups.

The comparisons between groups at day 1 showed a statistically significant difference between the Foster®+Glyco 100µg group and the Foster®+placebo group, whereas there were no statistically significant differences in the other comparisons.

At day 14, the mean maximum 24-hour heart rate slightly increased in the Foster®+Glyco 50µg group and slightly decreased in the Foster®+Glyco 100µg group, thus leading to a statistically significant diference, whereas there were no statistically significant differences in the other comparisons.

Heart rate profile vs. mean values of plasma concentration of B17MP, GB and formoterol

All profiles were comparable in the three treatment groups.

Change from baseline of heart rate at GB average C_{max} at day 14

The natural logarithm of GB plasma concentration (-3.376) was statistically significant, thus indicating that an increase of GB plasma concentration was associated with a decrease of the change from baseline in heart rate.

ECG parameters:

QTcF interval profile at any time point

The time profile of the mean changes from baseline to any post-dose time point in QTcF interval was comparable in the three treatment groups at both day 1 and day 14. The comparisons between groups in changes from baseline of QTcF interval did not show any statistically significant difference at any time point at both day 1 and day 14.

QTcF interval abnormalities

Only one male patient in the Foster®+placebo group had a QTcF interval > 480 msec at any measurement at day 1 and day 14 (however below the limit of clinical significance of 500 msec). There were no female patients in all the three treatment groups with QTcF values > 470 msec at both day 1 and day 14, and none of male or female patients in all groups had a change of QTcF interval ≥ 60 msec from baseline to any time point at both visits.

QTcF maximum change from baseline

The mean maximum QTcF interval slightly increased from baseline in the Foster®+placebo group at day 1 and slightly decreased from baseline in the same group at day 14, compared to no substantial changes from baseline in the two combination groups at both day 1 and day 14. The comparisons between groups did not show any statistically significant difference at both day 1 and day 14.

QTcF interval profile vs. mean values of plasma concentration of B17MP, GB and formoterol

All profiles were comparable in the three treatment groups.

QTcF change from baseline at GB average C_{max} at day 14

The natural logarithm of GB plasma concentration (2.665) was statistically significant, thus indicating that an increase of GB plasma concentration was associated with an increase of the change from baseline in QTcF.

QTcP interval profile at any time point

The time profile of the mean changes from baseline to any post-dose time point in QTcP interval was comparable in the three treatment groups at both day 1 and day 14. The comparisons between groups in changes from baseline of QTcF interval did not show any statistically significant difference at any time point at both day 1 and day 14, except in the comparison between the Foster®+Glyco 50µg group and the Foster®+placebo group at 10 minutes (90% CI of the difference in adjusted means: 1.119 to 8.181; p = 0.031) and at 24 hours (90% CI of the difference in adjusted means: 0.861 to 9.121; p = 0.047).

QTcP maximum change from baseline

The mean maximum QTcP interval slightly decreased from baseline in the two combination groups at day 1 and slightly decreased from baseline in all the groups at day 14. The comparisons between groups did not show any statistically significant difference.

PR, QRS and QT interval profile at any time point

There were negligible changes of PR, QRS and QT interval from baseline to day 1 and day 14 in all the three treatment groups.

Incidence of 24-hour digital ECG Holter findings:

For all the examined variables, there were no substantial or clinically relevant changes from baseline to both day 1 and day 14 in mean values in all the three treatment groups, except for a small increase from baseline to both day 1 and day 14 in the mean number of paired SVE events in the Foster®+Glyco 50µg group and in the Foster®+placebo group, compared to small decreases in the Foster®+Glyco 100µg group. Only few patients had abnormalities in 24-hour digital ECG Holter (e.g. 2nd degree atrio-ventricular block, atrial fibrillation) at baseline, day 1 or day 14.

PVC and PAC burden:

There were no substantial changes in PVC and PAC burden from baseline to both day 1 and day 14 in all the three treatment groups.

Incidence of new myocardial infarction:

None of the patients in all treatment groups had new myocardial infarction at both baseline and day 14.

Vital signs measured pre- and post-dose:

The mean values of heart rate, and of systolic and diastolic blood pressure did not substantially change from pre- to post-dose at baseline, as well as from baseline to post-dose at both day 7 and day 14 in all treatment groups.

There were few abnormalities of vital signs in all the three treatment groups at any time point. The most common abnormalities were observed in the Foster® + placebo group and consisted of DBP ≤ 65 or ≥ 90 mmHg at day 7 post-dose (13 patients, 20.6%), at day 14 post-dose (9 patients, 14.3%) and at day 14 pre-dose (8 patients, 12.7%).

Adverse events:

TEAEs were reported in a slightly lower proportion of patients in the Foster®+Glyco 50µg group (8 events in 5 patients, 7.7%) than in the Foster®+Glyco 100µg group (11 events in 9 patients, 14.3%) and in the Foster®+placebo group (13 events in 7 patients, 11.1%). The proportion of patients with ADRs was marginally higher in the Foster®+Glyco 100µg group (5 ADRs in 5 patients, 7.9%) than in the Foster®+Glyco 50µg group (3 ADRs in 2 patients, 3.1%) and in the Foster®+placebo group (6 ADRs in 1 patient, 1.6%). Dry mouth (assessed as related to treatment in all cases), was the most frequently reported TEAE [2 events in 2 patients (3.2%) in the Foster®+Glyco 100µg group and 1 event in 1 patient (1.5%) in the Foster®+Glyco 50µg group]. There was one SAE leading to death in the Foster®+placebo group (haemorrhagic stroke, not related to treatment). This was the only severe event reported during the study, all other events were mild or moderate in intensity. TEAEs leading to study discontinuation occurred in 2 patients (3.2%) in the Foster®+Glyco 100µg group (ventricular extrasystoles and non sustained ventricular tachycardia [PT:ventricular tachycardia]), 1 patient each) and in 3 patients (4.8%) in the Foster®+placebo group (tuberculosis, haemorrhagic stroke and COPD exacerbation [PT:COPD]), 1 patient each). There were no TEAEs leading to study discontinuation in the Foster®+Glyco 50µg group.

Laboratory tests:

In all three treatment groups, there were no substantial changes from baseline to day 14 in mean values of haematology and laboratory parameters, and there were no laboratory abnormalities considered by the Investigators as Adverse Events in any parameter that were reported as TEAEs.

Pharmacodynamic Results:

Serum concentration of potassium and glucose showed a similar profile in all the three treatment groups at both day 1 and day 14, as shown by superimposable values of potassium mean C_{min}, t_{min} and AUC_{0-12h} and glucose mean C_{max}, t_{max} and AUC_{0-12h}.

The time profile plot of the mean change from baseline in heart rate, QTcF interval and QT interval vs. the mean values of serum concentration of both potassium and glucose was comparable in the three treatment groups.

The time profile plot of the mean values of serum concentration of both potassium and glucose vs. mean values of plasma concentration of B17MP, GB and formoterol at day 14 was comparable in the three treatment groups.

Conclusions:

- A 14-day treatment with Foster® (BDP + formoterol fumarate 100/6 µg BID) given in combination with Glycopyrrolate bromide 12.5 µg or 25 µg BID was not associated with an increased risk of elevation of heart rate (measured by means of 24-hour digital ECG Holter) in comparison with Foster® BID given alone. Although the upper 97.5% CI bound slightly exceeded (0.226 BPM in 24h), the pre-defined margin of equivalence in the comparison between Foster® combined with GB 50 µg/day and Foster® given alone, the two groups can be considered as clinically equivalent with respect to the primary safety variable (change from baseline in average 24-hour heart rate at day 14, measured by means of 24-hour digital ECG Holter). Equivalence in the primary study endpoint between Foster® combined with GB 100 µg/day and Foster® given alone, and between the two combination groups, was fully demonstrated.
- Using short terms time basis for calculation of heart rate, the time profile of heart rate and ECG parameters (including QTcF interval) were comparable in the three groups at both the first and the last day of study treatment, as well as a superimposable time profile plot of the mean change from baseline in heart rate and QTcF interval as a function of mean values of plasma concentration of B17MP, GB and formoterol was observed in the three treatment groups.
- None of patients in any group had clinically significant prolongation of the QTcF interval.
- There were no substantial differences between groups in incidence of 24-hour digital ECG Holter abnormal

findings.

- The pharmacokinetics of B17MP, GB and formoterol was in line with the known profile for Foster. Systemic exposure of GB increased dose proportionally and its half-life slightly increased with the dose. No difference between doses in time to maximal concentration and accumulation ratio was observed.
- Serum concentration of potassium and glucose showed similar profiles in the three treatment groups at both the first and the last treatment dose.
- The general safety (adverse events and laboratory parameters) was comparable in the three treatment groups;
- The mean heart rate, systolic and diastolic blood pressure did not substantially change from pre- to post-dose at baseline, day 7 and day 14 in the three treatment groups.
- The results of efficacy (lung function parameters) showed small differences between groups. However, treatment with the two combination regimens was associated with marginally greater bronchodilating effect compared to Foster given alone.

Date of the report: 10 October 2013