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 5993 pMDI**	**Volume:**	
Name of Active Ingredient: **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, double dummy, randomized, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide administered via pMDI (CHF 5993) versus indacaterol/glycopyrronium (Ultibro®) via DPI in patients with Chronic Obstructive Pulmonary Disease (TRIBUTE)

Investigators: 187 recruiting Investigators in 17 countries.

Study Centres: Multicentre, 212 centres were initiated and 187 were active in 17 countries.

Publication (reference): None

Studied Period: First Patient First Visit (FPFV): 29 May 2015 Last Patient Last Visit (LPLV): 10 July 2017	**Phase of development:** Phase IIIb

Objectives:

Primary objective:

To demonstrate the superiority of CHF 5993 pressurised metered dose inhaler (pMDI) over Ultibro® in terms of moderate and severe chronic obstructive pulmonary disease (COPD) exacerbation rate over 52 weeks of treatment.

Secondary objectives:

- To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures;
- To assess the safety and the tolerability of the study treatments.

Methodology *(Study Design):*

This was a phase IIIb, multinational, multicentre, randomised, double-blind, double-dummy, active-controlled, 2-arm, parallel group study.

The study comprised a pre-screening visit, occurring no more than 7 days prior to a screening visit (Visit [V] 1, Week -2), followed by a 2-week open-label run-in period of indacaterol/GB (85/43 µg/day). At V2 (Week 0), patients were randomised in a 1:1 ratio to receive one of the following treatments for 52 weeks:

- CHF 5993 pMDI 100/6/12.5 µg (delivered dose: 87/5/9 µg BDP/FF/GB), 2 puffs twice daily (b.i.d.) (total daily nominal dose: 400/24/50 µg BDP/FF/GB);
- Indacaterol/GB dry powder inhaler (DPI) 85/43 µg, 1 capsule once daily (o.d.) via Breezhaler® inhaler (total daily nominal dose: 85/43 µg indacaterol/GB).

Subsequent visits were performed after 4 weeks (V3), 12 weeks (V4), 26 weeks (V5), 40 weeks (V6) and 52 weeks (V7).

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

Number of patients *(planned and analysed)*:

It was planned to randomise a total of 1534 patients (767 patients per group). Of note, approximately 20% of patients with very severe airflow limitation (post-bronchodilator forced expiratory volume in the 1st second [FEV_1] at screening < 30% of the predicted normal value) were to be randomised in the study.

A total of 2103 patients were screened, of whom 1532 were randomised to one of the two treatments:

- CHF 5993 pMDI (Trimbow®)
- Indacaterol/GB (Ultibro®)

	CHF 5993 pMDI	Indacaterol/GB
Randomised population	764	768
ITT population	764	768
Safety population	764	768
PP population	742	737

GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; PP = Per-protocol.

Diagnosis and main criteria for inclusion:

Eligible patients included male or female patients aged ≥ 40 years with a diagnosis of severe or very severe COPD made at least 12 months prior to screening (according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] document, updated 2014) and treated with a double therapy (inhaled corticosteroid [ICS]/Long-acting β_2-agonist [LABA], ICS/Long-acting muscarinic antagonist [LAMA] or LABA/LAMA) or with monotherapy with LAMA for at least 2 months prior screening. Patients were current or ex-smokers (who quit smoking at least 6 months before screening) with a smoking history of at least 10 pack-years and a documented history of at least one COPD exacerbation in the 12 months before screening. Patients had a post-bronchodilator FEV_1 < 50% of the predicted normal value and a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio < 0.7 within at least 10-15 minutes after 4 puffs (4 x 100 µg) of salbutamol 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 b.i.d.

Total daily nominal dose: BDP 400 µg, FF 24 µg, GB 50 µg.

Each delivered dose per actuation contained 87 µg BDP, 5 µg FF and 9 µg glycopyrronium (as 11 µg GB).

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

Batch number:

Campaign	Packaging Batch Number	Manufacturing Batch	Expiry Date
1	[redacted]	[redacted]	[redacted]
2		[redacted]	[redacted]
3		[redacted]	[redacted]
4			

Duration of treatment:

A 2-week open-label run-in period under indacaterol/GB followed by a 52-week randomised treatment period.

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

Reference product: Indacaterol/GB (Ultibro®) DPI.

Dose: Indacaterol 85 µg, GB 43 µg, 1 capsule o.d.

Total daily nominal dose: indacaterol 85 µg, GB 43 µg.

Mode of administration: DPI Breezhaler® inhaler.

Batch number:

Campaign	Packaging Batch Number	Manufacturing Batch / Commercial Batch	Expiry Date
1	[redacted]	[redacted]	[redacted]
1A			
2A			
2B			
3A			
3B			
4			
5			
6			

Criteria for evaluation:

Efficacy:

Primary efficacy variable:

The primary efficacy variable was the number of moderate and severe COPD exacerbations over 52 weeks of treatment.

Secondary efficacy variables:

- Time to first moderate or severe COPD exacerbation;
- Number of severe COPD exacerbations over 52 weeks of treatment;
- Time to first severe COPD exacerbation;
- Number of moderate COPD exacerbations over 52 weeks of treatment;
- Change from baseline in pre-dose morning FEV_1 at each visit and over the entire treatment period;
- 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 pre-dose morning FVC at each visit and over the entire treatment period;
- Change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score and domain scores at all clinic visits and over the entire treatment period;
- SGRQ response (change from baseline in total score ≤ -4) at Week 26 and Week 52;
- Change from baseline to each inter-visit period and over the entire treatment period in the percentage of days, nights and complete days (i.e. day + night) without intake of rescue medication;
- Change from baseline to each inter-visit period and over the entire treatment period in the average use of rescue medication during the day (number of puffs/day), during the night (number of puffs/night) and overall (number of puffs/complete day);
- Change from baseline to each inter-visit period and over the entire treatment period in the Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (E-RS) total and domain scores;
- Nocturnal symptoms (with an EXAcerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcome [EXACT-PRO] specific domain);
- Change from baseline in COPD assessment test (CAT) score at the end of treatment.

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 days in intensive care unit (ICU) 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);
- Pneumonias;
- Vital signs (pulse rate, systolic and diastolic blood pressure [SBP] and [DBP], respectively);
- 12-lead electrocardiogram (ECG) parameters: heart rate (HR), Fridericia's corrected QT interval (QTcF), PR interval (PR) and QRS interval (QRS);
- 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 (primary or secondary efficacy variables) after baseline;
- Per-protocol (PP) population, defined as all patients from the ITT population without any major protocol deviations (e.g. wrong inclusions, poor compliance, non-permitted medications).

The comparison between CHF 5993 pMDI and indacaterol/GB in terms of the primary efficacy variable was performed in the ITT and PP populations. The secondary efficacy variables and the health economic variables were analysed in the ITT population and the safety variables were analysed in the Safety population.

Efficacy analysis

Primary efficacy variable:

The number of moderate and severe COPD exacerbations over 52 weeks of treatment 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.

The adjusted exacerbation rate in each treatment group and the adjusted rate ratio with associated 95% Wald confidence intervals (CIs) were estimated by the model. Superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated if the upper limit of 95% CI for the adjusted exacerbation rate ratio was < 1.

In order to assess the potential impact of missing data on the results of the primary efficacy analysis, sensitivity analyses based on multiple imputation (MI) were performed on the randomised population: Missing at Random (MAR) and copy reference imputation. A sensitivity analysis was also performed to assess the impact of the discrepancy between severity of airflow limitation recorded in the centralised spirometry and entered in the Interactive Response Technology (IRT).

The analysis of the primary efficacy variable was also performed in the ITT population stratifying by: severity of airflow limitation, smoking status at screening, gender, degree of reversibility, main COPD phenotype, blood eosinophil absolute and relative counts and number of COPD exacerbations in the year prior to screening.

Secondary efficacy variables:

- Time to first moderate or severe COPD exacerbation and time to first severe COPD exacerbation were analysed using a Cox proportional hazard regression model including treatment, country, number of COPD exacerbations during the previous year, severity of airflow limitation and smoking status as factors;
- Number of severe COPD exacerbations and number of moderate COPD exacerbations were analysed using the same model as for the primary efficacy variable;
- Changes from baseline in pre-dose morning FEV_1 and FVC as well as changes from baseline in the SGRQ total score and domain scores, at each visit and over the entire treatment period were analysed using a linear mixed model for repeated measures (MMRM) including treatment, country, visit, treatment by visit interaction, number of COPD exacerbations during the previous year, severity of airflow limitation and smoking status at screening as fixed effects, and baseline and baseline by visit interaction as covariates;
- FEV_1 and SGRQ responses at Week 26 and Week 52 were analysed using a logistic regression model including treatment, country, number of COPD exacerbations during the previous year, severity of airflow limitation and smoking status at screening as factors and baseline FEV_1 or SGRQ as a covariate;
- Changes from baseline to each inter-visit period and over the entire treatment period in the percentage of days, nights and complete days (i.e. day + night) without intake of rescue medication as well as in the average day-time, night-time and overall (i.e. day-time + night-time) use of rescue medication were analysed using a linear MMRM including treatment, country, inter-visit period, treatment by inter-visit period interaction, number of COPD exacerbations during the previous year, severity of airflow limitation and smoking status as fixed effects, and baseline and baseline by inter-visit period interaction as covariates;
- Changes from baseline to each inter-visit period and over the entire treatment period in the E-RS total and domain scores were analysed using the same model as for the rescue medication use;
- Nocturnal symptoms were collected in the EXACT-PRO domain and were analysed using the same model as for the rescue medication use;
- Change from baseline in the CAT score at the end of treatment was summarised using descriptive statistics.

The analysis of pre-morning FEV_1 was also performed in the ITT population stratifying by the same factors used for the subgroup analyses of the primary efficacy variable, except for the number of COPD exacerbation in the previous year prior to screening.

Health economic variables:

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

Post-hoc analysis

The analysis of the change from baseline in SGRQ total score was also performed in the ITT population stratifying by the same factors used for the subgroup analyses of the primary efficacy variable, except for the number of COPD exacerbations in the previous year prior to screening.

Safety analysis

The number of treatment-emergent AEs (TEAEs), serious AEs (SAEs), non-serious AEs, ADRs, serious ADRs, severe AEs, AEs leading to study treatment 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. The type of pneumonia, its method of diagnosis and potential causes were also summarised using descriptive statistics. The analyses of AEs and pneumonias were also performed in the Safety population stratifying by age group.

Mean change in SBP, DBP and pulse rate from baseline to each time point after the first study treatment intake and from pre-dose to post-dose at each clinic visit was calculated with its 95% CI by treatment group.

The mean absolute values of the 12-lead ECG parameters at Week 26 and at the end of treatment were calculated with their 95% CIs by treatment group. The mean changes from baseline to Week 26 and to the end of treatment in these parameters were calculated with their 90% CIs by treatment group. Abnormalities in QTcF absolute values and changes from baseline were presented by treatment group.

Shift tables from screening to Week 26 and to the end of treatment with regard to normal ranges, were presented by treatment group for each of the laboratory parameters

Summary - Results:

Efficacy Results:

A total of 1532 patients were randomised to receive either CHF 5993 pMDI (N=764) or indacaterol/GB (N=768). The majority of patients (85.8%) completed the study, with fewer discontinuations in the CHF 5993 pMDI group, in particular from Week 12, compared to the indacaterol/GB group. Demographic and baseline characteristics were similar between treatment groups. Over 20% of patients had very severe airflow limitation (i.e. post-bronchodilator FEV_1 at screening < 30% of the predicted normal value).

Primary Efficacy Analyses

The superiority of CHF 5993 pMDI over indacaterol/GB was demonstrated in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment (see table below).

The adjusted exacerbation rate per patient per year was lower with CHF 5993 pMDI than with indacaterol/GB (0.504 and 0.595, respectively) and the adjusted rate ratio represented a statistically significant difference between treatments in favour of CHF 5993 pMDI (adjusted rate ratio [95% CI] 0.848 [0.723, 0.995], p=0.043). These results indicated an important reduction of 15.2% in the rate of moderate/severe COPD exacerbations with CHF 5993 pMDI compared to indacaterol/GB.

Moderate and severe COPD exacerbations – ITT population

			CHF 5993 pMDI N=764	Indacaterol/GB N=768
Total follow up time (years)			717.97	707.36
All Moderate/ Severe COPD Exacerbations	Number (%) of Patients with Exacerbations		273 (35.7)	288 (37.5)
	Number of Exacerbations		433	485
	Exacerbation Rate per Patient per Year		0.603	0.686
	Adj. Exacerbation Rate per Patient per Year (95% CI)		0.504 (0.447, 0.569)	0.595 (0.530, 0.668)
	CHF 5993 pMDI vs. Indacaterol/GB	Adj. rate ratio (95% CI)	0.848 (0.723, 0.995)	
		p-value	0.043	

Adj. = Adjusted; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; GB = Glycopyrronium bromide; ITT = Intention-to-treat; pMDI = Pressurised metered dose inhaler; vs. = Versus.
N = Number of patients in the ITT population.

The above results were confirmed in the PP population and in the sensitivity analyses.

In general, in the stratified analyses, the comparison of the moderate/severe COPD exacerbation rate between CHF 5993 pMDI and indacaterol/GB showed similar trends to those seen in the overall analysis, consistently indicating a reduction of exacerbation rate with CHF 5993 pMDI compared to indacaterol/GB.

Secondary Efficacy Analyses

Moderate and Severe COPD Exacerbations

Although not statistically significant, results showed that, compared to indacaterol/GB, CHF 5993 pMDI prolonged the time to the first moderate/severe exacerbation (hazard ratio [95% CI] 0.901 [0.763, 1.064], p=0.219) and the time to the first severe exacerbation (0.864 [0.613, 1.219], p=0.405). The differences were already evident from the first month of treatment, as shown by the early separation of Kaplan-Meier analysis curves.

There were numerical differences between CHF 5993 pMDI and indacaterol/GB in the rate of moderate exacerbations (adjusted rate ratio [95% CI] 0.866 [0.723, 1.037], p=0.118) and of severe exacerbations (adjusted rate ratio [95% CI] 0.787 [0.551, 1.125], p=0.189), indicating a reduction of moderate (13.4%) and of severe exacerbations (21.3%) in favour of CHF 5993 pMDI.

Pre-dose Morning FEV_1 at Each Visit and Over the Entire Treatment Period

With CHF 5993 pMDI, the adjusted mean change from baseline in pre-dose morning FEV_1 increased significantly up to Week 12 followed by a slight decrease at subsequent visits, whereas with indacaterol/GB there was a consistent decrease from Week 4. The adjusted mean difference between treatments was consistently in favour of CHF 5993 pMDI throughout the 52-week treatment period. The difference was statistically significant at Week 12 and Week 40 (p=0.005 and p=0.006, respectively). Averaged over the entire treatment period, the adjusted mean change in pre-dose morning FEV_1 from baseline did not change from baseline in the CHF 5993 pMDI group, while it decreased in the indacaterol/GB group, with a statistically significant treatment difference of 0.022 L observed in favour of CHF 5993 pMDI compared to indacaterol/GB (p=0.018).

FEV_1 Response at Week 26 and Week 52

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 (i.e. change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) was numerically greater with CHF 5993 pMDI than with indacaterol/GB at Weeks 26 and 52.

Pre-dose Morning FVC at Each Visit and Over the Entire Treatment Period

Averaged over the entire treatment period, the adjusted mean change in pre-dose morning FVC significantly decreased from baseline in both CHF 5993 pMDI and indacaterol/GB groups, with a numerical treatment difference of 0.024 L observed in favour of CHF 5993 pMDI compared to indacaterol/GB.

SGRQ Total and Domain Scores at Each Visit and Over the Entire Treatment Period

The adjusted mean change from baseline in SGRQ total score was a statistically significant decrease (i.e. improvement) with both treatments at all time points. The decrease was statistically significantly greater with CHF 5993 pMDI than with indacaterol/GB at all time points, with an average treatment difference over the entire treatment period of -1.68. Treatment differences averaged across the entire treatment period were statistically significantly in favour of CHF 5993 pMDI for all SGRQ domain scores (symptoms, impacts and activity scores). The percentage of patients who were SGRQ responders (i.e. with a change from baseline in total score $\leq$ -4) was numerically greater with CHF 5993 pMDI than with indacaterol/GB at Weeks 26 and 52.

Use of Rescue Medication

The adjusted mean change from baseline in the percentage of days, nights and complete days (day + night) without rescue medication, as well as in the day-time, night-time and overall use of rescue medication all showed a statistically significant improvement over the entire treatment period and at every inter-visit period with both treatments. Overall, the improvements observed in each parameter were comparable in both treatment groups.

E-RS Total and Domain Scores

The adjusted mean change from baseline in E-RS total score was a statistically significant decrease (i.e. improvement) with both treatments at all time points. The decrease was statistically significantly greater with CHF 5993 pMDI than with indacaterol/GB up to inter-visit period Week 5-12 and remained numerically greater at all other inter-visit periods. Treatment differences averaged across the entire treatment period for all individual E-RS domain scores (breathlessness, cough and sputum and chest symptoms) were numerically in favour of CHF 5993 pMDI.

Nocturnal Symptoms

The adjusted mean change from baseline in the EXACT-PRO nocturnal symptoms score was a statistically significant decrease (i.e. improvement) with both treatments at all time points. The improvements observed were comparable between treatment groups.

CAT Score

With both CHF 5993 pMDI and indacaterol/GB, CAT score decreased (i.e. improved) from baseline by a similar extent.

Health Economics

The increase (i.e. improvement) from baseline in health economic variables (EQ-5D-3L index and VAS values) was comparable for both CHF 5993 pMDI and indacaterol/GB.

Safety Results:

TEAEs

TEAEs were experienced by 490 (64.1%) patients reported with 1292 TEAEs in the CHF 5993 pMDI group and by 516 (67.2%) patients reported with 1432 TEAEs in the indacaterol/GB group. Those reported in $\geq$ 2% of patients in any treatment group were: COPD exacerbation, nasopharyngitis, headache, pneumonia, back pain, dyspnoea, hypertension and cough. The majority of TEAEs were mild or moderate in intensity and resolved by the end of the study.

The incidence of ADRs in this study was low and similar between treatments. Treatment-emergent ADRs were experienced by 43 (5.6%) patients reported with 50 ADRs in the CHF 5993 pMDI group and 37 (4.8%) patients reported with 53 ADRs in the indacaterol/GB group. The treatment emergent ADRs reported in > 2 patients in any treatment group were: oral candidiasis, dry mouth, cough, muscle spasms, hypertension, dry throat, dysphonia and throat irritation. The majority of reported treatment-emergent ADRs were mild or moderate in intensity and resolved by the end of the study.

There were 20 TEAEs leading to death reported in 16 (2.1%) patients in the CHF 5993 pMDI group and 26 TEAEs leading to death reported in 21 (2.7%) patients in the indacaterol/GB group. The most common TEAEs leading to death were from the "cardiac disorders" SOC, with 2 events reported in 2 (0.3%) patients in the CHF 5993 pMDI group and 9 events reported in 8 (1.0%) patients in the indacaterol/GB group, or from the "general disorders and administration site conditions" SOC, with 3 TEAEs leading to death reported in 3 (0.4%) patients in the CHF 5993 pMDI group and 8 TEAEs leading to death in 8 (1.0%) patients in the indacaterol/GB group. None of the deaths were considered related to the study treatment.

There were 170 serious TEAEs reported in 117 (15.3%) patients in the CHF 5993 pMDI group and 208 serious TEAEs reported in 130 (16.9%) patients in the indacaterol/GB group. COPD exacerbation and pneumonia were the most common serious TEAEs.

A total of 2 serious treatment-emergent ADRs were reported: one event of dysuria in the CHF 5339 pMDI group, which was resolved by the end of the study, and one event of permanent atrial fibrillation in the indacaterol/GB group, which did not resolve before study participation ended.

There were 45 TEAEs leading to study treatment discontinuation reported in 37 (4.8%) patients in the CHF 5993 pMDI group and 56 TEAEs leading to study treatment discontinuation reported in 47 (6.1%) patients in the indacaterol/GB group. Those reported in > 2 patients in any treatment group, were COPD exacerbation, death (cause of death unknown), acute myocardial infarction, lung neoplasm malignant, pneumonia and sudden cardiac death.

Treatment-emergent pneumonias and serious pneumonias were reported with a similar and low incidence in both treatment groups: 32 pneumonias in 28 (3.7%) patients with CHF 5993 pMDI and 29 pneumonias in 27 (3.5%) patients with indacaterol/GB, with 18 serious events reported in each treatment group. One non-serious event of pneumonia of moderate intensity was considered treatment-related in the CHF 5993 pMDI group only. Four events of pneumonia led to study treatment discontinuation: 3 events in 3 (0.4%) patients in the CHF 5993 pMDI group and 1 event in 1 (0.1%) patient in the indacaterol/GB group; all of these events also led to death, except for one patient in the CHF 5993 pMDI group, who died of an unknown cause. The pneumonia rate per 1,000 patients per year was comparable in both groups: 44.6 in the CHF 5993 pMDI and 41.0 in the indacaterol/GB group.

Overall, safety results in the analysis stratified by age, were in line with the overall analysis.

Haematology and Biochemistry Evaluation

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

Vital Signs

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

12-Lead ECG

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

Conclusion:

This study demonstrated superiority of CHF 5993 pMDI over indacaterol/GB in highly symptomatic COPD patients with severe or very severe airflow limitation, in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment. Compared to indacaterol/GB, CHF 5993 pMDI provided an important reduction of the exacerbation rate as well as improvements in lung function (FEV_1) and quality of life (QoL) (SGRQ). CHF 5993 pMDI was well-tolerated and no particular safety concerns were raised in comparison to approved indacaterol/GB in terms of TEAEs and changes in vital signs, ECG and laboratory parameters. Notably, no difference in pneumonias was observed between treatments.

Date of report: Final 1.0 – 22 November 2017