People and ideas for innovation in healthcare

Sharing Clinical Study Report Synopsis

This synopsis is part of the full Clinical Study Report (CSR), which is property of Chiesi Farmaceutici S.p.A.

Chiesi Farmaceutici S.p.A. makes the CSR Synopsis available, consistently with the need to protect the patient privacy, publication rights, and commercially confidential information, through appropriate redaction.

The CSR synopsis is supplied for information only, with the purpose of disclosing scientific data. Hence, it cannot be used, in parts or its entirety, for commercial purposes, nor distributed, published, reused or used for any other purpose without the express written permission of Chiesi Farmaceutici S.p.A.

Results reported in the CSR synopsis are related to a specific study and may not reflect the overall evidence obtained across the product development. Therefore, it is not aimed at providing an exhaustive analysis of all the data currently available on a particular drug. You can learn more about Chiesi Farmaceutici S.p.A. medicinal product consulting the approved product labelling, which may vary from country to country.

The CSR synopsis is not intended to promote any product or indication and is not intended to replace the advice of a health care professional.

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 1535 Beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg	**Volume:** **Page:**	
Name of Active Ingredient: beclomethasone dipropionate + formoterol fumarate		

Title of the study:

A 48-week, double-blind, randomised, multinational, multicentre, 2-arm parallel-group, reference treatment-controlled clinical trial of "fixed combination" beclomethasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535 FOSTER®) versus formoterol in patients with Severe Chronic Obstructive Pulmonary Disease.

Investigators: 133 Investigators in 18 countries (Northern and Southern Hemispheres).

Coordinating Investigator: Prof. [redacted]

Study Centre(s): 127 centres in 18 countries (Northern and Southern Hemispheres). See Appendix 16.1.3.

Publication (reference): Singh D, Kampschulte J, Wedzicha JA et al. A trial of beclomethasone/formoterol in COPD using EXACT-PRO to measure exacerbations. Eur Respir J, 2013, 41:12-17. (Methods only)

Studied Period: FPFV: 02.10.2009; LPLV: 06.03.2012	**Phase of development:** III

Objectives:

Primary

To demonstrate that CHF 1535 (beclomethasone dipropionate [BDP]/formoterol fumarate [FF] 100/6 µg [Foster®]) twice daily is superior to FF (12 µg [Atimos®]) twice daily in terms of the chronic obstructive pulmonary disease (COPD) exacerbation rate during 48 weeks of treatment, and in terms of pulmonary function (change in pre-dose morning forced expiratory volume in 1 second [FEV_1] from baseline to Week 12), in patients with severe COPD.

Secondary

To assess the efficacy of CHF 1535 in terms of pulmonary function parameters (change in pre-dose morning FEV_1 from baseline to Week 12 within treatment groups, change in pre-dose morning FEV_1 from baseline to 48 weeks, pre-dose morning FEV_1 and pre-dose forced vital capacity [FVC] at all clinic visits, average pre-dose FEV_1 over the treatment period, post-dose 2-hour FEV_1), time to first COPD exacerbation, patient's health status assessed by St. George's Respiratory Questionnaire (SGRQ), use of rescue medication and to evaluate the safety profile in terms of adverse events (AEs), adverse drug reactions (ADRs), blood haematology/chemistry and vital signs.

Methodology (Study Design):
This was a phase III, multinational, multicentre, randomised, double-blind, 2-arm, parallel-group, active-controlled study designed to compare the efficacy and tolerability of CHF 1535 with that of FF both administered with a pressurised metered dose inhaler (pMDI), over 48 weeks, twice daily, in patients with severe COPD.

This study included a pre-screening visit (5 ± 2 days prior to the run-in phase), a 2-week run-in phase and a 48-week treatment phase. During the 2-week run-in phase, all patients discontinued their usual COPD treatments (except tiotropium and oral theophylline, which could be continued) and began treatment with FF (12 µg), one puff, twice daily. At the end of the run-in phase (randomisation visit), patients were randomised to receive one of the following treatments every day for 48 weeks:

- CHF 1535 (BDP/FF 100/6 µg): two puffs, twice daily,
- FF (12 µg): one puff + one puff of placebo, twice daily.

During the run-in and treatment phases safety and efficacy measures were taken at each visit, and diaries were used to record the daily use of run-in, treatment and rescue medications, and symptoms.

Number of patients:

A total of 1199 patients (targeted:1102) were randomised.

	Randomised	Safety	Intent-to-treat	Per Protocol
Total	1199	1197	1186	1032
CHF 1535 group	602	601	595	517
FF group	597	596	591	515

Source: Table T14.1-4.1

Diagnosis and main criteria for inclusion:

Eligible patients included male or female outpatients aged >40 years with a diagnosis of severe COPD (stage III from Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines 2008), characterised by shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations having an impact on the patients' quality of life, and including patients with smoking history (current and ex-smokers) of at least 10 pack-years, post-bronchodilator 30% ≤FEV_1 <50% of the predicted normal value, and post-bronchodilator FEV_1/FVC < 0.7. Patients had a documented history of at least one exacerbation in the previous 12 months.

Test product, dose and mode of administration, batch number:
Test Product: CHF 1535: fixed combination of "extrafine" BDP 100 µg plus FF 6 µg pMDI solution marketed as Foster®.
Dose: BDP 100 µg plus FF 6 µg, two puffs twice daily.
Mode of administration: Metered dose inhalation of solution using a pressurised standard actuator.
Batch Numbers: refer to Section 9.4.2.

Duration of treatment: Two-week run-in phase with FF, followed by a 48-week randomised treatment phase.

Reference therapy, dose and mode of administration, batch number:
Reference Therapy: FF 12 µg pMDI solution marketed as Atimos®.
Dose: FF 12 µg, one puff twice daily.
Mode of administration: Metered dose inhalation of solution using a pressurised standard actuator.
Batch Numbers: refer to Section 9.4.2.

Criteria for evaluation:

Efficacy:

The primary efficacy variables were defined as:

- Symptoms-based endpoint: annual COPD exacerbation rate;
- Lung function based endpoint: change in pre-dose morning FEV_1 (L) from baseline to Week 12.

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

- Lung function-based secondary endpoints:
    - Change in pre-dose morning FEV_1 from baseline to Week 12 within treatment groups;
    - Change in pre-dose morning FEV_1 from baseline to Week 48 and at all clinic visits;
    - Change from baseline in average pre-dose morning FEV_1 over the treatment period;
    - Change from baseline in pre-dose morning FVC at all clinic visits;
    - Change from baseline in 2-hour post-dose FEV_1 at all clinic visits;
    - Change from pre-dose to 2-hour post-dose FEV_1 at all clinic visits;
    - Change from baseline in 2-hour post-dose FVC at all clinic visits;
    - Change from pre-dose to 2-hour post-dose FVC at all clinic visits;
    - Pre-dose and 2-hour post-dose FEV_1/FVC.
- Symptoms-based secondary endpoints:
    - Time to first COPD exacerbation;
    - Change from baseline to the end of treatment in SGRQ total score and component scores;
    - Change from baseline to the entire randomised treatment period, and to each inter-visit period, in the average use of rescue medication (number of puffs/day), and the percentage of days without intake of rescue medication.

Exploratory endpoints:

Change from baseline to the entire randomised treatment period and to each inter-visit period in the Exacerbation of Chronic Pulmonary Disease Tool – Patient Reported Outcome (EXACT-PRO) average total score and domain scores (breathlessness, cough and sputum, chest symptoms).

Safety:

Safety assessments included the following:

- AEs and ADRs;
- Vital signs (heart rate [HR] and blood pressure [BP]);
- Routine haematology and blood chemistry parameters (including serum potassium and plasma glucose);
- Electrocardiogram (ECG) abnormalities.

Statistical methods:

The following populations were considered for analysis:

- Randomised population, which included all randomised patients;
- Safety population, which included all randomised patients who received at least one administration of the study drug;
- Intent-to-treat (ITT) population, which included all randomised patients who received at least one administration of the study drug and with at least one available evaluation of efficacy after baseline;
- Per protocol (PP) population, which included all patients from the ITT population without any major protocol deviations.

The primary efficacy variables were analysed in both the ITT and PP populations. Of the secondary efficacy variables, change in pre-dose morning FEV_1 at all clinic visits, change in average pre-dose morning FEV_1 over the entire treatment period and time to first COPD exacerbation were analysed in both the ITT and PP populations. All the other secondary variables were analysed only in the ITT population.

Variables recorded daily by the patient were summarised for the entire treatment period and for each inter-visit period. For quantitative variables, all the available measurements were averaged over each period, while the percentages of days were calculated considering all the days with available data in each period.

Descriptive statistics were provided for all variables by treatment group. For quantitative efficacy variables and vital signs, analysis within treatment groups was presented: mean changes from baseline and their 95% confidence intervals (CIs) were calculated.

For all inferential analyses, p-values were rounded to three decimal places. Statistical significance was declared if the rounded two-sided p-value was ≤ 0.05.

Primary efficacy analyses

The superiority of CHF 1535 vs. FF in terms of COPD exacerbation rate was evaluated using a Poisson regression model, with the number of exacerbations as dependent variable and treatment, country, smoking status, tiotropium use at randomisation and number of COPD exacerbations in the last year as factors, and post-bronchodilator FEV_1 at Visit 1 as covariate. Log-time on study (in years) was used as an offset and standard errors were estimated allowing for extra-Poisson variation. Superiority was demonstrated if the adjusted rate ratio between treatments was significantly different than 1 in favour of CHF 1535.

The superiority of CHF 1535 vs. FF in terms of change in pre-dose morning FEV_1 at Week 12 was evaluated using a mixed model for repeated measures (MMRM), with the change from baseline at each visit as dependent variable, treatment, visit, treatment x visit interaction, country, smoking status and tiotropium use at randomisation as fixed effects and baseline and baseline x visit interaction as covariates. Superiority was demonstrated if the adjusted mean difference between treatments at Week 12 was significantly different from 0 in favour of CHF 1535.

The analyses to determine the superiority of CHF 1535 vs. FF in terms of COPD exacerbation rate and change in pre-dose morning FEV_1 at Week 12 were also performed stratifying by sex and smoking status in the ITT population and by tiotropium use at randomisation in the ITT and PP populations. A sensitivity analysis based on the smoking status entered in the Interactive Response System (IRS) instead of in the case report form (CRF) was also conducted in the ITT population. In addition, a sensitivity analysis on change in pre-dose morning FEV_1 was conducted in the ITT population using an analysis of covariance (ANCOVA) model with the last observation carried forward (LOCF) approach for missing data.

Secondary efficacy analyses

- *Change from baseline in pre-dose morning FEV_1 at Week 12 (within group analysis)* – same MMRM used for the primary analysis of FEV_1;
- *Change from baseline in pre-dose morning FEV_1 at Week 48 and at all clinic visits* – same MMRM used for the primary analysis of FEV_1. The analysis was also performed stratifying by sex and smoking status in the ITT population and by tiotropium use at randomisation in the ITT and PP populations;
- *Change from baseline in average pre-dose morning FEV_1* – same MMRM used for the primary analysis of FEV_1. The analysis was also performed stratifying by sex and smoking status in the ITT population and by tiotropium use at randomisation in the ITT and PP populations;
- *Change from baseline in pre-dose morning FVC at all clinic visits* – MMRM similar to the one used for the primary analysis of FEV_1;
- *Change from baseline in 2-hour post-dose FEV_1 and 2-hour post-dose FVC at all clinic visits* – MMRM similar to the one used for the primary analysis of FEV_1;
- *Change from pre-dose to 2-hour post-dose FEV_1 and FVC at all clinic visits* – ANCOVA model, with change from pre-dose as dependent variable, treatment, country, smoking status and tiotropium use at randomisation as factors and the pre-dose value at the visit as covariate;
- *FEV_1/FVC* – pre-dose and 2-hour post-dose FEV_1/FVC summarised at each visit using descriptive statistics by treatment;
- *Time to first COPD exacerbation* – Cox proportional hazard regression model with treatment, country, smoking status, tiotropium use at randomisation and number of COPD exacerbations in the last years as factors, and post-bronchodilator FEV_1 at Visit 1 as covariate;
- *SGRQ total score and component scores* – ANCOVA model, with change from baseline as dependent variable, treatment, country; smoking status and tiotropium use at randomisation as factors and baseline as a covariate;
- *Percentage of days without intake of rescue medication and average use of rescue medication* – MMRM similar to the one used for the primary analysis of FEV_1 (to analyse change at each inter-visit period) and ANCOVA

model, with change from baseline to entire randomised treatment period as dependent variable, treatment, country, smoking status and tiotropium use at randomisation as factors and baseline as covariate (to analyse change to the entire randomised treatment period).

Analysis of safety

Extent of exposure, AEs, ADRs and vital signs were presented by means of descriptive statistics. COPD exacerbations (preferred term [PT] COPD) were reported as AEs only when considered to be serious. Mean changes from baseline and their 95% CIs were also calculated for vital signs.

Haematology and blood chemistry parameters were presented with regard to normal range (low clinically significant [CS], low non clinically significant [NCS], normal, high NCS and high CS) in shift tables (from Visit 1 to end of treatment).

ECG abnormalities (CS abnormal and not CS abnormal) were presented in shift tables (from Visit 1 to end of treatment).

Other planned analysis

Average EXACT-PRO total score and domain scores – MMRM (to analyse change at each inter-visit period) and ANCOVA (to analyse change to the entire randomised treatment period), as described above for the percentage of days without intake of rescue medication and average use of rescue medication.

Post-hoc analyses

- A sensitivity analysis of the number of COPD exacerbations was performed on the ITT population using a negative binomial model;
- The primary efficacy analysis of the number of COPD exacerbations was performed on the ITT population stratifying by number of COPD exacerbations in the year prior to study entry (0-1 vs. >1) and by the presence of concomitant cardiovascular diseases of clinical relevance;
- A responder analysis on change from baseline in pre-dose morning FEV_1 at Week 12, classifying patients with a change $\geq$ 0.1 L as responders, was performed in the ITT population using a logistic model including treatment, country, smoking status and tiotropium use at randomisation as factors and baseline as covariate.
- Change from baseline in pre-dose morning FEV_1 at all clinic visits and in average pre-dose morning FEV_1 was analysed with the same MMRM used for the primary analysis of FEV_1 in the ITT population, stratifying by occurrence of at least one exacerbation during the treatment period (non-exacerbators vs. exacerbators).
- A responder analysis on the SGRQ total score (improvement, no change or deterioration based on a change of 4 units) was performed using a proportional odds model including treatment, country, smoking status and tiotropium use at randomisation as factors and baseline as covariate.

Efficacy Results:

Primary efficacy analyses

The primary efficacy analyses showed that CHF 1535 was superior to FF both in terms of COPD exacerbation rate and improvement of pulmonary function (change in pre-dose morning FEV_1 from baseline to Week 12).

- *COPD exacerbations*
  - The adjusted rate ratio of COPD exacerbations between the two treatment groups was statistically significantly different from 1 in favour of CHF 1535 (0.719 [95% CI: 0.619, 0.837], $p < 0.001$ for the ITT population and 0.721 [95% CI: 0.613, 0.848], $p < 0.001$ for the PP population). These results were consistent with those obtained in the sensitivity analyses conducted using the smoking status entered in the IRS instead of in the CRF and the negative binomial model instead of the Poisson model (post-hoc analysis);
  - The results obtained in the overall study population were confirmed in the male population, in tiotropium and non–tiotropium users at randomisation, in current smokers and ex-smokers. Consistent results were also found in the post-hoc analyses stratified by number of COPD exacerbations in the year prior to study entry and by the presence of concomitant cardiovascular diseases of clinical relevance. In all these subgroups, CHF 1535 treatment resulted in a statistically significant lower COPD exacerbation rate than FF treatment. In the female population, a lower exacerbation rate with CHF 1535 compared to FF was obtained but the difference between treatments did not reach the statistical significance.
- *Change in pre-dose morning FEV_1 from baseline to Week 12*

- The difference in the adjusted mean change in pre-dose morning FEV_1 from baseline to Week 12 between the two treatment groups was statistically significantly different from 0 in favour of the CHF 1535 group (0.069 L [95% CI: 0.043, 0.095] $p < 0.001$ for the ITT population; 0.065 L [95% CI: 0.037, 0.093] $p < 0.001$ for the PP population). These results were consistent with those obtained in the sensitivity analysis that used the smoking status entered in the IRS (instead of in the CRF), in the sensitivity analysis that used an ANCOVA model and the LOCF approach for missing data and in a post-hoc responder analysis based on a change ≥ 0.1 L;
- The results obtained in the overall study population were confirmed in both genders, in tiotropium and non–tiotropium users at randomisation, in current smokers and ex-smokers and, in a post-hoc analysis, in exacerbators and non-exacerbators. In all these subgroups, CHF 1535 treatment resulted in a statistically significantly greater increase of FEV_1 from baseline to Week 12 than FF treatment.

Secondary efficacy analyses

Several secondary efficacy analyses confirmed the greater benefit of combination therapy with CHF 1535 vs. FF monotherapy in terms of pulmonary function and symptoms based parameters.

Overall, compared to FF treatment, CHF 1535 treatment resulted in a greater improvement of all pulmonary function parameters tested. Treatment with CHF 1535, but not FF, resulted in a statistically significant improvement of pre-dose morning FEV_1 from baseline to Week 12 (within group analysis). Compared to FF, CHF 1535 treatment led to a statistically significantly greater improvement in pre-dose morning FEV_1 from baseline to each clinic visit and in average pre-dose FEV_1 over the entire randomised treatment period. These results were confirmed in both genders, in tiotropium and non-tiotropium users at randomisation, in current smokers and ex-smokers and, in a post-hoc analysis, in exacerbators and non-exacerbators. In addition, treatment with CHF 1535 resulted in statistically greater improvement than FF treatment at all or some clinic visits in terms of change in pre dose morning FVC from baseline, change in 2 hour post dose FEV_1 and FVC from baseline, and change in 2 hour post dose FEV_1 and FVC from pre dose. Finally, pre dose and 2 hour post dose FEV_1/FVC increased over time with CHF 1535 remained constant with FF.

In terms of symptoms based parameters, compared to FF treatment, CHF 1535 treatment resulted in statistically significantly greater improvement in time to first COPD exacerbation and SGRQ total and component scores. In addition, the use of rescue medication (quantified as percentage of days without intake of rescue medication and average use of rescue medication) was statistically significantly improved in favour of the CHF 1535 group at some inter visit periods.

Exploratory analyses

Change in the average EXACT-PRO total score and domain scores (breathlessness, cough and sputum and chest symptoms domains) from baseline at each inter visit period and over the randomised treatment period was assessed as exploratory endpoint.

Improvement in EXACT-PRO total score (i.e. reduced values) was statistically significantly greater in the CHF 1535 group than in the FF group at almost each inter-visit period. In particular, an improvement in the EXACT-PRO breathlessness domain was statistically significantly greater in the CHF 1535 group than in the FF group at each inter visit period and over the entire randomised treatment period suggesting a particular benefit of the combination therapy on patients' perceived dyspnoea.

Overall, efficacy data showed that CHF 1535 treatment resulted in greater benefits than FF treatment in terms of COPD annual exacerbation rate, pulmonary function and symptoms based parameters.

Safety Results:

Overall, TEAEs were reported with a similar frequency in the two treatment groups (52.1% and 49.2% of patients in the CHF 1535 group and FF group, respectively). The percentage of patients experiencing treatment emergent ADRs, severe TEAEs, serious TEAEs, serious treatment emergent ADRs, TEAEs leading to study drug discontinuation and TEAEs leading to death was generally low in both treatment groups.

The most common TEAEs were COPD exacerbation (PT COPD), hypertension and nasopharyngitis in both treatment groups. Overall, oral candidiasis was the most common treatment emergent ADR, and it was reported in a higher percentage of patients in the CHF 1535 group than in the FF group (2.2% vs. 0.3%). The most commonly reported severe and serious TEAEs were COPD exacerbation (PT COPD) and pneumonia (PTs of bronchopneumonia, lobar pneumonia and pneumonia) in both treatment groups. These events were also amongst the most commonly reported TEAEs leading to study drug discontinuation in both treatment groups.

Of the severe TEAEs reported during the study only 3 were related to the study drug: oropharyngeal candidiasis and pruritus in the CHF 1535 group, and tachyarrhythmia in the FF group. Of the serious TEAEs, only atrial fibrillation

was related to the study drug (specifically to FF) and it was reported in one patient in each treatment group. Of the TEAEs leading to study drug discontinuation, a total of 14 were related to the study drug (candidiasis, urticaria, muscle spasms and oropharyngeal candidiasis in the CHF 1535 group and hypertension, tachycardia, hyperhidrosis, pruritus, atrial fibrillation, dyspnoea [in 2 patients], chest pain, pain in extremity and dry mouth in the FF group).

Pneumonia was reported more frequently in the CHF 1535 group (3.8%) than in the FF group (1.8%). However, with the exception of one non serious case in the CHF 1535 group, treatment emergent pneumonia was never related to the study drug.

The most common TEAE leading to death was COPD exacerbation (PT COPD) in both treatment groups. None of the TEAEs leading to death was related to the study drug and in a few cases (4 patients in the CHF 1535 group) they had onset after study discontinuation.

The majority of patients did not show changes of clinical concern in terms of haematology and blood chemistry parameters, vital signs and ECG.

Overall, safety data showed an acceptable safety profile and did not reveal any event of particular concern.

Conclusion:

CHF 1535 was shown to be superior to FF in terms of COPD exacerbation rate and change in pre-dose morning FEV_1 from baseline to Week 12. The superiority of CHF 1535 vs. FF was also supported by the results obtained in the secondary efficacy analyses for both pulmonary function and symptom-based parameters. The number of treatment-emergent ADRs was relatively small in both treatment groups. Pneumonia was more frequent with CHF 1535 than with FF, compatible with findings described with all other ICS-LABA combinations. The majority of patients did not show changes of clinical concern in laboratory parameter values, ECG or vital signs.

Date of report: 06 February 2013