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 200 µg plus formoterol fumarate 6 µg	**Volume:**	
Name of Active Ingredient: Beclomethasone dipropionate and formoterol fumarate	**Page:**	

Title of Study: A 12-week, multinational, multicentre, randomised, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 µg (fixed combination beclomethasone dipropionate/formoterol) versus beclomethasone dipropionate in adult asthmatic patients not adequately controlled on high doses of inhaled corticosteroids or on medium doses of inhaled corticosteroids plus long-acting β_2-agonists.

Investigators: 57 Principal Investigators in 9 European countries

Coordinating Investigator: Prof. [redacted]

Study Centres: 57 centres in 9 European countries: Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia and United Kingdom.

Publication (reference): None

Studied Period:	**Phase of Development:** III
FPFV: 20/04/2012 LPLV: 29/11/2012	

Objectives:

Primary objective: To show the superiority of CHF 1535 (beclomethasone dipropionate [BDP]/formoterol fumarate [FF]) pressurised metered dose inhaler (pMDI) (800/24 µg per day) over BDP hydrofluoralkane (HFA) pMDI (800 µg per day) in terms of change from baseline to the entire treatment period in average pre-dose morning peak expiratory flow (PEF) in adult asthmatic patients not adequately controlled on high doses of inhaled corticosteroid (ICS) or on medium doses of ICS plus long-acting β_2-agonist (LABA).

Secondary objective: To evaluate the effect of CHF 1535 pMDI on clinical outcome measures and other lung function parameters and to evaluate the safety and tolerability profile.

Methodology *(Study Design):*

This was a phase III, multinational, multicentre, randomised, double-blind, double-dummy, active control, 2-arm parallel group study designed to demonstrate the superiority of CHF 1535 (200/6 µg fixed dose combination [FDC]; 800/24 µg/day) vs. BDP (100 µg; 800 µg/day).

A total of 9 visits, 2 weeks apart from each other, were performed during the study: pre-screening visit (Visit 0), screening visit (Visit 1), randomisation visit (Visit 2) and visits at Weeks 2, 4, 6, 8, 10 and 12 (Visit 3 to 8). Screening visit was followed by a 2-week run-in period (open-label), during which the patients received BDP (800 µg/day). At the randomisation visit, patients were randomised to receive either CHF 1535 (800/24 µg/day) or BDP (800 µg/day) for a total of 12 weeks.

During the randomised treatment period, lung function measurements, rescue/concomitant/study medication use, asthma symptom scores, and safety variables (treatment-emergent adverse events [TEAEs], adverse drug reactions [ADRs] heart rate [HR] and blood pressure [BP]) were assessed at each visit. Patients recorded pre-dose morning and evening PEF, rescue and study medication use and asthma symptom scores daily on their electronic peak flow meter.

Number of Patients *(Planned and Analysed)*:

A total of 151 evaluable patients per treatment group were required to demonstrate the superiority of CHF 153 vs. BDP. Estimating a non-evaluable rate of 20%, a total of about 378 patients were required to be randomised (189 patients/group).

	Randomised N	Intent-to-treat N	Per protocol N	Safety N
Total	376	359	333	369
CHF 1535 group	192	184	174	189
BDP group	184	175	159	180

Source: Table T14.1-4.1

Diagnosis and Main Criteria for Inclusion:

Eligible patients included male or female patients aged ≥ 18 years with persistent asthma not optimally controlled on high doses of ICS or medium doses of ICS+LABA at a stable dose for at least 4 weeks before screening. At screening and at the end of the run-in period, the lack of optimal asthma control had to be evidenced by an Asthma Control Questionnaire (ACQ) score > 0.75 and at least one of the following at any of the previous 2 weeks:

- Daytime symptoms more than twice/week;
- Any limitation of activities;
- Nocturnal symptoms/awakening;
- Need for reliever/rescue treatment more than twice/week.

Patients had to exhibit a forced expiratory volume in the first second (FEV_1) ≥ 40% and < 80% of the predicted normal value and an absolute value of at least 0.9 L at screening and at the end of the run-in period (after appropriate washout from bronchodilators). In addition, patients had to have a positive response to the reversibility test (ΔFEV_1 ≥ 12% and ≥ 200 mL over baseline within 30 minutes after administration of 400 µg of salbutamol pMDI) at screening or before randomisation (after an appropriate washout from bronchodilators), or had to have a documented positive response to salbutamol within 3 months prior to the screening visit.

Test Product, Dose and Mode of Administration, Batch Number:

Test product: CHF 1535 extrafine FDC of BDP 200 µg plus FF 6 µg pMDI solution

Daily dose: 4 puffs/day, 2 in the morning and 2 in the evening (total dose: 800 µg BDP plus 24 µg FF)

Batch Number: [redacted]

Duration of Treatment:

Two-week run-in period with BDP extrafine 100 µg pMDI (4 puffs in the morning and 4 puffs in the evening: total dose 800 µg), followed by 12-week randomised treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Reference product: BDP extrafine 100 µg pMDI solution marketed as Qvar®

Daily dose: 8 puffs/day, 4 in the morning and 4 in the evening (total dose: 800 µg)

Batch number: [redacted] and [redacted]

Criteria for Evaluation:

Efficacy:

Primary efficacy variable: Change from baseline to the entire treatment period in average pre-dose morning PEF.

Secondary efficacy variables:

- Change from baseline to each inter-visit period in average pre-dose morning PEF;
- Change from baseline to each inter-visit period and to the entire treatment period in:
  - Average pre-dose evening PEF and daily PEF variability;
  - Percentage of rescue-use free days;
  - Average use of rescue medication (number of puffs/day);
  - Average total day-time and night-time asthma symptom scores;
  - Percentage of asthma symptom-free days;
  - Percentage of asthma control days (days without asthma symptoms and rescue use);
- Change from baseline in pre-dose morning FEV_1 and forced vital capacity (FVC) at each clinic visit and over the entire treatment period;
- Change from baseline in ACQ score;
- Number of moderate/severe asthma exacerbations.

Safety:

Safety variables comprised:

- Adverse events (AEs) and ADRs;
- Vital signs (HR, systolic and diastolic BP [SBP and DBP, respectively]);
- 12-lead electrocardiogram (ECG);
- Standard haematology and blood chemistry parameters;
- Serum cortisol area under the concentration-time curve calculated between time 0 and 24 hours (AUC_{0-24h}) and minimum concentration (C_{min}) in a subset of 15% of patients.

Statistical Methods:

The following populations were considered for analysis:

- Randomised population, which included all randomised patients;
- 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;
- Safety population, which included all randomised patients who received at least one administration of the study drug.

The primary efficacy variable was analysed both in the ITT and PP population. Secondary efficacy variables were assessed only in the ITT population, except for change from baseline to each inter-visit period in average pre-dose morning PEF, which was analysed in both the ITT

and PP populations. Safety variables were assessed in the safety population.

Descriptive statistics were provided for each variable by treatment group. Quantitative variables were summarised using n (sample size), mean, median, standard deviation, minimum and maximum. Log-transformed variables were summarised by geometric mean and coefficient of variation (CV). Categorical variables were summarised using frequency distributions and percentages.

Variables recorded daily by the patient were summarised for each inter-visit period: for quantitative variables, all the available measurements were averaged over the period, while for categorical variables, percentages were calculated considering all the days with available data.

For quantitative efficacy and safety variables, analysis within treatment groups was presented, and mean changes from screening/baseline were calculated. Hypothesis testing was carried out at the alpha = 0.05 level (two-sided) when comparing treatments.

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

Primary efficacy analysis:

The superiority of CHF 1535 (200/6 µg) vs. BDP in terms of change from baseline to the entire treatment period in PEF (L/min) was analysed using an analysis of covariance (ANCOVA) model including treatment, country and sex as factors and baseline as covariate.

Superiority of CHF 1535 vs. BDP was demonstrated if the lower confidence limit of the 95% confidence interval (CI) of the adjusted mean difference between treatments was > 0.

Secondary efficacy analysis:

All the variables measured repeatedly during the randomised treatment period were analysed using a linear mixed model for repeated measures (MMRM) including treatment, period, treatment x period interaction, country and sex as fixed effects and baseline and baseline x period interaction as covariates. An unstructured covariance matrix was considered and the Kenward-Roger adjustment was used for the degrees of freedom.

With the exception of average change from baseline in pre-dose morning FEV_1 and FVC, all the variables calculated over the entire treatment period and the change from baseline in ACQ score were analysed using the same model as for the primary efficacy variable. For change in pre-dose morning FEV_1 and FVC over the entire treatment period, comparison between groups was based on the differences between adjusted means and their two-sided 95% CI obtained from the MMRM.

The number of moderate/severe asthma exacerbations and the number and the percentage of patients experiencing moderate/severe asthma exacerbations were summarised by treatment group.

Safety analysis:

The extent of exposure was analysed by calculating the number of days each patient was exposed to the study drug. Descriptive statistics were provided by treatment group.

The number and the percentage of patients experiencing TEAEs, treatment-emergent ADRs, serious TEAEs, serious treatment-emergent ADRs, severe TEAEs and TEAEs leading to discontinuation or to death, and the respective number of events were summarised by treatment group. TEAEs and ADRs were also summarised by System Organ Class (SOC) and Preferred Term (PT).

Vital signs (HR, SBP and DBP) and their change from baseline at each visit were summarised by treatment group using descriptive statistics.

A shift table from screening to the end of treatment showing the overall clinical evaluation (normal, not clinically significant [NCS] abnormal, clinically significant [CS]) abnormal, was presented by treatment group for 12-lead ECG. Fridericia-corrected QT (QTcF), and changes from screening were summarised by treatment group using descriptive statistics. The number and percentage of patients with a QTcF at the end of treatment > 450 ms, > 480 ms and > 500 ms, and with change from baseline in QTcF > 30 ms and > 60 ms were presented by treatment group.

Serum cortisol $AUC_{0\text{-}24h}$ and C_{min} and their changes from baseline were summarised by treatment group using descriptive statistics.

Haematology and blood chemistry parameters were listed by treatment group and visit and were classified in 3 categories: normal, NCS abnormal and CS abnormal.

Post-hoc analyses:

- A post-hoc analysis of the change from baseline to each visit and over the entire treatment period in pre-dose morning FEV_1 was performed, in order to take into account a slight difference between the two treatment groups in terms of mean reversibility before randomisation (change in FEV_1 [mL] from pre-salbutamol) and the possible effects of reversibility test results on subsequent ICS/LABA responses. That analysis was based on a linear MMRM with change from baseline at each visit as dependent variable, treatment, visit, treatment x visit interaction, country and sex as fixed effects and baseline, baseline x visit interaction and reversibility results (ΔFEV_1) as covariate. An unstructured covariance matrix for each patient was considered and the Kenward-Roger adjustment was used for the degree of freedom.
- A post-hoc analysis of the change in average pre-dose morning PEF (L/min) from baseline to the entire treatment period was performed to explore treatment effect by country. The analysis was conducted in the ITT population and it was based on an ANCOVA model with change from baseline to the entire treatment period as dependent variable, treatment, country, treatment x country interaction and sex as factors and baseline as covariate. Countries contributing the most patients were taken into account individually (i.e. Bulgaria, Germany, Hungary, Poland). Countries contributing minimally to the patient population (i.e. Czech Republic, France, Great Britain, Italy and Russia) were pooled and included in the analysis as well;
- A post-hoc sensitivity analysis of change in average pre-dose morning PEF (L/min) (from baseline to each inter-visit period and entire treatment period) and pre-dose morning FEV_1 (L) (from baseline to each visit and average change over treatment period) was performed to explore the possible impact of missing data. The analysis was conducted in the ITT population and was based on two multiple imputation methods (i.e. a pattern-mixture model where missing values were replaced based on the distribution of completers from the respective group, and a pattern-mixture model where missing values were replaced based on the distribution of patients in the BDP group).
- As part of post-hoc analyses, the BDP non-extrafine equivalent dosage at study entry (µg) was calculated.

Other analyses:

During the data review meeting (before treatment unblinding), a systematic difference in change

from baseline to the entire treatment period in average pre-dose morning PEF (primary efficacy analysis) between means and medians was observed suggesting a possible departure from normality. Even though the ANCOVA model is a robust method for moderate departure from normality, a sensitivity analysis was carried out on log transformed average pre-dose morning PEF. This model included treatment, country and sex as factors and log transformed baseline as covariate.

Summary – Conclusions:

Efficacy Results:

Primary efficacy analysis

The primary efficacy analysis showed that CHF 1535 was superior to BDP in terms of improvement of average pre-dose morning PEF from baseline to the entire treatment period, supporting the benefit of CHF 1535 therapy in asthmatic patients not adequately controlled on high doses of ICS or medium doses of ICS+LABA.

In both the ITT and PP populations, the difference in the adjusted mean change in average pre-dose morning PEF from baseline to the entire treatment period was statistically (ITT population: 18.53 L/min, 95% CI: 10.33, 26.73, $p < 0.001$; PP population: 18.48 L/min, 95% CI: 9.88, 27.08, $p < 0.001$) and clinically significant in favour of the CHF 1535 group. These results were confirmed in the post-hoc sensitivity analyses in the ITT population conducted to explore the impact of missing data. The treatment effect was consistent across countries.

Secondary efficacy analyses

Several secondary efficacy analyses confirmed the greater benefit of CHF 1535 vs. BDP in this category of asthmatic patients. Specifically, compared to BDP, CHF 1535 resulted in a statistically significantly greater improvement of the following lung function parameters:

- Average pre-dose morning PEF from baseline to each inter-visit period in both the ITT and PP populations. Results in the ITT population were confirmed in the post-hoc sensitivity analyses conducted to explore the impact of missing data;
- Average pre-dose evening PEF from baseline to each inter-visit period and to the entire treatment period;
- Daily PEF variability from baseline to Week 1-2, Week 3-4, Week 7-8 and to the entire treatment period.

CHF 1535 resulted also in a greater improvement of FEV_1 and FVC from baseline to each visit and to the entire treatment period than BDP treatment (statistically significant only at Week 4). At the end of the treatment period, the adjusted mean differences in FEV_1 and FVC between CHF 1535 and BDP were 0.071 L (95% CI: -0.009, 0.151; $p = 0.081$) and 0.066 L (95% CI: -0.030, 0.162; $p = 0.175$), respectively. Of note, when FEV_1 reversibility before randomisation was included in the statistical model (post-hoc analysis) the improvement in FEV_1 was statistically significantly greater in the CHF 1535 group than in the BDP group at all visits after Week 2 and over the entire treatment period. According to this analysis the adjusted mean difference between CHF 1535 and BDP at the end of the treatment period was 0.089 L (95% CI: 0.012, 0.165; $p = 0.023$). These results were confirmed in the post-hoc sensitivity analyses applying two different methods for handling missing data. In addition, the number of patients with asthma exacerbation and the corresponding number of moderate/severe asthma exacerbations were lower with CHF 1535 than with BDP.

CHF 1535 and BDP resulted in a comparable improvement of the following symptoms-based parameters:

- Average total day-time and night-time asthma symptom scores from baseline to each inter-visit period and to the entire treatment period;
- Percentage of asthma symptom-free days and asthma control days from baseline to each inter-visit period and to the entire treatment period;
- ACQ scores from baseline to the end of the treatment period.

In addition, CHF 1535 and BDP resulted in a comparable improvement of average use of rescue medication and percentage of rescue use-free days from baseline to each inter-visit period and to the entire treatment period.

Overall, the efficacy data showed that compared to BDP, CHF 1535 resulted in greater benefits in terms of lung function parameters and similar benefits in terms of symptoms-based parameters.

Safety Results:

- TEAEs – Overall, TEAEs were reported with similar frequency in the two treatment groups (in 15.3% and 16.7% of patients in the CHF 1535 group and BDP group, respectively). The most common TEAEs were nasopharyngitis and asthma exacerbation (PT: asthma). All TEAEs were mild or moderate in severity and the majority resolved by the end of the study;
- Treatment-emergent ADRs – Although rare, treatment-emergent ADRs were reported slightly less frequently in the CHF 1535 group than in the BDP group (in 1.1% vs. 2.8% of patients). Each treatment-related ADR was reported in no more than 1 patient in either treatment group. All treatment-emergent ADRs were mild or moderate in severity and the majority resolved by the end of the study;
- Significant TEAEs – Only 1 TEAE leading to discontinuation (asthma exacerbation [PT: asthma]) was reported during the study in 1 patient in the BDP group. This TEAE was not related to the study drug and it resolved after appropriate treatment. No serious TEAEs, serious treatment-emergent ADRs or TEAEs leading to death were reported during the study;
- Haematology and blood chemistry parameters and serum cortisol – All patients exhibited normal or NCS abnormal haematology and blood chemistry parameters. In addition, treatment with CHF 1535 did not reduce serum cortisol from baseline to the end of the treatment period, indicating a lack of effect on the hypothalamus-pituitary-adrenal axis. On the contrary, treatment with BDP resulted in a reduction of serum cortisol;
- Vital signs – No noticeable changes in SBP, DBP and HR were observed from baseline to each visit and to the end of the treatment period;
- ECG – With the exception of 1 patient in the BDP group, for whom the ECG reading was CS abnormal at the end of the treatment period, ECG readings were considered normal or NCS abnormal. Overall, QTcF abnormalities were infrequent and observed in a similar percentage of patients in the two treatment groups.

Overall, the safety data of CHF 1535was similar to that of BDP and did not reveal any event of particular clinical concern.

Conclusion:

In conclusion, the FDC BDP/FF was shown to be more effective than BDP alone and had a good safety profile over the 12 weeks. CHF 1535 could therefore be considered as a treatment preferable to BDP for patients with asthma not adequately controlled by high doses of ICS monotherapy or medium doses of ICS+LABA combinations.

Date of report: 09 April 2014