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: Foster®		
Name of Active Ingredient: Beclomethasone dipropionate 100 µg/unit dose plus formoterol 6 µg/unit dose	**Volume:** **Page:**	

Title of Study: A 12-week, multicentre, randomised, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6 (beclomethasone dipropionate 100 µg plus formoterol 6 µg/actuation), 2 puffs b.i.d., versus Symbicort® 200/6 (budesonide 200 µg plus formoterol 6 µg/actuation), 2 inhalations b.i.d., on parameters of small airway function in patients with Chronic Obstructive Pulmonary Disease

Investigators: 7 Principal Investigators in The Netherlands

Study Centre(s): The study was conducted in 7 centres in The Netherlands

Publication (reference): None

Studied Period: FPFV: 30 Sep 2011; LPLV: 19 Feb 2013	**Phase of development:** IIIb

Objectives:

Primary:

The primary objective of the study was to demonstrate the higher efficacy of small particles Foster® 100/6 (two puffs b.i.d.) versus large particles Symbicort® 200/6 (two inhalations b.i.d.), in terms of residual volume reduction in patients with COPD.

Secondary: The secondary objectives of the study were:

- To evaluate the efficacy of the test treatments in terms of reduction of symptoms, improvements in health status (assessed by specific questionnaires) and in parameters related to the function of small airway function in patients with COPD;
- To assess the safety of study treatments.

Methodology (Study Design):

This was a phase IIIb, multicentre, randomized, double-blind, double-dummy, 2-arm parallel group design preceded by a 4-week run-in period in patients aged ≥ 40 years with COPD. The study compared the efficacy and safety of Foster® 100/6 (two puffs b.i.d.) versus Symbicort® 200/6 (two inhalations b.i.d.), over a 12-week treatment period.

Visits at the clinics took place at pre-screening (V0), at screening (V1), at randomization (V2, end of the run-in period), and after 4 (V3) and 12 weeks (V4) of randomised treatment.

Number of patients (planned and analyzed):

	Foster®	**Symbicort®**
Planned evaluable patients	64	64
Randomised population	31	29
Safety population	30	29
ITT population	30	29
PP population	29	28

Diagnosis and main criteria for inclusion:

1. Male or female patients aged ≥ 40 years, who had signed an Informed Consent form prior to initiation of any study-related procedure or once applicable written informed consent obtained by legal representative.
2. Outpatients with a diagnosis of severe to very severe COPD and including: a) Smoking history of at least 10 pack years; b) Regular use of bronchodilators in the 2 months before visit 1; c) post-bronchodilator FEV_1< 50% of the predicted normal value at visit 1; d) post-bronchodilator FEV_1/FVC < 0.7 at visit 1; e) An increase in FEV_1< 15% and < 200 mL from baseline following administration of 400 µg of salbutamol at visit 1 (removed with Protocol amendment); f) Plethysmographic Functional Residual Capacity (FRC) > 120% of predicted normal value (at visit 1 and visit 2); g) A Baseline Dyspnoea Index (BDI) focal score ≤ 10 (at visit 1 and at visit 2).
3. A cooperative attitude and ability to be trained to the proper use of pMDI and DPI (Turbohaler®, inspiratory flow-driven, multidose powder inhaler) inhalers.

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

Foster® 100/6 µg, 2 puffs in the morning and 2 puffs in the evening (total daily dose BDP 400 µg plus formoterol 24 µg), plus 2 inhalations of Symbicort® Turbohaler®placebo b.i.d.

Batch numbers: refer to Appendix 16.1.6.

Duration of treatment: 12 weeks (following a 4-week run-in period with Symbicort® 200/6 µg 1 inhalation b.i.d.)

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

Symbicort® Turbohaler®200/6 µg, two inhalations in the morning and two inhalations in the evening (total daily dose budesonide 800 µg plus formoterol 24 µg), plus 2 puffs of Foster® placebob.i.d.

Batch numbers: refer to Appendix 16.1.6.

Criteria for evaluation:

Efficacy:

Primary variable

The primary efficacy variable of the study was the change in residual volume from baseline to 120 minutes post dose at end of treatment (V4).

Secondary variables

The secondary efficacy variables of the study were:

- Body plethysmography data: changes from baseline in FEV_1, FVC, FEV_1/FVC, sGaw, Raw, FRC actual, FRC % predicted, IC, TLC, IVC, RV, RV/TLC, FRC/TLC, RV/IVC, IVC/FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$ and $FEF_{25-75\%}$.
- Impulse oscillometry (IOS) data: changes from baseline in airways resistance (R5, R20, R5-20), RF and reactance at 5 Hertz (X5) in a subset of at least 50% of patients from pre-selected sites.
- Changes from baseline in COPD symptom scores (for each single score and the total score).
- Change from baseline in percentage of COPD symptom-free days.
- Change from baseline in rescue salbutamol or ipratropium bromide consumption (puffs per day).
- Change from baseline in percentage of rescue salbutamol or ipratropium bromide-free days.
- Transition Dyspnoea Index (TDI) score at day 84 (V4).
- Clinical COPD Questionnaire (CCQ).
- Physical activity (by means of pedometer).
- Nasal brushing (mRNA). Results of nasal brushing will be provided in a separate report.
- Number of patients with COPD exacerbations.

Safety:

The safety variables of the study were:

- Adverse events and adverse drug reactions.
- Heart rate, systolic and diastolic blood pressure in sitting position at V1 and pre-dose at each visit from V2.
- 12-lead ECG at V1 and pre-dose at V4.
- Standard haematology and blood chemistry at V1 and pre-dose at V4.

Health resource consumption assessments

The following health resource consumption parameters were evaluated:

- Use of rescue medication
- Number and severity of exacerbations
- Use of concomitant medications to treat exacerbations
- Unscheduled hospitalisations
- Emergency room visits
- Unscheduled outpatient visits and other health care provider's visits
- Unscheduled instrumental examinations
- Unscheduled laboratory tests
- Working days lost by the patient and/or by the leading caregiver.

Statistical methods

The following populations were considered for data analysis: Intention-to-Treat (ITT) population, which included all randomised subjects who received at least one administration of the study medication and had at least one available post-baseline evaluation of efficacy; Per-protocol (PP) population, which included allsubjects from the ITT population without any major protocol deviations; safety population, which included all randomized patients who took at least one dose of the study medication. The primary efficacy variable was analyzed both in the ITT and in the PP populations. The other efficacy variables were analyzed in the ITT population only. Analysis of safety variables was performed in the safety population.

Descriptive statistics was provided for each variable in summary tables by treatment group. Quantitative variables were summarized by using n (number of patients), mean, median, and standard deviation, minimum and maximum. Categorical variables were summarized by using frequency count and percent distribution.

Efficacy:

The analysis of changes from baseline of RV (pre-dose value at V2) were performed using a mixed model for repeated measures (MMRM) with treatment, time point, and treatment x time point interaction as fixed effects, baseline as a covariate and baseline x time point interaction, and unstructured covariance matrix. The following time points were defined: 120 and 180 minutes post-dosing at V2; pre-dose, 120 and 180 minutes post-dosing at V3; pre-dose, 120 and 180 minutes post-dosing at V4. The adjusted means for treatments and the relative 95% CIs were presented. The difference between the adjusted means for Foster® vs. Symbicort® was calculated with the relative 95% CI and p-value. Superiority of Foster® vs. Symbicort® was to be demonstrated if the two-sided 95% CI for the adjusted mean difference between Foster® and Symbicort® after 120 minutes from dosing at V4 lied entirely above 0 (this means that the p-value was < 0.05).

The results of body plethysmography and IOS were analysed as for the primary efficacy variable. In the analysis of diary card data (COPD symptom scores, percentage of COPD symptom-free days, use of rescue medication, percentage of rescue medication-free days, physical activity/pedometer), mean baseline values and mean values over the entire treatment period were summarised using descriptive statistics by treatment group. Mean and SD of the change from baseline with the relative 95% CI were tabulated.

BDI scores at V2 and TDI scores at V4 were summarized using descriptive statistics. Mean and SD of the TDI scores and their 95% CIs were calculated by treatment group. A comparison of TDI scores between treatment groups was performed by means of an ANCOVA model with treatment as fixed effect and with BDI scores at visit 2 as a covariate. The adjusted means for treatments and the relative 95% CIs were presented. The difference between the adjusted means for Foster® vs. Symbicort® was calculated with the relative 95% CI and p-value.

In the analysis of the results of the CCQ, domain and total scores derived at V2 and V4 were summarized by treatment group using descriptive statistics. Mean and SD of the change from baseline to V4 and their 95% CIs were calculated by treatment group. A comparison of total scores changes from baseline to V4 between treatment groups was performed by means of an ANCOVA model with treatment as fixed effect and with baseline scores (total score at V2) as a covariate. The adjusted means for treatments and the relative 95% CIs were presented. The difference between the adjusted means for Foster® vs. Symbicort® was calculated with the relative 95% CI and p-value.

The number and the percentage of patients with a post-treatment COPD exacerbation were summarised by treatment group. Treatment effect was presented as a hazard ratio with the associated 95% CI.

Safety:

AEs were coded using the MedDRA dictionary (version 14.0). The SOCs and PTs were used for tabulation. The number of treatment-emergent AEs, SAEs, ADRs, severe AEs and AEs leading to discontinuation, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, severe AEs and AEs leading to discontinuation was summarised by treatment group. Comparisons between treatment groups were performed by means of Chi-square or Fisher's exact test (if more than 20% of the cells in a contingency table had expected counts less than 5).

SBP, DBP and heart rate were summarised at each visit by means of descriptive statistics. At each visit, mean and SD of the change from baseline (Visit 2) and the relative 95% CIs were calculated by treatment group.

A shift table presenting the number and the percentage of patients in each bivariate category (Visit 1 and Visit 4) with regards to overall clinical evaluation (Clinically Significant (CS) abnormal, not CS abnormal) was provided.

Shift tables presenting the number and the percentage of patients in each bivariate category (Visit 1 and Visit 4) with regards to normal range (low, normal, high) was provided for all parameters.

Health resource consumption:

The results of health resource consumption parameters were analysed by means of descriptive statistics.

Summary – Conclusions:

Efficacy Results

Primary variable: change in residual volume from baseline to 120 minutes post dose at V4

ITT population:

The mean (± SD) change of RV from baseline to 120 minutes post dose at week 12was -0.564 ± 0.484 L in the Foster® group and -0.526 ± 0.463 L in the Symbicort® group. The adjusted difference between the Foster® group and the Symbicort® group was -0.013 L (95% CI: -0.291 to 0.266 L) and was not statistically significant (p = 0.928).

PP population:

The results in the PP population were consistent with those observed in the ITT population. The mean (± SD) change of RV from baseline to 120 minutes post dose at week 12was -0.595 ± 0.477 L in the Foster® group and -0.526 ± 0.463 L in the Symbicort® group. The adjusted difference between the Foster® group and the Symbicort® group was -0.022 L (95% CI: -0.304 to 0.259 L; p = 0.873).

Secondary variables (ITT population):

Body plethysmography:

The mean RV decreased from baseline to the other post-dose time points in both groups. The extent of the changes from baseline was comparable in the two groups at any post-dose time point.

The mean sGaw increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.136± 0.174 L/kPa*sec in the Foster® group and 0.094 ± 0.141 L/kPa*sec in the Symbicort® group.

The mean Raw decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -0.219± 0.185 kPa*sec in the Foster® group and -0.164 ± 0.206 kPa*sec in the Symbicort® group.

The mean FRC (absolute values and % of predicted normal) decreased from baseline to any post-dose time point in both groups. The mean (± SD) change in absolute values from baseline to 120 minutes post-dose at week 12 was -0.418± 0.554 L in the Foster® group and -0.322 ± 0.311 L in the Symbicort® group.

The mean IC increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.380± 0.324 L in the Foster® group and 0.228 ± 0.233 L in the Symbicort® group.

The mean TLC did not substantially change from baseline to any post-dose time point in the Foster® group, except for a small increase at 180 minutes post-dose at week 12, and slightly decreased in the Symbicort® group. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.011± 0.320 L in the Foster® group and -0.081 ± 0.275 L in the Symbicort® group.

The mean IVC increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.422± 0.836 L in the Foster® group and 0.510 ± 0.470 L in the Symbicort® group.

The mean RV/TLC ratio decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -6.863 ± 4.355 % in the Foster® group and -6.324 ± 4.724 % in the Symbicort® group.

The mean FRC/TLC ratio decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -5.295± 5.545 % in the Foster® group and -3.405 ± 2.814 % in the Symbicort® group.

The mean RV/IVC ratio decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -34.358± 68.348 % in the Foster® group and -44.957 ± 46.376 % in the Symbicort® group.

The mean IVC/FVC ratio slightly decreased from baseline to any post-dose time point at week 4 and week 12 in the Foster® group and slightly increased in the Symbicort® group. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -1.786± 21.822 % in the Foster® group and 2.787 ± 14.446 % in the Symbicort® group.

The mean FEV_1 increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.199± 0.097 L in the Foster® group and 0.139 ± 0.131 L in the Symbicort® group.

The mean FVC increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.547± 0.414 L in the Foster® group and 0.431 ± 0.395 L in the Symbicort® group.

The mean FEV_1/FVC ratio did not substantially change from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.002± 0.038 % in the Foster® group and -0.002 ± 0.021 % in the Symbicort® group.

The mean $FEF_{25\%}$ increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.161± 0.125 L/sec in the Foster® group and 0.112 ± 0.138 L/sec in the Symbicort® group.

The mean $FEF_{50\%}$ did not substantially change from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.035± 0.094 L/sec in the Foster® group and 0.044 ± 0.056 L/sec in the Symbicort® group.

The mean $FEF_{75\%}$ did not substantially change from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.027± 0.032 L/sec in the Foster® group and 0.008 ± 0.025 L/sec in the Symbicort® group.

The mean $FEF_{25-75\%}$ slightly increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.045± 0.050 L/sec in the Foster® group and 0.036 ± 0.040 L/sec in the Symbicort® group.

No statistically significant differences between groups were observed for all body plethysmography parameters at any time point, except for FVC at 120 minutes post dose at week 4 (V3), in which the mean (± SD) change from baseline was 0.583± 0.361 L in the Foster® group and 0.307 ± 0.331 L in the Symbicort® group (difference in adjusted means: 0.226 L; 95% CI: 0.003 to 0.449 L; p = 0.047), and for FEV_1/FVC ratio at pre-dose at week 4 (V3), in which the mean (± SD) values were -0.011± 0.037 % in the Foster® group and 0.010 ± 0.024 % in the Symbicort® group (difference in adjusted means: -0.021 %; 95% CI: -0.043 to -0.000 %; p = 0.046).

Impulse oscillometry (IOS):

The mean R5 decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -0.075± 0.151 kPa/L/sec in the Foster® group and -0.056 ± 0.192 kPa/L/sec in the Symbicort® group.

The mean R20 slightly decreased from baseline to any post-dose time point in both groups, except at 180 minutes post-dose at week 12 in the Symbicort® group. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -0.017± 0.050 kPa/L/sec in the Foster® group and -0.006 ± 0.055 kPa/L/sec in the Symbicort® group.

The mean delta R5-20 decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -0.093± 0.086 kPa/L/sec in the Foster® group and -0.056 ± 0.144 kPa/L/sec in the Symbicort® group.

The mean X5 increased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was 0.115± 0.108 kPa/L/sec in the Foster® group and 0.044 ± 0.165 kPa/L/sec in the Symbicort® group.

The mean RF decreased from baseline to any post-dose time point in both groups. The mean (± SD) change from baseline to 120 minutes post-dose at week 12 was -1.725± 4.259 Hz in the Foster® group and -0.692 ± 3.908 Hz in the Symbicort® group.

No statistically significant differences between groups were observed for all IOS parameters at any time point.

COPD symptoms score:

The mean COPD symptoms total score during the overall treatment period decreased from baseline in both groups. The mean (± SD) change from baseline was -0.473± 1.550 in the Foster® group and -0.224 ± 1.727 in the Symbicort® group. The results of single scores of the COPD symptoms showed no substantial changes from baseline in both groups for ability to perform the usual daily activities, a small decrease in both groups for breathlessness on rising, a small decrease in the Foster® group and a small increase in the Symbicort® group for both breathlessness and sputum production over the previous 24 hours, a more marked decrease in the Foster® group than in the Symbicort® group for cough over the previous 24 hours, and a small increase in the Foster® group and a small decrease in the Symbicort® group for waking at night due to respiratory symptoms. The percentage of symptoms free days slightly increased in the Foster® group and did not substantially change in the Symbicort® group.

Use of rescue medication:

The mean number of puff/day of rescue medication during the overall treatment period decreased from baseline in both groups. The mean (± SD) change from baseline was -0.849± 2.153 in the Foster® group and -0.248 ± 1.547 in the Symbicort® group.

The mean percentage of rescue medication free days during the overall treatment period slightly decreased from baseline in both groups. The mean (± SD) change from baseline was 3.29± 26.83 % in the Foster® group and 3.81 ± 22.72 % in the Symbicort® group.

Physical activity:

The mean (± SD) number of steps was 3826.23± 2096.60 in the Foster® group and 3509.53 ± 2408.84 in the Symbicort® group.

Baseline Dyspnoea Index (BDI) and Transition Dyspnoea Index (TDI):

The mean (± SD) BDI at baseline was 6.0± 1.8 in the Foster® group and 6.0 ± 1.5 in the Symbicort® group. The mean (± SD) TDI score at week 12 was -0.2± 2.7 (median 0.0) in the Foster® group and 0.0 ± 2.4 (median 0.0) in the Symbicort® group. The comparison between groups did not show statistically significant differences.

Clinical COPD questionnaire (CCQ):

The mean CCQ total score slightly increased from baseline to week 12 in both groups. The mean (± SD) change from baseline was 0.070± 0.525 in the Foster® group and 0.060 ± 0.459 in the Symbicort® group. The comparison between groups did not show statistically significant differences. The results of the CCQ domains showed that the mean decrease from baseline to week 12 was slightly higher in the Foster® group than in the Symbicort® group for the functional domain score and was slightly higher in the Symbicort® group than in the Foster® group for both the symptoms and the mental state domain score.

COPD exacerbations:

Eight COPD exacerbations were reported in 8 patients (26.7%) in the Foster® group and 7 COPD exacerbations were reported in 7 patients (24.1%) in the Symbicort® group. The hazard ratio between Foster® and Symbicort® was 1.12 (95% CI: 0.41 to 3.08).

Health resource consumption:

The number of patients with use of rescue medication was 25 (100.0% of evaluable patients) in the Foster® group and 24 (96.0%) in the Symbicort® group. The number of patients with use of concomitant medications to treat COPD exacerbations was 3 (12.0% of evaluable patients) in the Foster® group and 1 (4.0%) in the Symbicort® group. None of patients in both groups had unscheduled hospitalisations. Only 1 patient (4.0%) in the Foster® group had emergency room visits, and 2 patients (8.0%) in the Foster® group had unscheduled outpatient visits and other health care provider's visits. Only 1 patient (4.0%) in the Foster® group had 2 events of unscheduled instrumental examinations or laboratory tests. Only 1 patient (4.0%) in the Foster® group had 8 days of worked days lost by the patient and/or by the leading caregiver.

Safety Results:

Adverse events:

TEAEs were reported in 10 patients (33.3%) in the Foster® group (18 events) and in 15 (51.7%) in the Symbicort® group (32 events). One patient in each group had one non treatment-related SAE, which consisted of infected sebaceous cyst in the patient in the Foster® group and of COPD exacerbation in the patient in the Symbicort® group. This latter was the only TEAE recorded as Severe during the study. ADRs were reported in 3 patients (10.0%) in the Foster® group (5 events) and in 3 (10.3%) in the Symbicort® group (3 events). AEs leading to study discontinuation were reported in 3 patients (10.0%) in the Foster® group (3 events) and in 3 (10.3%) in the Symbicort® group (5 events). No relevant differences between groups were observed in the proportion of patients with treatment-emergent AEs, SAEs, ADRs, severe AEs and AEs leading to discontinuation.

Laboratory parameters:

Most of patients in both groups had normal values of haematology and blood chemistry parameters at both baseline and week 12 or (in a smaller extent) abnormal values that did not change category from baseline to week 12. Only few patients in both treatment groups showed shifts from normal values at baseline to low or high values at week 12. None of the abnormalities of haematology and blood chemistry parameters was considered as clinically significant and was reported as TEAEs, except for 1 patient (3.3%) in the Foster® group with blood glucose increased and 1 patient (3.4%) in the Symbicort® group with laboratory test abnormal (generic term).

Vital signs:

In both groups, there were no substantial changes from baseline to week 12 (V4) for all vital signs parameters (heart rate and blood pressure).

ECG:

No clinically significant changes in ECG from baseline to week 12 (V4) were observed in both groups.

Conclusions:

- Although the low number of evaluable patients (which was less than half of the planned number) may have reduced the possibility of detecting statistically significant differences between groups, the results of the primary variable showed that the decrease of mean residual volume from baseline to 120 minutes post dose at the end of treatment was similar in the Foster® and in the Symbicort® group, and that the difference between groups was not statistically significant in both the ITT and the PP population.
- The results of the other parameters of lung hyperinflation and pulmonary function, as well as of impulse oscillometry parameters, did not show statistically significant differences between groups at the end of treatment.
- COPD exacerbations were reported in similar rates of patients in the two groups.
- No differences between groups were also observed in the results of physical activity, dyspnoea, quality of life and health resource consumption parameters.
- Both study drugs were well tolerated and the results of safety were in line with the known profile of the two ICS/LABA fixed combinations.