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# Sharing Clinical Study Report Synopsis

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## 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Company:**<br>**Chiesi Farmaceutici S.p.A.** | **Individual Study Table Referring to Part of the Dossier** | *(for National Authority Use only)* |
| **Name of Finished Product:**<br>**CHF 5993 pMDI** | **Volume:** | |
| **Name of Active Ingredient:**<br>**Beclometasone dipropionate (BDP) 100 µg + formoterol fumarate (FF) 6 µg + glycopyrronium bromide (GB) 12.5 µg** | **Page:** | |

**Title of Study:** A 52-week, double-blind, randomised, multinational, multicentre, 2-arm parallel-group, active-controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrrolate bromide administered via pMDI (CHF 5993) versus fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI in patients with Chronic Obstructive Pulmonary Disease.

**Investigators:** 159 recruiting Investigators in 14 countries

**Study Centre(s):** 159 recruiting centres in 14 countries

**Publication (reference):** None

| **Studied Period:** | **Phase of Development:** Phase III |
|---|---|
| FPFV: 21/MAR/2014<br>LPLV: 14/JAN/2016 | |

**Objectives:**

Primary objectives:

- To demonstrate the superiority of CHF 5993 pressurised metered dose inhaler (pMDI) over CHF 1535 pMDI in terms of lung function (change from baseline in pre-dose and 2-hour post-dose morning forced expiratory volume in the 1st second [$FEV_1$] at Week 26);
- To demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of dyspnoea (transition dyspnoea index [TDI] focal score at Week 26).

Secondary objectives:

- To evaluate the effects of CHF 5993 pMDI on other lung function parameters, patient's health status, clinical outcome measures and chronic obstructive pulmonary disease (COPD) exacerbations;
- To collect data in order to assess the impact of study treatments on health economic outcomes;
- To assess the safety and the tolerability of the study treatments.

**Methodology *(Study design):***

This was a phase III, double-blind, randomised, multinational, multicentre, 2-arm parallel-group, active-controlled study designed to demonstrate the superiority of CHF 5993 pMDI over CHF 1535 pMDI in terms of both lung function and dyspnoea (assessed by the change from baseline in pre-dose and 2-hour post-morning $FEV_1$ and TDI focal score at Week 26) over a 52-week treatment period in patients with severe to very severe COPD.

This study included a pre-screening visit (1 week maximum prior to the run-in period), a 2-week run-in period and a 52-week treatment period. During the run-in period, all patients discontinued their usual COPD treatments and took CHF 1535 pMDI, 2 puffs, twice daily (bid). At the end of the run-in period (i.e. at the randomisation visit), patients were randomised to receive one of the following treatments over 52 weeks:

- CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg per actuation): 2 puffs bid;
- CHF 1535 pMDI (BDP/FF 100/6 µg per actuation): 2 puffs bid.

During the run-in and treatment periods, efficacy and safety measures were taken at each visit and an electronic diary was used to record daily use of run-in, treatment and rescue (salbutamol) medications and COPD symptoms.

**Number of patients *(Planned and analysed)*:**

It was planned to randomise 1304 patients (652 patients per group) in order to reach a total of 1088 evaluable patients at Week 26 (544 patients per group). Of note, at least 20% of patients with very severe airflow limitation (i.e. post-bronchodilator $FEV_1$ at screening <30% of predicted normal value) were to be randomised in the study.

A total of 1812 patients were screened, of whom 1368 were randomised to one of the two treatments:

- CHF 5993 pMDI: n=687;
- CHF 1535 pMDI: n=681.

| | **CHF 5993 pMDI** | **CHF 1535 pMDI** |
|---|---|---|
| **Randomised population** | 687 | 681 |
| **Safety population** | 687 | 680 |
| **ITT population** | 687 | 680 |
| **PP population** | 637 | 635 |
| **Holter subset** | 67 | 71 |

**Diagnosis and main criteria for inclusion:**

Eligible patients included male or female patients aged ≥40 years with a diagnosis of COPD (according to Global Initiative for Chronic Obstructive Lung Disease [GOLD] document, updated February 2013) and a documented history of at least one COPD exacerbation in the 12 months prior to screening. COPD patients had to be current or ex-smokers (who quit smoking at least 6 months prior to screening visit) with a smoking history of at least 10 pack-years, and with a fixed airway limitation as shown by a post-bronchodilator $FEV_1$ <50% of the predicted normal value and post-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio <0.7 within 30 min after 4 puffs (4 x 100 µg) of salbutamol via pMDI.

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

Test product: CHF 5993 pMDI, fixed-dose combination (FDC) of BDP+FF+GB.

Dose: BDP 100 µg, FF 6 µg, GB 12.5 µg per actuation, 2 puffs bid. Total daily dose: BDP 400 µg, FF 24 µg, GB 50 µg.

Mode of administration: pMDI using a standard actuator. If patients inhaled their usual COPD pMDI medications with a spacer device, they were provided with the AeroChamber Plus™ Flow-Vu antistatic valved holding chamber (simply referred to as AeroChamber Plus™) to be used when taking the pMDI study treatments.

Batch number:

| Campaign | Batch Number | Expiry Date |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3&4 | [redacted] | [redacted] |

**Duration of treatment:**

A 2-week open-label run-in period with CHF 1535 pMDI followed by a 52-week treatment period.

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

Reference product: CHF 1535 pMDI, FDC of BDP+FF.

Dose: BDP 100 µg, FF 6 µg per actuation, 2 puffs bid. Total daily dose: BDP 400 µg, FF 24 µg.

Mode of administration: pMDI using a standard actuator. If patients inhaled their usual COPD pMDI treatments with a spacer device, they were provided with the AeroChamber Plus™ to be used when taking the pMDI study treatments.

Batch number:

| Campaign | Batch Number | Expiry Date |
|---|---|---|
| 1 | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] |
| 3&4 | [redacted] | [redacted] |

**Criteria for evaluation:**

**Efficacy:**

Primary efficacy variables:

- Change from baseline in pre-dose morning $FEV_1$ at Week 26;
- Change from baseline in 2-hour post-dose $FEV_1$ at Week 26;
- TDI focal score at Week 26.

Secondary efficacy variables:

- Change from baseline in pre-dose morning $FEV_1$ at all the other clinic visits;
- Change from baseline to the average over the treatment period in pre-dose morning $FEV_1$;
- $FEV_1$ response (change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) at Week 26 and Week 52;
- Change from baseline in 2-hour post-dose $FEV_1$ at all the other clinic visits;
- Change from pre-dose in 2-hour post-dose $FEV_1$ at all clinic visits;
- TDI focal score at all the other clinic visits;
- TDI response (focal score $\geq 1$) at Week 26 and Week 52;
- Change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score and domain scores at all clinic visits;
- SGRQ response (change from baseline in total score $\leq -4$) at Week 26 and Week 52;
- Change from baseline to each inter-visit period and to the entire treatment period in the percentage of days without intake of rescue medication and in the average use of rescue medication (number of puffs/days);
- Moderate and severe COPD exacerbation rate over 52 weeks of treatment;
- Time to first moderate or severe COPD exacerbation.

Exploratory efficacy variables:

- Change from baseline in pre-dose morning FVC at all clinic visits;
- Change from baseline in 2-hour post-dose FVC at all clinic visits;
- Change from pre-dose in 2-hour post-dose FVC at all clinic visits;
- Change from baseline to each inter-visit period and to the entire treatment period in the average Exacerbations of Chronic Pulmonary Disease Tool (EXACT)–Respiratory Symptoms (E-RS) total score and domain scores.

Health economic variables:

- EQ-5D-3L Visual Analogue Scale (VAS) score and EQ-5D-3L index at all clinic visits;
- Number of hospital admissions due to COPD and other causes;
- Number of hospital days due to COPD and other causes;
- Number of emergency room (ER) visits due to COPD and other causes;
- Number of ambulance rides to hospital due to COPD and other causes;
- Number of unscheduled contacts due to COPD:
  - Family practitioner;
  - Specialist outpatients setting;
  - Specialist hospital outpatients setting;
- Number of days with professional home assistance due to COPD;
- Number of days with family caregivers due to COPD;
- Number of days with oxygen therapy use due to COPD;
- Unplanned diagnostic or instrumental tests performed due to COPD;
- Lost productivity due to COPD (sick leave days from work, anticipated retirement);
- Mortality.

**Safety:**

- Adverse events (AEs) and adverse drug reactions (ADRs);
- Vital signs (systolic and diastolic blood pressure [SBP and DBP, respectively]);
- Body mass index (BMI);
- 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia's corrected QT interval (QTcF), PR interval (PR) and QRS interval (QRS);
- 24-hour ECG Holter (on a subset of 10% of the randomised patients; referred to as the Holter patient subset);
- Standard haematology and blood chemistry.

**Statistical methods:**

The following populations were considered for analysis:

- Safety population defined as all randomised patients who received at least one dose of the study treatment;
- Intention-to-treat (ITT) population defined as all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy after baseline;
- Per protocol (PP) population defined as all patients from the ITT population without any major protocol deviation (e.g. wrong inclusions, poor compliance, non-permitted medications).

The primary efficacy analyses and the secondary efficacy analyses on $FEV_1$ and TDI were performed in the ITT and PP (for sensitivity purposes) populations. The other secondary efficacy variables and the health economic variables were analysed in the ITT population. The safety variables were analysed in the Safety population.

Efficacy analysis

***Primary efficacy variables:***

The comparisons between CHF 5993 pMDI and CHF 1535 pMDI were conducted according to a hierarchical testing procedure. The primary efficacy variables were considered in the following order:

1. Change from baseline in pre-dose morning $FEV_1$ at Week 26;
2. Change from baseline in 2-hour post-dose $FEV_1$ at Week 26;
3. TDI focal score at Week 26.

At each step of the procedure, no confirmatory claims were made unless the superiority of CHF 5993 pMDI over CHF 1535 pMDI was demonstrated in all the preceding steps.

Change from baseline in pre-dose morning $FEV_1$, change from baseline in 2-hour post-dose $FEV_1$ and TDI focal score were all analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline value (defined as pre-dose morning $FEV_1$ or baseline dyspnoea index (BDI) focal score at Visit 2 [V2], Week 0) and baseline by visit interaction as covariates.

Superiority of CHF 5993 pMDI over CHF 1535 pMDI was demonstrated by a statistically significant difference between treatments at Week 26 (defined as $p<0.05$) favouring CHF 5993 pMDI.

In order to assess the potential impact of missing data on the results of the primary efficacy analyses, the following sensitivity analyses were performed on all randomised patients:

- Change from baseline in pre-dose morning $FEV_1$: missing at random (MAR), copy reference (CHF 5993 pMDI) and baseline observation carried forward (BOCF) – like multiple imputation (MI);
- Change from baseline in 2-hour post-dose $FEV_1$ and TDI focal score: MAR and copy reference MI, single imputation BOCF.

A sensitivity analysis was also performed to assess the impact of the differences between severity of airflow limitation recorded in the electronic case report form (eCRF) and entered in the interactive response technology (IRT) at randomisation on the results for the primary efficacy variables.

***Secondary efficacy variables:***

The following secondary efficacy variables were analysed using similar statistical model as for the primary efficacy variables:

- Change from baseline in pre-dose morning $FEV_1$ at other clinic visits and change from baseline to the average over the treatment period in pre-dose morning $FEV_1$;
- Change from baseline in 2-hour post-dose $FEV_1$ at other clinic visits;
- TDI focal score at other clinic visits;
- Changes from baseline in the SGRQ total score and domain (symptoms, impacts and activity) scores at all clinic visits;
- Change from baseline (i.e. run-in period) to each inter-visit period and to the entire treatment period in the percentage of days without intake of rescue medication and in the average use of rescue medication;
- Change from baseline to each inter-visit period and to the entire treatment period in the average E-RS total score and domain scores.

The analysis of change from baseline in pre-morning $FEV_1$ to each clinic visit and to the average over the treatment period, change from baseline to the 2-hour post-dose value of $FEV_1$ at each clinic visit and TDI focal score at each clinic visit were also performed in the ITT population stratified by severity of airflow limitation, smoking status at screening, gender, degree of reversibility, main COPD phenotype, blood eosinophil count at screening, age and presence/absence of relevant concomitant cardiovascular diseases (for TDI focal score only).

The $FEV_1$ response at Week 26 and Week 52 was defined as a change from baseline in pre-dose morning $FEV_1$ ≥100 mL at these timepoints. The patient was classed as a non-responder if the change from baseline was <100 mL or if pre-dose morning $FEV_1$ was missing. $FEV_1$ response was compared between treatment groups using a logistic model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors and baseline $FEV_1$ as a covariate. In order to assess the sensitivity of the results to the definition of "responder", similar analyses were conducted considering the alternative thresholds of 50, 70 and 120 mL. A similar model was used to analyse the TDI response (defined as a focal score ≥1) and the SGRQ response (defined as a change from baseline in total score ≤-4) at Week 26 and Week 52.

Change from pre-dose to 2-hour post-dose $FEV_1$ at each visit was analysed using an analysis of covariance (ANCOVA) model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and the pre-dose value at the visit as a covariate.

The number of moderate and severe COPD exacerbations during the treatment period was analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and log-time on study as an offset.

A Kaplan-Meier plot for time to first COPD exacerbation was presented. The time to first moderate or severe COPD exacerbation was analysed using a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status at screening as factors.

The EQ-5D-3L VAS scores/index values and other health economic data were described using summary statistics by treatment group and visit.

***Exploratory efficacy variables:***

The following exploratory efficacy variables were analysed using a similar statistical model as for the primary efficacy variables:

- Change from baseline in pre-dose morning FVC and in 2-hour post-dose FVC at all clinic visits;
- Change from baseline (i.e. run-in period) to each inter-visit period and to the entire treatment period in the average E-RS total score and domain scores.

Change from pre-dose to 2-hour post-dose FVC at each visit was analysed using a similar model as for $FEV_1$.

***Health economic variables:***

Health economics variables were summarised by treatment group using descriptive statistics.

Post-hoc analyses

- Analysis of percentage change from baseline in pre-dose morning $FEV_1$ stratified by severity of airflow limitation (using log-transformed data);
- Analysis of moderate and severe COPD exacerbation rate in the ITT population stratifying by severity of airflow limitation, smoking status at screening, gender, degree of reversibility, main COPD phenotype, number of COPD exacerbations in the 12 months before screening (1 or >1), presence/absence of relevant concomitant cardiovascular diseases, blood eosinophil count at screening, age and in the PP population;
- Analysis of time to first moderate or severe COPD exacerbation based on Cox proportional hazards model in the PP population.

Safety analysis

The number of treatment-emergent AEs (TEAEs), serious AEs (SAEs), ADRs, serious ADRs, severe AEs, AEs leading to study drug discontinuation and AEs leading to death, and the corresponding number and percentage of patients experiencing them were summarised by treatment group by system organ class (SOC) and preferred term (PT). The same statistics, along with the event rate, were presented for treatment-emergent pneumonias and major adverse cardiovascular events (MACEs). The type of pneumonia and its method of diagnosis and potential causes were also summarised using descriptive statistics. The analyses of AEs, pneumonias and MACEs were also performed stratifying by age, presence/absence of relevant concomitant cardiovascular diseases, use of spacer and gender (for MACEs only).

Mean change in SBP and DBP from baseline to each timepoint after the first study treatment intake and from pre-dose to post-dose at each clinic visit was calculated with its 95% confidence interval (CI) by treatment group.

Mean change in BMI from baseline to each clinic visit was calculated with its 95% CI by treatment group.

Change from baseline in pre-dose and post-dose 12-lead ECG parameters was analysed using a similar model as for the primary efficacy variables. At each visit, the change from pre-dose to post-dose was analysed using an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and the pre-dose value at the visit as a covariate.

Abnormalities in QTcF absolute values and changes from baseline and 12-lead ECG abnormal findings at each timepoint and at any timepoint were presented by treatment group.

Change from baseline in 24-hour average HR from Holter ECG was analysed using a similar model as for the primary efficacy variables. The other variables from Holter ECG were summarised by treatment group using descriptive statistics.

The analysis of HR and QTcF from 12-lead ECG was conducted and descriptive statistics for Holter ECG variables were presented also stratifying by use of spacer.

Laboratory results and their changes from screening at V5 (Week 26) and V7 (Week 52) were summarised by treatment group. Shift tables with regard to normal range were also presented by treatment group for each of the laboratory parameters.

**Summary – Results:**

**Efficacy Results:**

A total of 1368 patients were randomised to receive either CHF 5993 pMDI (n=687) or CHF 1535 pMDI (n=681). The majority of patients completed the study. Demographic and baseline characteristics were similar between treatment groups. Overall, 22.7% of the patients had a very severe airflow limitation (post-bronchodilator $FEV_1$ at screening <30% of the predicted normal value).

Primary Efficacy Analyses

With CHF 5993 pMDI, there was a statistically significant improvement from baseline to Week 26 in the three co-primary efficacy endpoints: pre-dose morning $FEV_1$, 2-hour post-dose $FEV_1$ and TDI focal score (see table below). With CHF 1535 pMDI, there was no change in pre-dose morning $FEV_1$, but there were statistically significant improvements in 2-hour post-dose $FEV_1$ and TDI focal score.

Based on the pre-specified hierarchical testing procedure, analysis of the three co-primary efficacy endpoints found CHF 5993 pMDI to be superior to CHF 1535 pMDI for the change from baseline to Week 26 in pre-dose morning $FEV_1$ and 2-hour post-dose $FEV_1$. The adjusted mean difference between treatments in favour of CHF 5993 pMDI in TDI focal score at Week 26 did not reach statistical significance.

**Change from baseline in pre-dose morning $FEV_1$, 2-hour post-dose $FEV_1$ and TDI focal score at Week 26 – ITT population**

| | CHF 5993 pMDI N=687 | CHF 1535 pMDI N=680 |
|---|---|---|
| **Change from baseline in pre-dose morning $FEV_1$ at Week 26 (L)** | | |
| n | 642 | 616 |
| Adjusted mean (95% CI) | 0.082 (0.062; 0.102) | 0.001 (-0.019; 0.021) |
| p-value | <0.001 | 0.922 |
| Adjusted mean difference (95% CI) | 0.081 (0.052; 0.109) | |
| p-value | <0.001 | |
| **Change from baseline in 2-hour post-dose $FEV_1$ at Week 26 (L)** | | |
| n | 631 | 609 |
| Adjusted mean (95% CI) | 0.261 (0.240; 0.283) | 0.145 (0.123; 0.166) |
| p-value | <0.001 | <0.001 |
| Adjusted mean difference (95% CI) | 0.117 (0.086; 0.147) | |
| p-value | <0.001 | |
| **TDI focal score at Week 26** | | |
| n | 642 | 619 |
| Adjusted mean (95% CI) | 1.71 (1.50; 1.92) | 1.50 (1.29; 1.71) |
| p-value | <0.001 | <0.001 |
| Adjusted mean difference (95% CI) | 0.21 (-0.08; 0.51) | |
| p-value | 0.160 | |

CI = Confidence interval; $FEV_1$ = Forced expiratory volume in the 1st second; TDI = Transition dyspnoea index; ITT = Intention-to-treat.
N = Number of patients in the ITT population; n = Number of patients with available data.

The above results were confirmed in the PP population and in the sensitivity analyses conducted to evaluate the impact of different methods for handling missing data and the impact of the differences between severity of airflow limitation recorded in the eCRF and entered in the IRT at randomisation.

The results on pre-dose morning $FEV_1$ were further supported by the responder analysis. In the ITT and PP populations, the percentage of patients classified as $FEV_1$ responders was statistically significantly greater with CHF 5993 pMDI than with CHF 1535 pMDI at Week 26, regardless of the threshold used to define response (50, 70, 100 or 120 mL).

Although statistical significance was not reached in the comparison between treatments in terms of mean TDI focal scores at Week 26, the responder analysis showed a statistically significantly greater percentage of TDI responders (i.e. patients with TDI focal score ≥1) with CHF 5993 pMDI than with CHF 1535 pMDI at Week 26 (57.4% vs. 51.8%). This result was confirmed in the PP population.

For all three co-primary endpoints, the stratified analyses showed that smoking status, gender, degree of reversibility, COPD phenotype, blood eosinophil count, age and significant cardiovascular comorbidities (evaluated for TDI focal score only) did not have a relevant impact on the treatment effect.

Severity of airflow limitation had an effect on the three co-primary endpoints. For pre-dose morning $FEV_1$ at Week 26, the results of the overall analysis were confirmed in severe patients (i.e. with post-bronchodilator $FEV_1$ at screening ≥30% and <50% of predicted normal value), but the adjusted mean difference between treatments did not reach statistical significance in the very severe subgroup (i.e. post-bronchodilator $FEV_1$ at screening <30% of predicted normal value). For 2-hour post dose $FEV_1$ at Week 26, the superiority of CHF 5993 pMDI was confirmed in both subgroups (with a smaller difference between treatments in very severe patients). For TDI focal score at Week 26, a significant difference between treatments in favour of CHF 5993 pMDI was observed in severe, but not in very severe patients.

Secondary Efficacy Analyses

***Pre-dose morning $FEV_1$ and 2-hour post-dose $FEV_1$***

CHF 5993 pMDI was statistically significantly superior to CHF 1535 pMDI in terms of the adjusted mean change in pre-dose morning $FEV_1$ and 2-hour post-dose $FEV_1$ at all timepoints.

The results on pre-dose morning $FEV_1$ were further supported by the responder analysis, where the percentage of patients classified as $FEV_1$ responders was statistically significantly greater with CHF 5993 pMDI than with CHF 1535 pMDI at Week 52, regardless of the threshold used to define response (50, 70, 100 or 120 mL).

In general, the stratified analyses of mean changes from baseline in pre-dose and 2-hour post-dose $FEV_1$ at each timepoint showed similar trends to those seen in the overall analyses. The exception to this was the analysis stratified by severity of airflow limitation. In patients with severe airflow limitation, there was a statistically significantly greater increase from baseline in pre-dose morning $FEV_1$ with CHF 5993 pMDI compared to CHF 1535 pMDI at all visits. In very severe patients, the difference between treatments in the change from baseline in pre-dose morning $FEV_1$ reached statistical significance (in favour of CHF 5993 pMDI) at Weeks 4 and 12 and averaged over the entire treatment period. A post-hoc analysis evaluating the percentage change from baseline in pre-dose morning $FEV_1$ found statistically significant differences favouring CHF 5993 pMDI at all timepoints except Week 52 in very severe patients.

***TDI focal score***

The adjusted mean TDI focal score showed a statistically significant improvement from baseline at all timepoints with both treatments, with a general trend for an increase over time. The improvement in TDI focal score was numerically greater with CHF 5993 pMDI than with CHF 1535 pMDI at all visits and this difference reached statistical significance at Weeks 4 and 12.

The difference between treatments in the percentage of TDI responders (i.e. patients with TDI focal score $\geq$1) did not reach statistical significance at Week 52.

In general, the stratified analyses of mean TDI focal score at each timepoint showed similar trends to those seen in the overall analysis. Statistically significant differences between treatment groups, if present, were generally only seen at Weeks 4 and 12 and were always in favour of CHF 5993 pMDI. However, in patients with severe airflow limitation, statistically significant differences in favour of CHF 5993 pMDI were seen at all timepoints except Week 40.

***SGRQ total and domain scores***

There was a statistically significant adjusted mean decrease (i.e. improvement) from baseline in SGRQ total score with both treatments at all visits, with the difference between treatments in favour of CHF 5993 pMDI reaching statistical significance at Weeks 4, 12 and 52 and approaching statistical significance at Weeks 26 and 40. A similar trend was observed in SGRQ domain scores (symptoms, activity and impacts on daily life). The percentage of patients who were SGRQ responders (i.e. with a change from baseline in total score $\leq$-4) was statistically significantly greater with CHF 5993 pMDI than with CHF 1535 pMDI at Weeks 26 and 52.

***Use of rescue medication***

With both treatments there was a statistically significant increase in the percentage of days without rescue medication over the entire treatment period and for each inter-visit period except for Weeks 41-52 with CHF 1535 pMDI. There was a statistically significant decrease in the average use of rescue medication over the entire treatment period and for all inter-visit periods up to Week 26 with CHF 5993 pMDI compared with no significant change with CHF 1535 pMDI. Statistically significant differences between treatments in favour of CHF 5993 pMDI were found for the percentage of days without rescue medication use up to Week 12 and for the average use of rescue medication up to Week 26.

***Moderate and severe COPD exacerbations***

The rate of moderate and severe COPD exacerbations was statistically significantly lower with CHF 5993 pMDI (adjusted exacerbation rate per patient per year: 0.410) than with CHF 1535 pMDI (0.530). The adjusted rate ratio (95% CI) was 0.773 (95% CI: 0.647; 0.924, p=0.005), indicating a 23% reduction in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to CHF 1535 pMDI. In general, the post-hoc stratified analyses showed similar trends to those seen in the overall analysis, with the exception of the following subgroups: patients with very severe airflow limitation (adjusted rate ratio: 0.941), smokers (0.921) and patients whose main COPD phenotype was chronic bronchitis and emphysema (1.086).

CHF 5993 pMDI significantly prolonged the time to first moderate or severe COPD exacerbation compared to CHF 1535 pMDI, with a hazard ratio (95% CI) of 0.803 (0.668; 0.967) (p=0.020).

Exploratory Efficacy Analyses

***Pre-dose morning FVC and 2-hour post-dose FVC***

For pre-dose morning FVC and 2-hour post-dose FVC, the difference between treatments was statistically significant in favour of CHF 5993 pMDI at all timepoints.

***E-RS total and domain scores***

At all timepoints, there was a statistically significant decrease (i.e. clinical improvement of symptoms) in the E-RS total score from baseline with both treatments, which was statistically significantly greater with CHF 5993 pMDI for all periods up to Week 26 and averaged over the entire treatment period. A similar trend was observed in the analysis of E-RS domain scores, with statistically significant differences favouring CHF 5993 pMDI at all timepoints for breathlessness score and at the earlier periods for cough and sputum score (Weeks 1-4) and chest symptoms score (up to Week 26).

**Safety Results:**

TEAEs

TEAEs were experienced by 368 (53.6%) patients reported with 927 TEAEs in the CHF 5993 pMDI group and 379 (55.7%) patients reported with 928 TEAEs in the CHF 1535 pMDI group. Those reported in ≥2% of patients in either treatment group were: COPD exacerbation, nasopharyngitis, pneumonia, hypertension, headache and respiratory tract infection viral. The majority of TEAEs were mild or moderate in intensity and resolved by the end of the study.

Overall, the incidence of ADRs in both treatment groups was very low. Treatment-emergent ADRs were experienced by 26 (3.8%) patients reported with 31 ADRs in the CHF 5993 pMDI group and 14 (2.1%) patients reported with 15 ADRs in the CHF 1535 pMDI group. The only treatment-emergent ADRs reported in >2 patients in either treatment group were oral candidiasis, muscle spasms and dry mouth.

There were 15 TEAEs leading to death reported in 15 (2.2%) patients in the CHF 5993 pMDI group and 17 TEAEs leading to death reported in 16 (2.4%) patients in the CHF 1535 pMDI group. The most common TEAEs leading to death were from the Cardiac Disorders SOC, with 5 events reported in 5 (0.7%) patients in the CHF 5993 pMDI group and 7 events reported in 7 (1.0%) patients in the CHF 1535 pMDI group. COPD exacerbation led to death in 2 (0.3%) patients in the CHF 5993 pMDI group and in 4 (0.6%) patients in the CHF 1535 pMDI group. None of the deaths were considered related to the study treatment.

There were 180 serious TEAEs reported in 106 (15.4%) patients in the CHF 5993 pMDI group and 162 serious TEAEs reported in 123 (18.1%) patients in the CHF 1535 pMDI group. COPD exacerbation and pneumonia were the most frequently reported serious TEAEs. There was only one serious treatment-emergent ADR of atrial fibrillation (AF), an AE known to be associated with formoterol treatment, reported in 1 (0.1%) patient in the CHF 5993 pMDI group, which was also the only ADR considered severe and which resolved by the end of the study.

There were 43 and 35 TEAEs leading to study drug discontinuation reported in 35 (5.1%) patients and 33 (4.9%) patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively. Those reported in >2 patients in either treatment group were COPD exacerbation (5 [0.7%] and 8 [1.2%] patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively) and [redacted] (4 [0.6%] and 1 [0.1%] patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively).

There were 25 and 18 treatment-emergent pneumonias (including PTs of pneumonia, bronchopneumonia and pneumonia aspiration) reported in 23 (3.3%) patients and 18 (2.6%) patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively. Serious pneumonias were experienced by 15 (2.2%) patients reported with 17 events in the CHF 5993 pMDI group and 7 (1.0%) patients reported with 7 events in the CHF 1535 pMDI group. None were considered treatment-related and none were fatal. One event of pneumonia led to study drug discontinuation in 1 (0.1%) patient in each treatment group. The pneumonia rate per 1,000 patients per year was slightly higher in the CHF 5993 pMDI group than in the CHF 1535 pMDI group (38.9 vs. 28.8).

In both treatment groups, treatment-emergent MACEs were reported in 15 (2.2%) patients. Most of these events were heart failures (6 [0.9%] and 3 [0.4%] patients in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively) and acute myocardial infarctions (1 [0.1%] and 6 [0.9%] patients, respectively). The MACE rate per 1,000 patients per year was similar in both treatment groups (24.9 and 25.6 in the CHF 5993 pMDI and CHF 1535 pMDI groups, respectively).

None of the subgroup analyses (by age, cardiovascular comorbidities, spacer use and gender) highlighted relevant differences in the safety profiles compared with the overall population.

Haematology and Biochemistry Evaluation

The majority of patients did not show changes of clinical concern in terms of changes in haematology and biochemistry parameters.

Vital Signs and BMI

The mean changes in pre-dose and 10-minute post-dose SBP and DBP were minimal and similar in both treatment groups.

There were no relevant changes in BMI during the study for either treatment group.

12-Lead ECG and Holter ECG

The mean changes in pre-dose and 10-minute post-dose 12-lead ECG parameters (HR, QTcF, PR, and QRS) were minimal and similar in both treatment groups. The percentage of abnormalities in QTcF absolute values and changes was similar in both treatment groups.

The most commonly reported 12-lead ECG abnormalities (reported in >2% of patients in either treatment group) were right bundle branch block, AF and ectopic supraventricular rhythm.

The mean changes from baseline in Holter ECG average HR to Weeks 26 and 52 were minimal and similar in both the CHF 5993 pMDI and CHF 1535 pMDI groups.

**Conclusion:**

CHF 5993 pMDI was shown to be superior to CHF 1535 pMDI in terms of the change from baseline to Week 26 in pre-dose morning and 2-hour post-dose $FEV_1$. For TDI focal score at Week 26, the treatment difference in favour of CHF 5993 pMDI did not reach statistical significance. Additional results on TDI focal score and the analysis of other relevant symptoms-based and lung function parameters (including moderate/severe COPD exacerbation rate, SGRQ and E-RS scores and FVC) consistently showed the superior clinical efficacy of CHF 5993 pMDI compared to CHF 1535 pMDI. Both treatments were well-tolerated and with a comparable safety profile.

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