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CLINICAL STUDY PROTOCOL

STUDY CODE No.: CCD-5993AA1-14

A 24-week, Double Blind, Double dummy, Randomized, 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 the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease

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GENERAL INFORMATION

SPONSOR:	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
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VERSION HISTORY

Version	Date	Change History
1.0	9 February 2016	First version
2.0	2 May 2016	Second version Administrative updates Revisions according to the new Chiesi Protocol Template
3.0	6 March 2019	Third version Administrative updates Revisions according to the new Chiesi Protocol Template Interim analysis ECG and K^+ assessments for patient eligibility

PROTOCOL OUTLINE

Study title	A 24-week, Double Blind, Double dummy, Randomized, 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 the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 100/6/12.5µg pMDI (beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide [GB])
Centre(s)	Multicenter, in approximatively 70 sites
Indication	Chronic Obstructive Pulmonary Disease (COPD)
Study design	Double-blind, double-dummy, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled study
Study phase	III
Objectives	***Primary objective*** To demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 and 2-hour post-dose morning FEV_1 at Week 24). ***Key secondary objective*** To demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 and 2-hour post-dose morning FEV_1 at Week 24) in the subgroup of Chinese population. ***Other secondary objectives*** • To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures. • 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.
Treatment duration	A 2-week open-label run-in period under Symbicort® Turbuhaler® followed by a 24-week randomised treatment period.
Test product dose/route/regimen	**CHF 5993 100/6/12.5 µg**

	Fixed combination of extrafine beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose (BDP/FF/GB) **Dose regimen**: BDP/FF/GB 100/6/12.5 µg per inhalation, 2 inhalations BID, daily dose 400/24/50 µg **Administration**: pressurised metered dose inhaler (pMDI) for CHF 5993 Note: Patients used to inhale their COPD pMDI medications with a spacer should continue using a spacer (AeroChamber Plus Flow Vu Antistatic™) to take the pMDI study drugs.
Reference product dose/route/regimen	**Symbicort® Turbuhaler®:** Fixed combination of 160 µg budesonide + 4.5 µg formoterol fumarate (160 µg + 4.5 µg expresses the delivered dose; 200 µg + 6 µg expresses the metered dose) (BUD/FF). **Dose regimen:** BUD/FF, 160/4.5 µg per inhalation, 2 inhalations BID, daily dose 800/24 µg **Administration:** dry powder inhaler (Turbuhaler®, AstraZeneca AB, Sweden)
Number of patients	A total of 990 patients (495 patients per group) will be randomised in order to reach a total of 832 evaluable patients at Week 24 (416 per group), considering a non-evaluable rate of approximately 16% at this time point. The study is planned to recruit 75% of patients in China and 25% of patients in Korea and Taiwan (with at least 96 patients randomized in Taiwan in order to reach at least 80 evaluable Taiwanese patients). A screen failure rate of 20% is anticipated; therefore a total of 1238 patients will be screened. A lower number of patients could be enrolled in case the interim analysis outcome is positive (see section 12.4.4 for additional information).
Study population	Patients with severe to very severe COPD
Inclusion/exclusion criteria	**Inclusion criteria** Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study: 1. Male and female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure. 2. Patients with a diagnosis of COPD (according to GOLD 2015 strategic document [20], updated January 2015) at least 12 months before the screening visit.

3. A smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20]. Current and ex-smokers are eligible.

   Smoking cessation therapy must be completed 6 months prior to screening visit.

4. A post-bronchodilator $FEV_1 < 50\%$ of the predicted normal value **and** a post-bronchodilator FEV_1/FVC ratio < 0.7 at least 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI

   If this criterion is not met at screening, the test can be repeated once before randomisation visit.

5. A **documented** history of at least one exacerbation in the 12 months preceding the screening visit.

   COPD exacerbation will be defined according to the following:

   "A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization".

6. Patients under therapy for at least 2 months prior to screening with either:
   - Inhaled corticosteroids/long-acting β-agonist or
   - Inhaled corticosteroids/long-acting muscarinic antagonist or
   - Inhaled long-acting β-agonist and inhaled long-acting muscarinic antagonist or
   - Long-acting muscarinic antagonist or
   - Long-acting β-agonist
7. A cooperative attitude and ability to be trained to use correctly the study drugs inhalers (pMDI and DPI Turbuhaler®).
8. A cooperative attitude and ability to be trained to use correctly the COPD questionnaires.

At screening visit (Visit 1), all inclusion criteria will be checked.

At the randomisation visit (Visit 2), the following criteria will be re-checked: 7, 8

Exclusion criteria

The presence of any of the following will exclude a patient from study enrolment:

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more of the following reliable methods of contraception:
   a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   b. Hormonal contraception (implantable, patch, oral).

	c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository. d. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). Reliable contraception should be maintained throughout the study until last study visit. "True abstinence" is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening (V1) and end of treatment (V6), urine pregnancy test will be performed at all visits except V0 and V6. Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea") or women permanently sterilized (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) can be enrolled in the study. 2. Diagnosis of asthma, history of allergic rhinitis or atopy (atopy which may raise contra-indications or impact the efficacy of the study according to Investigator's judgment). 3. Patients requiring use of the following medications: a. Systemic steroids for COPD exacerbation in the 4 weeks prior to screening. b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening. c. PDE inhibitors in the 4 weeks prior to screening. d. Use of antibiotics for a lower respiratory tract infection (e.g pneumonia) in the 4 weeks prior to screening. 4. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period. 5. Changes in dose, schedule, formulation or product of oral xanthine derivatives (e.g. theophylline) in the month prior to screening visit or during the run-in period. Stop of xanthines prior to screening visit is allowed. 6. Patients treated with non-cardioselective β-blockers in the week preceding the screening visit or during the run-in period. 7. Patients treated with long-acting antihistamines (e.g. astemizole, terfenadine) unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study, or if taken as PRN. 8. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.

	9. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according the Investigator's judgment. This can include but is not limited to α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease. 10. Patients who have clinically significant cardiovascular condition (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV, left ventricular failure, acute myocardial infarction), advanced atrio-ventricular conduction blocks. 11. Patients with atrial fibrillation (AF): • Paroxysmal (i.e. intermittent). • Persistent as defined by continuous atrial fibrillation diagnosed for less than 6 months. • Persistent for at least 6 months with a resting ventricular rate ≥ 100/min controlled with a rate control strategy (i.e. selective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy). 12. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgement. Patients whose electrocardiogram (ECG) (12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening and at randomisation visits are not eligible. 13. Medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would prevent use of anticholinergic agents. 14. History of hypersensitivity to M3 antagonists, β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial. 15. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to Investigator's judgement. 16. Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L) at screening. 17. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to Investigator's judgment.

	18. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit. 19. Participation in another clinical trial where investigation drug was received less than 8 weeks prior to screening visit. 20. Patients treated with Traditional Chinese Medicines used for respiratory diseases. At screening visit (Visit 1), all exclusion criteria will be checked except criterion 4. At the randomisation visit (Visit 2), the following criteria will be re-checked: 1 ,4 ,5 , 6, 7, 10, 11, 12, 17, 20
Study plan	A total of 7 clinic visits (V0 to V6) will be performed during the study, as follows: - A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients, to obtain the written informed consent from the patient and to instruct the patient on screening visit procedures (such as medication restrictions) - A screening visit (V1, no more than 7 days after V0) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, a 12-lead ECG, spirometric parameters after salbutamol, vital signs and training for the use of inhalers). This visit will be followed by a 2-week open-label run-in period where patients will be on Symbicort® Turbuhaler® 160/4.5 µg per inhalation, 2 inhalations bid. - After the randomisation (V2), patients will be assessed after 4, 12, 18 and 24 weeks of treatment (V3 to V6) at clinic/hospital. - A safety follow-up call, 1 week after the last visit (V6) or the Early Termination visit, will occur to check the status of any unresolved adverse events and to record any new AEs that have occurred after the last visit Inhaled salbutamol will be provided to be administered as rescue medication on an as-needed basis for both the run-in and the randomized period. AEs and COPD exacerbations will be monitored throughout the study. A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6.
Most relevant allowed concomitant treatments	1. Inhaled salbutamol administered as rescue medication on an as-needed basis. A minimum period of 6 hours should elapse between the use of rescue salbutamol and the spirometric measurements. 2. Xanthine derivatives (e.g. theophylline) if taken at stable regimen for at least one month prior to screening and to be maintained constant during the study.

	3. Long-acting antihistamines if taken at stable regimen at least 2 months prior to screening or if taken PRN. For patients not under stable long-acting antihistamines, short courses are allowed during the study period (≤7 days). Other antihistamines are allowed during the study period for short course (≤10 days) or if taken PRN. 4. **In case of COPD exacerbation**, short courses of the following medications are allowed during the treatment period: a) Systemic corticosteroid (oral/IV/IM). b) Inhaled short acting β_2-agonists and/or short acting muscarinic antagonists or combination of both. c) Nebulised β_2-agonists, anticholinergics and/or steroids. d) Antibiotics. e) Oxygen. f) Mechanical ventilation at the Investigator's discretion. 5. Short courses (≤ 10 days) of nasal inhaled corticosteroids (maximum 4 courses) are allowed during the treatment period 6. In case of other concomitant diseases, any appropriate treatment that, according to the Investigator, does not interfere with the study evaluation parameters is allowed. All concomitant medications should be noted in the relevant section of the CRF.
Most relevant forbidden concomitant treatments	1. Depot corticosteroids. 2. Oral/IV/IM corticosteroids (short courses allowed in case of COPD exacerbation during the treatment period). 3. Nebulised β2-agonists, anticholinergics and/or steroid (short courses allowed in case of COPD exacerbation during the treatment period). 4. Inhaled corticosteroids. 5. Inhaled long-acting β_2-agonists or fixed combination of corticosteroids and long-acting β_2-agonists other than study treatments (e.g. salmeterol/fluticasone). 6. Inhaled long-acting muscarinic antagonist. 7. Inhaled short acting β_2-agonists (other than salbutamol) (Short course allowed in case of COPD exacerbation during the treatment period). 8. Inhaled fixed combinations of a short-acting β2-agonist and a short-acting muscarinic antagonist (Short course allowed in case of COPD exacerbation during the treatment period). 9. Inhaled short-acting muscarinic antagonists (ipratropium and oxytropium) (Short course allowed in case of COPD exacerbation during the treatment period). 10. Non-cardioselective β-blockers 11. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and other drugs known to prolong the QTc interval.

	12. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit. 13. PDE inhibitors (e.g. roflumilast). 14. Leukotriene modifiers. 15. Traditional Chinese Medicines used for respiratory diseases. ***Prior to screening spirometry, the following wash out periods for concomitant medications must be respected:*** • Inhaled short-acting β_2-agonists: 6 hours • Inhaled short-acting muscarinic antagonist: 12 hours • Inhaled SABA/SAMA fixed combinations: 12 hours • Inhaled long acting muscarinic antagonist : 72 hours • Inhaled long-acting β_2-agonists: 12 hours • Inhaled daily long-acting β_2-agonists (indacaterol): 24 hours • Inhaled corticosteroids: 12 hours • Inhaled ICS/LABA fixed combinations: 12 hours • Leukotriene modifiers: 72 hours ***Prior to each spirometry, the following wash out periods for concomitant medications must be respected:*** • Inhaled short-acting β_2-agonists: 6 hours • Inhaled short-acting muscarinic antagonist: 12 hours • Inhaled SABA/SAMA fixed combinations: 12 hours
Efficacy variables	**Primary efficacy variables** • Change from baseline in pre-dose FEV_1 at Week 24. • Change from baseline in 2-hour post-dose FEV_1 at Week 24. **Secondary efficacy variables** • Change from baseline in pre-dose and 2-hour post-dose FEV_1 at all the other clinic visits. • FEV_1 response (change from baseline $\geq$ 100 mL) at Week 24. • Time to first COPD exacerbation. • Rate of COPD exacerbations over 24 weeks of treatment. • Change from baseline in pre-dose FVC and IC at all clinic visits and change from baseline to 2-hour post-dose FVC at all clinic visits. • Pre-dose FEV_1/FVC at all clinic visits. • Change from baseline in Forced Expiratory Flow ($FEF_{25-75\%}$). • Change from baseline in the SGRQ total score and domain scores at all clinic visits.

	• SGRQ response (change from baseline in total score ≤-4) at Week 24. • Change from baseline in COPD Assessment Test (CAT) at all clinical visits. • 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/day). **Health economic variables** • EQ-5D-3L VAS score and EQ-5D-3L index at all clinic visits. • Number of hospital admissions due to COPD and other causes. • Number of days with oxygen therapy use due to COPD. • Unplanned diagnostic or instrumental tests performed due to COPD. • Mortality.
Safety variables	• Adverse Events (AEs) and Adverse Drug Reactions (ADRs) • Vital signs (systolic and diastolic blood pressure) • 12-lead ECG parameters: heart rate (HR), PR, QRS, QTcF (baseline, pre-dose and 10 min post-dose at Week 12 and Week 24) • Standard Haematology and Blood Chemistry
Sample size calculation	The sample size has been calculated to demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of change from baseline in pre-dose morning FEV_1 and change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the overall study population and in the Chinese population. A total of 990 patients (495 patients per group) will be randomised in order to reach a total of 832 evaluable patients at Week 24 (416 per group), considering a non-evaluable rate of approximately 16% at this time point. The study is planned to recruit 75% of patients in China and 25% of patients in Korea and Taiwan (with at least 96 patients randomized in Taiwan in order to reach at least 80 evaluable Taiwanese patients). This sample size will provide: • approximately 93.3% power to detect a mean difference of 60 mL in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 mL; • approximately 98.1% power to detect a mean difference of 70 mL in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 mL.

	An overall study power for the primary efficacy analysis of approximately 91.5% will therefore be ensured. Under the assumptions of 75% of patients recruited in China (742 randomized, 624 evaluable), this sample size will provide: • approximately 85% power to detect a mean difference of 60 mL in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 mL; • approximately 93.8% power to detect a mean difference of 70 mL in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 mL. An overall power for the primary efficacy analysis in the subgroup of Chinese population of approximately 80% will therefore be ensured. A lower number of patients could be enrolled in case the interim analysis outcome is positive (see section 12.4.4 for additional information).
Statistical methods	**Primary efficacy variables** • Change from baseline (Visit 2) in pre-dose morning FEV_1 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, number of COPD exacerbations in the previous year (1 or >1) and smoking status as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) and p-values at Week 24 will be estimated by the model. Superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® will be demonstrated by a statistically significant difference between treatments at Week 24 (defined as $p<0.05$) favouring CHF 5993 pMDI. • Change from baseline (Visit 2 pre-dose) to the 2-hour post-dose value of FEV_1 will be analysed using a similar model as for change from baseline in pre-dose morning FEV_1. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs and p-value at Week 24 will be estimated by the model. Superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® will be demonstrated by a statistically significant difference between treatments at Week 24 favouring CHF 5993 pMDI. The primary efficacy variables will be tested in the overall population first and then in the subgroup of Chinese population. **Secondary efficacy variables** • For change from baseline in pre-dose morning FEV_1 and change from baseline in 2-hours post-dose FEV_1 the adjusted means in each treatment group and the adjusted mean differences between

	treatments at all the other clinic visits will be estimated with their 95% CIs by the same model used for the primary efficacy analysis. • FEV_1 response at Week 24 will be compared between treatment groups using a logistic model including treatment, country, number of COPD exacerbations in the previous year and smoking status as factors and the baseline value as a covariate. • At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FEV_1 will be analysed using an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year and smoking status 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 will be analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year and smoking status as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model. • The time to first COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year and smoking status as factors. A Kaplan-Meier plot will also be presented. • Change from baseline in pre-dose FVC, pre-dose IC and change from baseline in 2-hour post dose FVC at all clinic visits will be analysed using a similar model as for the primary efficacy variables. • At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FVC will be analysed using a similar model as for FEV_1. • Pre-dose FEV1/FVC will be presented by descriptive statistics at all visits. • Change from baseline in Forced Expiratory Flow ($FEF_{25-75\%}$), the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis • Change from baseline (Visit 2) in the SGRQ total score and domain scores at all clinic visits will be analysed using a similar model as for the primary efficacy variables. • SGRQ response at Week 24 will be compared between treatment groups using a similar model as for FEV_1 response. • Change from baseline (Visit 2) in the CAT score at all clinic visits will be analysed using a similar model as for the primary efficacy variables

	• Change from baseline (run-in period) to each inter-visit period in the percentage of days without intake of rescue medication and in the average use of rescue medication will be analysed using a similar model as for the primary efficacy variables. The inter-visit period will be considered instead of visit in the model. For these variables, the change from baseline to the entire treatment period will be analysed using an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year and smoking status as fixed effects and the baseline value as a covariate.
	All secondary efficacy variables will be presented overall and in the subgroup of Chinese population.
	Health economic variables
	• Health economic variables will be summarised by treatment group using descriptive statistics (overall and by country). The details on other analyses of health economic data will be provided in a separate analysis plan. This health economic analysis will not be part of the Clinical Study Report.
	Safety variables
	• The number and the percentage of patients experiencing adverse events (AEs), adverse drug reactions (ADRs), serious AEs (SAEs), severe AEs, AEs leading to discontinuation and AEs leading to death will be summarised by treatment group. AEs will also be summarised by System Organ Class and Preferred Term using the MedDRA dictionary.
	• Mean change in vital signs (systolic and diastolic blood pressure) from baseline (Visit 2 pre-dose) to each time point after the first study drug intake and from pre-dose to post-dose at each clinic visit will be calculated with its 95% CI by treatment group.
	• At each time point after the first study drug intake, the mean absolute values of the 12-lead ECG parameters (HR, PR, QRS and QTcF) will be calculated with their 95% CIs by treatment group.
	• The number and the percentage of patients with a:
	  • QTcF >450 ms, >480 ms and >500 ms
	  • change from baseline (Visit 2 pre-dose) in QTcF >30 ms and >60 ms
	  • only for post-dose time points: change from pre-dose at the same visit in QTcF >30 ms and >60 ms
	At each time point after the first study drug intake and at any time point after the first study drug intake will be presented by treatment group.
	• Mean changes from screening in the laboratory parameters will be calculated with their 95% CIs by treatment group.
	• Shift tables from screening to any visit, with regard to normal range, will be presented by treatment group for the laboratory parameters.

	All safety variables will be presented overall and in the subgroup of patients in the Chinese population.
Interim analysis	An unblinded interim analysis will be conducted by an independent DMC on 534 evaluable patients (of whom 434 are expected to be recruited from China), testing the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of change from baseline in pre-dose morning FEV_1 and change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the overall study population and in the Chinese population (i.e. primary efficacy variables). The DMC will review the results of the primary efficacy endpoints, as well as safety data (summary of TEAEs), and will provide a final recommendation to: 1) ***stop the recruitment***: in case of successful interim analysis, namely ▪ the demonstration of superiority of CHF 5993 pMDI over Symbicort® Turbuhaler®for the two primary endpoints in both study main populations (i.e., overall and Chinese populations). 2) ***continue the recruitment***: in case of unsuccessful interim analysis, namely ▪ no demonstration of superiority of CHF 5993 pMDI over Symbicort® Turbuhaler®in at least one of the two primary endpoints and in at least one of the study main populations (i.e., overall or Chinese population).

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT (GPT)	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST (GOT)	Aspartate aminotransferase
BDP	Beclometasone dipropionate
BID	Bis in die, twice a day
BP	Blood Pressure
BUD	Budesonide
BUN	Blood Urea Nitrogen
Ca	Calcium
CAT	COPD Assessment Test
CI	Confidence Interval
Cl	Chloride
COPD	Chronic Obstructive Pulmonary Disease
e-CRF	Electronic Case Report Form
CRO	Clinical Research Organization
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
EC	Ethic Committee
ECG	Electrocardiogram
EMA	European Medicine Agency
EQ-5D-3L	Euro QoL – 5 Dimensions – 3 Levels
ER	Emergency Room
ETV	Early Termination Visit
$FEF_{25-75\%}$	Forced Expiratory Flow at 25-75%
FEV_1	Forced expiratory volume within the 1st second
FF	Formoterol Fumarate
FPFV	First Patient First Visit
FVC	Forced vital capacity
γ-GT	Gamma-glutamyltranferase
GB	Glycopyrrolate Bromide
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Haemoglobin
HcT	Haematocrit
HFA	Hydrofluoroalkane
HR	Heart Rate
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to Treat
IUD	Intrauterine Device

IUS	Intrauterine System
IV	Intravenous
K	Potassium
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
LPLV	Last Patient Last Visit
M3	Muscarinic M3 receptors
MAOIs	Monoamine Oxidase Inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
Na	Sodium
NYHA	New York Heart Association
PDE	Phosphodiesterase
PLT	Platelets
pMDI	pressurised Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval Between the P and R wave in the ECG
PRN	Pro Re Nata(as needed)
QRS	Time Interval Between the Q and R and S wave in the ECG
QTc	Time interval between the Q and T waves in the ECG (corrected for HR)
RBC	Red Blood Cell
SABA	Short-acting β2 agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
VAS	Visual Analogue Scale
WBC	White Blood Cell

CONTENTS

GENERAL INFORMATION **2**

PROTOCOL OUTLINE **3**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **16**

CONTENTS **17**

1 INTRODUCTION **21**

1.1 Background information 21
1.2 Study Rationale 21

2 STUDY OBJECTIVES **22**

2.1 Primary Objective 22
2.2 Secondary Objectives 22

3 STUDY DESIGN **22**

4 PATIENT SELECTION CRITERIA **23**

4.1 Patient recruitment 23
4.2 Inclusion Criteria 24
4.3 Exclusion Criteria 25
4.4 Patient Withdrawals 26

5 CONCOMITANT MEDICATIONS **27**

5.1 Permitted concomitant Medications 27
5.2 Non-permitted concomitant Medications (run-in and randomized treatment period) 28

6 TREATMENTS **29**

Appearance and content 29
6.1 Dosage and Administration 30
6.1.1 Selection of doses in the study 30
6.1.2 Dosage 30
6.1.3 Administration 31
- *Priming of the inhalers 33*
- *Cleaning of the inhalers 33*
- *Priming of the inhalers 34*

6.1.4 Patient training 34
6.2 Packaging 34
6.2.1 Training kit (placebo pMDI or placebo Turbuhaler®) 34
6.2.2 Run-in medication (Symbicort® Turbuhaler® 160/4.5 µg) 35
6.2.3 Study treatments (CHF 5993 pMDI 100/6/12.5 µg or Symbicort® Turbuhaler® 160/4.5 µg and matched placebos) 35
6.2.4 Rescue medication (salbutamol sulphate 100 µg pMDI HFA) 35
6.3 Labelling 36
6.4 Treatment allocation 36
6.5 Treatment Code 37
6.6 Treatment compliance 38
6.7 Drug Storage 38
6.8 Drug Accountability 39
6.9 Provision of additional care 40

7 STUDY PLAN **40**

7.1 Study Schedule 40
7.1.1 Visit 0 (Pre-screening visit) 42
7.1.2 Visit 1 (Screening visit / Week -2) 42
7.1.3 Visit 2 (Randomisation/ Start of Treatment Period /Week 0) 45
7.1.4 Visit 3 (Week 4 of Treatment Period) 47
7.1.5 Visit 4 (Week 12 of Treatment Period) 48

7.1.6 Visit 5 (Week 18 of Treatment Period) 50
7.1.7 Visit 6 (Week 24 / End of Treatment Period) 51
7.1.8 Early Termination Visit (for a patient withdrawn before Week 24) 53
7.1.9 Follow-up phone contact 53
7.2 INVESTIGATIONS 53
7.2.1 Spirometry 53
7.2.2 Use of rescue medication 54
7.2.3 Diary Card 54
7.2.4 Laboratory tests (including pregnancy test) 55
7.2.5 Vital signs: Blood pressure evaluation and body weight 55
7.2.6 12-lead ECG 55
7.2.7 COPD Assessment Test (CAT) 56
7.2.8 COPD exacerbations 56
7.2.9 St. George's Respiratory Questionnaire (SGRQ) 58
7.2.10 EQ-5D-3L Health Questionnaire 59
7.2.11 Health Economic information 59

8 EFFICACY ASSESSMENTS 60

8.1 PRIMARY VARIABLES 60
8.2 SECONDARY VARIABLES: 60

9 SAFETY ASSESSMENTS 60

10 ADVERSE EVENT REPORTING 61

10.1 DEFINITIONS 61
10.2 EXPECTEDNESS 62
10.3 INTENSITY OF ADVERSE EVENT 62
10.4 CAUSALITY ASSESSMENT 62
10.5 ACTION TAKEN WITH STUDY DRUG DUE TO THE AE 63
10.6 OTHER ACTIONS TAKEN 63
10.7 OUTCOME 63
10.8 RECORDING ADVERSE EVENTS 64
10.9 REPORTING SERIOUS ADVERSE EVENTS TO CHIESI 64
10.10 REPORTING SERIOUS ADVERSE EVENTS TO REGULATORY AUTHORITIES/ETHICS COMMITTEES/IRB 65
10.11 GENERAL NOTES 65

11 DATA MANAGEMENT 66

12 STATISTICAL ANALYSIS 66

12.1 SAMPLE SIZE 66
12.2 POPULATIONS FOR ANALYSIS 67
12.3 STATISTICAL PARAMETERS AND TESTS 68
12.3.1 Descriptive Statistics 68
12.3.2 Patients accountability 68
12.3.3 Description of the population-description of baseline characteristics 68
12.3.4 Missing data 68
12.4 PRINCIPLES OF STATISTICAL ANALYSIS 68
12.4.1 Primary efficacy variable 68
12.4.2 Secondary efficacy variables 69
12.4.3 Safety variables 70
12.4.4 Interim Analysis 71

13 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL 72

14 REGULATORY REQUIREMENTS 73

15 INFORMED CONSENT 73

16 DIRECT ACCESS TO SOURCE DOCUMENTS/DATA 73

17 STUDY MONITORING 73

18 QUALITY ASSURANCE 74

19 INSURANCE AND INDEMNITY 74

20 CONFIDENTIALITY 74

21 PREMATURE TERMINATION OF THE STUDY 75

22 CLINICAL STUDY REPORT 75

23 RECORD RETENTION 75

24 PUBLICATION OF RESULTS 75

25 REFERENCES 76

APPENDIX 1 - APPROVAL OF THE PROTOCOL BY CLINICAL INVESTIGATOR(S) 78

APPENDIX 2 – MINIMUM LIST OF SOURCE DATA REQUIRED 81

1 INTRODUCTION

1.1 Background information

Chronic obstructive pulmonary disease (COPD) is a disease characterised by airflow limitation not fully reversible which is usually both progressive and associated with an abnormal inflammatory response of the lungs to prolonged exposure to noxious particles or gases. Cholinergic tone is the major reversible component of airway obstruction in COPD and cholinergic mechanisms are also important in regulation of submucosal gland secretion which is increased in chronic bronchitis.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2015 update) strategic document [20] recommend that the main therapeutic goals, besides the prevention of disease progression, is to relieve symptoms, improve health status and prevent/treat exacerbations. Bronchodilators are the mainstay of pharmacologic therapy for chronic obstructive pulmonary disease (COPD), and are recommended by international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation.

The main classes of bronchodilators include β_2-agonists and anti-cholinergic agents. They are recommended in all current guidelines as appropriate treatment for first-line maintenance therapy of COPD. Anticholinergic drugs such as long-acting muscarinic antagonists (LAMAs) e.g. tiotropium bromide which are mostly used in COPD are ammonium quaternary. Similar to LAMAs, long-acting β2-agonists (LABAs) such as formoterol fumarate, exhibit sustained and prolonged effects and both have been shown to lessen symptoms and reduce exacerbations.

1.2 Study Rationale

Glycopyrrolate is a quaternary ammonium, antimuscarinic agent used orally to control gastric acidity, parenterally as an antisialogogue and to reverse neuromuscular blockade, and studied inhaled in asthma and COPD. Inhaled Glycopyrrolate has been shown to induce prolonged bronchodilation in patients with asthma [1], [2], [3] and has been found to be an effective bronchodilator in COPD [44], [5], [6]

GOLD 2015 strategic document [20] highlight that, for patients uncontrolled with bronchodilator monotherapy, combination therapy, LABA/ICS, is recommended. In patients with more severe disease, adding a long acting muscarinic antagonist (LAMA) to a LABA/ ICS combination is suggested considering the different molecular mechanisms of action of these drugs. Triple therapy with LABA, LAMA and ICS is widely used in clinical practice. Several clinical studies have investigated this treatment approach and showed that 'triple therapy' is more effective in terms of pulmonary function improvement and symptoms control as compared to bronchodilator monotherapy or ICS/LABA [7], [8], [9], [10].

Chiesi developed a fixed combination of Beclometasone Dipropionate (BDP) and Formoterol Fumarate (FF) pMDI which has been marketed under the trade name Foster®.

The efficacy and safety of Foster® 100/6 µg per actuation has been demonstrated in adult patients with both moderate or severe persistent asthma [11] and in severe to very severe COPD patients [12]. Both of which represent indications for which Foster® has received marketing authorization in EU. Currently the marketing authorization for Foster in Asian Countries includes asthma only.

Chiesi is now developing a triple fixed dose combination by combining Foster® with Glycopyrrolate bromide (GB), for COPD patients that would benefit from ICS/LABA and LAMA combined therapy. This triple fixed dose combination is named CHF 5993, or Beclometasone dipropionate/Formoterol fumarate/Glycopyrrolate bromide, or BDP/FF/GB within this document.

Indeed, this study has been designed to compare the efficacy and safety of the CHF 5993 pMDI combination to Symbicort® Turbuhaler® combination in Asian COPD patients after 24 weeks of treatment.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current Good Clinical Practices and all other applicable laws and regulations.

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 and 2-hour post-dose morning FEV_1 at Week 24).

2.2 Secondary Objectives

Key secondary objective

- To demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 and 2-hour post-dose morning FEV_1 at Week 24) in the subgroup of Chinese population.

Other secondary objectives

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

3 STUDY DESIGN

This will be a phase III, double-blind, double-dummy, randomized, multinational, multicentre, 2-arm parallel-group, active-controlled study.

Throughout the study, various assessments and tests will be performed according to the Study Flow Diagram and Time and Events Chart.

A total of 7 clinic visits (V0 to V6) will be performed during the study, as follows (Figure 1):

- A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients, to obtain the written informed consent from the patient and to instruct the patient on screening visit procedures (such as medication restrictions)
- A screening visit (V1, no more than 7 days after V0) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, a 12-lead ECG, spirometric parameters after

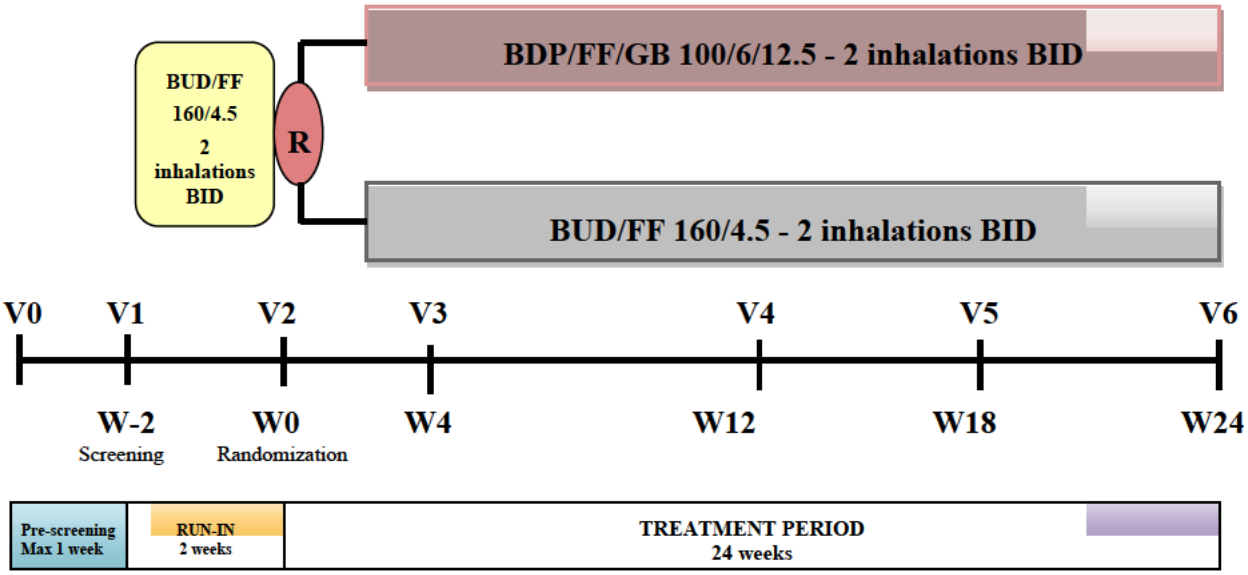
salbutamol, vital signs and training for the use of inhalers). This visit will be followed by a 2-week open-label run-in period where patients will be on Symbicort® Turbuhaler® 160/4.5 mcg per inhalation, 2 inhalations bid.

- After the randomisation (V2), patients will be assessed after 4, 12, 18 and 24 weeks of treatment (V3 to V6) at clinic/hospital.
- A safety follow-up call, 1 week after the last visit (V6) or the Early Termination visit, will occur to check the status of any unresolved adverse events and to record any new AEs that have occurred after the last visit.

Inhaled salbutamol will be provided to be administered as rescue medication on an as-needed basis for both the run-in and the randomized period.

AEs and COPD exacerbations will be monitored throughout the study.
A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6.

The end of the trial is defined as the last follow-up phone call of the last patient in the trial.
Figure 1. Study design



4 PATIENT SELECTION CRITERIA

4.1 Patient recruitment

A total of 990 patients (495 patients per group) will be randomised in order to reach a total of 832 evaluable patients at Week 24 (416 per group), considering a non-evaluable rate of approximately 16% at this time point.
The study is planned to recruit 75% of patients in China and 25% of patients in Korea and Taiwan (with at least 96 patients randomized in Taiwan in order to reach at least 80 evaluable Taiwanese patients).

A screen failure rate of 20% is anticipated; therefore a total of 1238 patients will be screened.

A lower number of patients could be enrolled in case the interim analysis outcome is positive (see section 12.4.4 for additional information).

Screening failure patients may be allowed to be re-screened 1 time based on Investigator's opinion and following sponsor approval. A re-screened patient will be considered as a new patient.

4.2 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Male and female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure.
2. Patients with a diagnosis of COPD (according to GOLD 2015 strategic document [20], updated January 2015) at least 12 months before the screening visit.
3. A smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20]. Current and ex-smokers are eligible.

   Smoking cessation therapy must be completed 6 months prior to screening visit.
4. A post-bronchodilator FEV_1 < 50% of the predicted normal value **and** a post-bronchodilator FEV_1/FVC ratio < 0.7 at least 10-15 min after 4 puffs (4 x 100 mcg) of salbutamol pMDI

   If this criterion is not met at screening, the test can be repeated once before randomisation visit.
5. A **documented** history of at least one exacerbation in the 12 months preceding the screening visit.

   COPD exacerbation will be defined according to the following:

   "A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization"
6. Patients under therapy for at least 2 months prior to screening with either:
   - Inhaled corticosteroids/long-acting β-agonist or
   - Inhaled corticosteroids/long-acting muscarinic antagonist or
   - Inhaled long-acting β-agonist and inhaled long-acting muscarinic antagonist or
   - Long-acting muscarinic antagonist or
   - Long-acting β-agonist
7. A cooperative attitude and ability to be trained to use correctly the study drugs inhalers (pMDI and Turbuhaler®).
8. A cooperative attitude and ability to be trained to use correctly the COPD questionnaires.

At screening visit (Visit 1), all inclusion criteria will be checked.

At the randomisation visit (Visit 2), the following criteria will be re-checked: 7, 8

4.3 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrolment:

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are willing to use one or more of the following reliable methods of contraception:
   a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
   b. Hormonal contraception (implantable, patch, oral).
   c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository.
   d. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

   Reliable contraception should be maintained throughout the study until last study visit.

   "True abstinence" is acceptable only if it is in line with the preferred and usual lifestyle of the patient.

   Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening (V1) and end of treatment (V6), urine pregnancy test will be performed at all visits except V0 and V6.

   Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea") or women permanently sterilized (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) can be enrolled in the study.
2. Diagnosis of asthma, history of allergic rhinitis or atopy (atopy which may raise contra-indications or impact the efficacy of the study according to Investigator's judgment).
3. Patients requiring use of the following medications:
   a. Systemic steroids for COPD exacerbation in the 4 weeks prior to screening.
   b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening.
   c. PDE inhibitors in the 4 weeks prior to screening.
   d. Use of antibiotics for a lower respiratory tract infection (e.g pneumonia) in the 4 weeks prior to screening.
4. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period.
5. Changes in dose, schedule, formulation or product of oral xanthine derivatives (e.g. theophylline) in the month prior to screening visit or during the run-in period. Stop of xanthines prior to screening visit is allowed.
6. Patients treated with non-cardioselective β-blockers in the week preceding the screening visit or during the run-in period.
7. Patients treated with long-acting antihistamines (e.g. astemizole, terfenadine) unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study, or if taken as PRN.
8. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.
9. Known respiratory disorders other than COPD which may impact the efficacy of the study drug according the Investigator's judgment. This can include but is not limited to α-1

antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.

10. Patients who have clinically significant cardiovascular condition (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV, left ventricular failure, acute myocardial infarction), advanced Atrio-ventricular conduction blocks.
11. Patients with atrial fibrillation (AF):
    - Paroxysmal (i.e. intermittent).
    - Persistent as defined by continuous atrial fibrillation diagnosed for less than 6 months.
    - Persistent for at least 6 months with a resting ventricular rate ≥ 100/min controlled with a rate control strategy (i.e. selective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy).
12. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgement.
    Patients whose electrocardiogram (ECG) (12 lead) shows QTcF >450 ms for males or QTcF >470 ms for females at screening and at randomisation visits are not eligible.
13. Medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would prevent use of anticholinergic agents.
14. History of hypersensitivity to M3 antagonists, β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial.
15. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study drug according to Investigator's judgement.
16. Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L) at screening.
17. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to Investigator's judgment.
18. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit.
19. Participation in another clinical trial where investigation drug was received less than 8 weeks prior to screening visit.
20. Patients treated with Traditional Chinese Medicines used for respiratory diseases. At screening visit (Visit 1), all exclusion criteria will be checked except criterion 4.

At the randomisation visit (Visit 2), the following criteria will be re-checked: 1 ,4 ,5 , 6, 7, 10, 11, 12, 17, 20.

4.4 Patient Withdrawals

Patients may be discontinued from the study for any of the following reasons:

- An adverse event occurs that, in the opinion of the Investigator, makes it unsafe for the patient to continue in the study. In this case, the appropriate measures will be taken.

- In case of COPD exacerbation(s) that make(s) the patient too unstable to continue the study according to investigator's judgement, the patient can be withdrawn and resume with the proper therapy regime.
- The patient is lost to follow-up.
- The patient withdraws consent.
- The patient's safety is affected by violation of inclusion or exclusion criteria or use of not-permitted concomitant medication.
- The patient undergoes unplanned surgical intervention and/or therapy (radio therapy or chemotherapy) due to malignancy.
- The patient is unwilling or unable to adhere to the study requirements, i.e, non-compliance.
- The Sponsor or the Regulatory Authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of patients should be avoided. Violations detected during the course of the study do not necessarily constitute reasons for discontinuation. Based on a common agreement between the Investigator and the Sponsor, the patient may continue his/her study participation if the detected violations do not affect either the protocol population targeted or the safety of the patient.

However, should a patient discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation, at the time of the withdrawal will be performed with an explanation of the exact reason why the patient is withdrawing from the study. In case of withdrawal, the Investigator must fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal.

The Investigator is responsible for the optimal individual treatment for the patient.

It must be emphasised that after a patient withdraws from a trial, the Investigator is still responsible for reporting serious adverse events he/she considers causally-related to the study drug. In addition, the Investigator needs to assure appropriate treatment and follow-up of each adverse event still ongoing at the time of patient's discontinuation. Even in case of premature discontinuation from the study, a follow-up phone contact will be performed 7-10 days after the last study medication intake or after the Early Termination visit to check the status of any unresolved AEs.

If a patient is withdrawn/drops-out of the study after receiving the study treatment, the patient study number and corresponding test treatments will not be reassigned to another patient.

5 CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

The following medications are allowed during the study.

1. Inhaled salbutamol administered as rescue medication on an as-needed basis. A minimum period of 6 hours should elapse between the use of rescue salbutamol and the spirometric measurements.

2. Xanthine derivatives (e.g. theophylline) if taken at stable regimen for at least one month prior to screening and to be maintained constant during the study.
3. Long-acting antihistamines if taken at stable regimen at least 2 months prior to screening or if taken PRN. For patients not under stable long-acting antihistamines, short courses are allowed during the study period (≤7 days). Other antihistamines are allowed during the study period for short course (≤10 days) or if taken PRN.
4. **In case of COPD exacerbation**, short courses (≤14 days) of the following medications are allowed during the treatment period:
   a) Systemic corticosteroid (oral/IV/IM).
   b) Inhaled short acting β_2-agonists and/or short acting muscarinic antagonists or combination of both.
   c) Nebulised β_2-agonists, anticholinergics and/or steroids.
   d) Antibiotics.
   e) Oxygen.
   f) Mechanical ventilation at the Investigator's discretion.
5. Short courses (≤ 10 days) of nasal inhaled corticosteroids (maximum 4 courses) are allowed during the treatment period.
6. In case of other concomitant diseases, any appropriate treatment that, according to the Investigator, does not interfere with the study evaluation parameters is allowed. All concomitant medications should be noted in the relevant section of the CRF.

5.2 Non-permitted concomitant Medications (run-in and randomized treatment period)

The following medications are not permitted during the study. Intake of such a drug during run-in constitutes a screening failure and the patient will not be randomized into the study. If any of these medications are taken during the randomized treatment period, the patient is to be withdrawn from the study.

1. Depot corticosteroids.
2. Oral/IV/IM corticosteroids (short courses (≤14 days) allowed in case of COPD exacerbation during the treatment period).
3. Nebulised β2-agonists, anticholinergics and/or steroid (short courses (≤14 days) allowed in case of COPD exacerbation during the treatment period).
4. Inhaled corticosteroids.
5. Inhaled long-acting β_2-agonists or fixed combination of corticosteroids and long-acting β_2-agonists other than study treatments (e.g. salmeterol/fluticasone).
6. Inhaled long-acting muscarinic antagonist.
7. Inhaled short acting β_2-agonists (other than salbutamol) (Short course (≤14 days) allowed in case of COPD exacerbation during the treatment period).
8. Inhaled fixed combinations of a short-acting β2-agonist and a short-acting muscarinic antagonist (Short course (≤14 days) allowed in case of COPD exacerbation during the treatment period).

9. Inhaled short-acting muscarinic antagonists (ipratropium and oxytropium) (Short course (≤14 days) allowed in case of COPD exacerbation during the treatment period).
10. Non-cardioselective β-blockers
11. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and other drugs known to prolong the QTc interval.
12. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit.
13. PDE-4 inhibitors (e.g. roflumilast).
14. Leukotriene modifiers.
15. Traditional Chinese Medicines used for respiratory diseases.

Prior to screening spirometry, the following wash out periods for concomitant medications must be respected:

- Inhaled short-acting β_2-agonists: 6 hours
- Inhaled short-acting muscarinic antagonist: 12 hours
- Inhaled SABA/SAMA fixed combinations: 12 hours
- Inhaled long acting muscarinic antagonist : 72 hours
- Inhaled long-acting β_2-agonists: 12 hours
- Inhaled daily long-acting β_2-agonists (indacaterol): 24 hours
- Inhaled corticosteroids: 12 hours
- Inhaled ICS/LABA fixed combinations: 12 hours
- Leukotriene modifiers: 72 hours

Prior to each spirometry, the following wash out periods for concomitant medications must be respected:

- Inhaled short-acting β_2-agonists: 6 hours
- Inhaled short-acting muscarinic antagonist: 12 hours
- Inhaled SABA/SAMA fixed combinations: 12 hours

6 TREATMENTS

The study medication will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity. The Sponsor will also provide rescue medications and spacer devices.

Appearance and content

Investigational drug:

- **CHF 5993 pMDI 100/6/12.5 µg - Test product**

  Active ingredient: Beclometasone dipropionate/Formoterol fumarate/Glycopyrrolate bromide 100/6/12.5 µg per metered dose

Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid

Presentation: Canister containining 120 doses plus white actuator

- ***Placebo CHF 5993 pMDI (*)***

Excipient: HFA-134a propellant, ethanol anhydrous

Presentation: Canister containining 120 doses plus white actuator

Control drug:

- **Symbicort® Turbuhaler® 160/4.5** (AstraZeneca AB [Sweden])

Active ingredient: Budesonide 200 µg and formoterol fumarate dihydrate 6 µg per metered dose (Delivered dose is budesonide 160µg/inhalation and formoterol fumarate dihydrate 4.5 µg/inhalation).

Excipients: Lactose monohydrate.

Presentation: Inspiratory flow-driven, multidose powder inhaler. Each inhaler contains 120 doses.

- **Symbicort® Turbuhaler® placebo *(*)***

Excipients: Inhalation grade Lactose.

Presentation: Inspiratory flow-driven, multidose powder inhaler. Each inhaler contains 120 doses.

(*) The placebo pMDI and the matched placebo powder for inhalation will be identical to the respective active drugs except for active principles and will be provided to realise a complete double blind, double dummy design. Both placebos will be used also for training.

Rescue medication:

Salbutamol, to be used as rescue medication, will be purchased locally and provided by Investigator site to patients. Patients will take the usual rescue (salbutamol) on an as-needed basis.**Dosage and Administration**

6.1.1 Selection of doses in the study

The selection of the dose for CHF 5993 HFA pMDI (100/6/12.5 µg per inhalation) is based on the results of previous studies performed in Chiesi with Glycopyrrolate pMDI (dose ranging study) with or without CHF 1535 100/6 µg in patients with COPD.

6.1.2 Dosage

6.1.2.1 Run-in period (from V1 to V2):

Symbicort®Turbuhaler® 160/4.5 µg/unit dose 2 inhalations b.i.d. (daily delivered dose of BUD 640 µg plus FF 18 µg).

6.1.2.2 Treatment period (from V2 to V6):

- Test product: CHF 5993 pMDI 100/6/12.5 µg 2 inhalations b.i.d. plus matched placebo of Symbicort®Turbuhaler® placebo 2 inhalations b.i.d (total daily metered dose: BDP 400 µg plus FF 24 µg plus GB 50 µg).
- Control drug: Symbicort® Turbuhaler® 160/4.5 µg/unit dose 2 inhalations b.i.d. plus CHF 5993 pMDI placebo 2 inhalations b.i.d. (total daily delivered dose: BUD 640 µg plus FF 18 µg).

Patients used to inhaling their COPD pMDI medications with a spacer shall continue using a spacer to take the pMDI study drugs.

6.1.3 Administration

To the extent possible, the time of dosing of study medication must remain constant for each patient for the whole duration of the study.

Run-in period:

At Visit 1 (screening), each eligible patient will receive one commercial pack of Symbicort® Turbuhaler® 160/4.5µg as run-in medication, in replacement of their current therapy.

Note: the run-in will be administered at V1 even if the inclusion criterion 4 should be re tested before the randomisation.

Symbicort® Turbuhaler® 160/4.5µg will be administered twice a day: **two** inhalations **in the morning** (between 8.00 and 10.00 am) and **two** inhalations **in the evening** (between 8.00 and 10.00 pm).

At visit 1 patients will also receive one box of **rescue** medication containing one pressurized metered dose inhaler with 200 doses of salbutamol pMDI 100µg/dose. Salbutamol pMDI 100µg/dose per actuation will be taken as needed in response to symptoms.

Treatment period:

At visit 2, the confirmed eligible patients will be randomised and will receive the **test product** (CHF 5993 pMDI 100/6/12.5 µg) or the **control drug** (Symbicort® Turbuhaler® 160/4.5 µg).

To cover a period of 24 weeks of treatment, each patient will receive at V2 (randomisation visit, 2 weeks after screening) and at V4 (12 weeks after randomization) two boxes:

- One box containing 4 pMDI inhalers of CHF 5993 pMDI 100/6/12.5 µg **or** 4 pMDI inhalers of placebo;

  and

- One box containing 4 dry powder inhalers of Symbicort® Turbuhaler® 160/4.5 µg **or** 4 matched placebo Turbuhaler® inhalers.

If the patient is used to take COPD pMDI medication via a spacer, he/she will be provided with a spacer at V2 and with a new one at V4.

The first administration of the study drug will take place in the morning at clinic visit under medical supervision.

Then, the study treatments (CHF 5993 pMDI or Symbicort® Turbuhaler®) will be administered daily by patients at home.

Patients will be instructed to take their study drug twice a day **in the morning** (between 8. 00 am and 10.00 am) and **in the evening** (between 8.00 pm and 10.00 pm).

In order to ensure the double dummy design of the trial, patients randomised to receive CHF 5993 pMDI will be administered Symbicort® Turbuhaler® matched placebo and patients randomised to receive Symbicort® Turbuhaler® will be administered pMDI placebo, as detailed in the scheme below:

Treatment Administration scheme	CHF 5993 pMDI Arm	Symbicort Turbuhaler Arm
pMDI	Two inhalations in the morning and two inhalations in the evening of CHF 5993 100/6/12.5 µg	Two inhalations in the morning and two inhalations in the evening of pMDI Placebo
Dry powder for inhalation	Two inhalations in the morning and two inhalations in the evening of Symbicort® Turbuhaler® matched placebo	Two inhalations in the morning and two inhalations in the evening of Symbicort® Turbuhaler® 160/4.5 µg

Administration will be done according to the package instruction leaflets provided along with the study medication.

On each day, 4 inhalations in the morning and 4 inhalations in the evening will be performed in the following order:

- **In the morning**: 1 from yellow label pMDI number 1 + 1 from yellow label pMDI number 2 + 1 from yellow label Turbuhaler® number 1 + 1 from yellow label Turbuhaler® number 2.
- **In the evening**: 1 from blue label pMDI number 1 + 1 from blue label pMDI number 2 + 1 from blue label Turbuhaler® number 1 + 1 from blue label Turbuhaler® number 2.

Each inhalation should be separated by a 30-second interval approximately. After each inhalation, the patient must hold his/her breath as long as possible.

Administration via a spacer in a subset of patients.
In case patients are used to inhaling their pMDI COPD medications using a spacer device, they will continue using the spacer that will be dispensed at V2 and V4.

At visit 2 and/or at the subsequent visits, further rescue medication (Salbutamol pMDI 100µg/dose per actuation) should be dispensed to the patients only in case of need. Each centre will receive an adequate amount of rescue medication to cover the run-in and all the study treatment period for the number of scheduled patients.

6.1.3.1 Use of pressurized Metered Dose Inhaler

- **Priming of the inhalers**

All the inhalers (CHF 5993 pMDI and placebo) must be primed **before** first use or if they have not been used for 14 days or more. The priming must be carried out according to the instructions provided along with the study drug.

- **Cleaning of the inhalers**

All the inhalers (CHF 5993 pMDI and placebo) must be cleaned regularly (once a week) by the patient, wiping the outside and inside of the mouthpiece with a dry cloth, according to the instructions provided along with the study drug.

6.1.3.2 Use of a spacer (for patients who need it)

The inhalation of study drugs via the spacer must be done according to the respective commercial leaflet respecting the cleaning rules indicated in the commercial leaflet.

6.1.3.3 Use of Turbuhaler® dry powder inhaler

- **Priming of the inhalers**

Before using a new Symbicort® Turbuhaler® for the first time, it must be prepared for use as follows:

- ✓ Unscrew the cover and lift it off. A rattling sound may be heard.
- ✓ Hold the Turbuhaler upright with the red grip at the bottom.
- ✓ Turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). A click sound should be heard.
- ✓ Repeating again once the steps above, turning the red grip in both directions, the Turbuhaler is now ready for use.

Then, the patient, every time she/he needs to take an inhalation has to load the dose according to the instructions provided along with the study drug.

- **Cleaning of the inhalers**

All the inhalers (Symbicort® Turbuhaler® and matched placebo) must be cleaned regularly (once a week) by the patient, wiping the outside of the mouthpiece with a dry tissue. Do not use water or liquids.

6.1.4 Patient training

During the screening visit, each patient will receive two training kits containing placebo only (see description in section 6.2.1).
Patient will be instructed on how to use the pressurised Meter Dose Inhaler and the Symbicort® Turbuhaler® inhaler according to the instructions provided along with the study drug.
If the patient is used to take COPD pMDI medications via a spacer, he/she will be trained to use the study spacer.
The proper use of the inhalers will be checked again at randomisation in all patients and the proper use of the spacer (if applicable) will be checked again as well.
These training kits will be kept at the site by the Investigator (will not be dispensed to the patients).

6.2 Packaging

All investigational products will be prepared in accordance with Good Manufacturing Practices (GMP) as required by the current Good Clinical Practices (GCP).

Chiesi Farmaceutici S.p.A. will supply the study drugs for the run-in and for the treatment period and the rescue medication (Salbutamol pMDI 100µg/dose).

6.2.1 Training kit (placebo pMDI or placebo Turbuhaler®)

At visit 1, the Investigator will train the eligible patients using placebo, to the proper use of pMDI and DPI. The Investigator will use two boxes.

One box will contain 1 CHF 5993 pMDI placebo.

- *Primary packaging*: canister plus standard actuator.
- *Secondary packaging*: box containing 1 canister plus 1 standard actuator.

A second box will contain 1 matched placebo Turbuhaler® inhaler.

- *Primary packaging*: Turbuhaler® inhaler.
- *Secondary packaging*: box containing 1 Turbuhaler® inhaler

If the patient is used to take COPD pMDI medication via a spacer, he/she will be trained to inhale using the study spacer.

- *Secondary packaging*: box containing 1 spacer.

6.2.2 Run-in medication (Symbicort® Turbuhaler® 160/4.5 µg)

At visit 1, the Investigator will deliver to each eligible patient one ambient box containing 1 Symbicort® Turbuhaler® 160/4.5µg inhaler.

- *Primary packaging*: Turbuhaler® inhaler.
- *Secondary packaging*: box containing 1 Turbuhaler® inhaler.

6.2.3 Study treatments (CHF 5993 pMDI 100/6/12.5 µg or Symbicort® Turbuhaler® 160/4.5 µg and matched placebos)

At randomisation (V2) and after 12 weeks (V4), each patient will be provided with 2 boxes. The first box will contain 4 pMDI inhalers of CHF 5993 pMDI 100/6/12.5µg **or** placebo. 2 of the 4 inhalers will be labelled with yellow colour and with a "sun" sticker (plus number 1 or 2) identifying the ones to be used for the morning administration. The remaining 2 inhalers will be labelled with a blue label and a "moon" sticker (plus number 1 or 2) identifying the ones to be used for the evening administration. Overall, there will be 2 pMDI boxes per patient, from V2 to V6.

- *Primary packaging*: canister plus standard actuator
- *Secondary packaging*: box containing 4 canisters plus 4 standard actuators

The second box will contain 4 DPIs of Symbicort® Turbuhaler® 160/4.5µg **or** placebo. 2 of the 4 inhalers will be labelled with yellow colour and with a "sun" sticker (plus number 1 or 2) identifying the ones to be used for the morning administration. The remaining 2 inhalers will be labelled with a blue label and a "moon" sticker (plus number 1 or 2) identifying the ones to be used for the evening administration. Overall, there will be 2 DPI boxes per patient, from V2 to V6.

- *Primary packaging*: Turbuhaler® inhaler
- *Secondary packaging*: box containing 4 Turbuhaler® inhalers

If the patient is used to take COPD pMDI medication via a spacer, he/she will be dispensed also with a box containing spacer. Overall, there will be 2 spacers per patient for the treatment period, one used at V2 to be used until V4, the second at V4 to be used until V6.

- *Secondary packaging*: box containing 1 spacer.

6.2.4 Rescue medication (salbutamol sulphate 100 µg pMDI HFA)

During the study, each centre will receive the necessary quantity of rescue medication to cover the 2-week run-in and the 24-week study period. The rescue medication will remain in its commercial packaging.

- *Primary packaging*: commercial canister plus actuator

- *Secondary packaging*: commercial box containing 1 canisters plus 1 actuator

6.3 Labelling

All labelling of primary/secondary packaging of treatment, run-in and training kits and secondary packaging of spacer will be in local language and according to local law and regulatory requirements and will be compliant with Annex 13 to the Volume 4 of the GMP.

Labels will contain at least the following information:

Primary packaging:

- Study code
- Kit number
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Instruction for use
- Storage conditions
- Code/Batch number
- Sponsor

Secondary packaging:

- Study code
- Kit number
- Patient number
- Pharmaceutical dosage form, quantity of dosage units
- Route of administration
- Code/Batch number
- Sponsor
- Instruction for use
- Storage conditions
- For clinical trial use only
- Keep out of reach of children.

The run-in medication and the study treatments will have a tear-off label which will have to be removed and attached to a specific form at the time the medication is dispensed.

6.4 Treatment allocation

A balanced block randomisation scheme stratified by country will be prepared via a computerised system. Patients will be centrally assigned, in each centre, to one of the two treatment arms at the end of the run-in period through an Interactive Response Technology (IRT, combination of voice and web response system).
The Investigators at the sites will connect to the IRT to enrol and randomise patients. The IRT will allocate the patient ID, will assign the patient to a certain treatment group using a list-based randomisation algorithm and will assign the study medication kit number corresponding to the treatment group assigned to the patient. The IRT will also generate a confirmation after every IRT transaction is performed.

The Investigator will connect to the IRT at each visit (from pre-screening to follow-up) to register the patient status in the system.

6.5 Treatment Code

Study drug will be kitted and uniquely numbered. The IRT will be used to assign run-in and treatment kits as well as training kits. The IRT will track quantities, kit numbers, drug types, batch/code numbers, expiration dates and dispensing limiting dates. The IRT will monitor inventory levels at all sites and manage the re-supply. The IRT will track patient screen failures and withdrawals from the study.

The randomisation list will not be available to patients, Investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data. The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomisation list.

For interim analysis purposes, (see section 12.4.4 for additional details), treatment allocation codes will be unblinded only for patients who have completed the study or have prematurely discontinued from the study on the pre-determined cut-off date and will be used to prepare the full statistical output which the independent DMC recommendation will be based on. Unblinded information will be available only to the independent DMC members; in case DMC recommendation will be to stop study recruitment, unblinded results will be disclosed to CRO study team and Sponsor.

In case of emergency, unblinding of the treatment code will be done through IRT. The Investigator will be provided with usernames and passwords for randomization purposes and to unblind the study treatment in case of emergency situation, where he/she considers essential to know what treatment the patient was taking. The IRT will promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.
Users from Chiesi Corporate Pharmacovigilance will have their own passwords to unblind patients in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees.
The patient will be provided with a card with the phone numbers of Hospital site and Investigator to be called in case of emergency.

Note:

At pre-screening visit (Visit 0), the Investigator will access IRT to register the patient in the system and obtain a patient number.

At screening visit (Visit 1), he/she will connect again to the IRT system to obtain the two training kit numbers (placebo pMDI and placebo Turbuhaler®) and one Run-in kit number (of Symbicort® Turbuhaler® 160/4.5 µg).

At randomisation visit / Week 0 (Visit 2) the Investigator will connect again to the IRT to randomize the patient and to obtain the study treatments kit numbers to cover the first 12 weeks of the treatment period.

At Visit 3, Visit 5 and Visit 6/Early Termination visit he/she will connect again to the IRT to register the status of the patient.

At Visit 4 (12 weeks after randomisation), he/she will connect again to the IRT to obtain the study treatments to cover the last 12 weeks of the treatment period.

At the follow up , the Investigator will connect to the IRT to enter the final patient status in the study.

6.6 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the patient on the diary card.

The evaluation of the compliance will be done using the following formula:

$$\frac{\text{TOTAL NUMBER OF ADMINISTERED DOSES}}{\text{TOTAL NUMBER OF SCHEDULED DOSES}} \times 100 = \%\ \text{OF ADMINISTERED DRUG}$$

The total number of administered doses will also be checked on the basis of the unused drug returned by the patient.

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each patient. A range between 75-125% will be taken into account for a satisfactory level of compliance.

To optimise patients' compliance to test treatments, a compliance check will be periodically done by means of phone calls to the patients during the study.

6.7 Drug Storage

The Pharmacist/Investigator will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of temperature. It is also recommended to protect the study medication from humidity.

Run-in medication:
The boxes containing Symbicort® Turbuhaler® used as study medication for the run-in period must be stored **not above 30˚C** protect from moisture either by Pharmacist/Investigator at the Hospital and by patients at home.

***Study drug for randomized treatment period*:**

pMDI medication: CHF 5993 or placebo.

pMDI kits must be stored between 2˚C and 8˚C by Pharmacist/Investigator at the Hospital. At clinic visits, the medication kits should be removed from the refrigerator before patient's administration. If the inhaler has been exposed to severe cold, the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. It must never be warmed by artificial means. The patient should never inhale a cold medication. The canisters contain a pressurised liquid. It must not be exposed to temperatures higher than 50°C. Do not pierce the canister.

Once dispensed, the patients will be instructed to keep the boxes at home at ambient temperature not above 25°C.
At this temperature condition the residual shelf life of the pMDI kits will be four months (**120 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the kit labels** once the kits are removed from the refrigerator, before assigning to the

patients. The **use-by-date corresponds to the dispensing date plus 4 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

DPI medication: Symbicort® Turbuhaler® or matched placebo

DPI kits must be stored at ambient temperature, not above 30°C and protect from moisture either by Pharmacist/Investigator at the Hospital and by patients at home.

***Medication for training*:**

pMDI training must be kept at site and **not** dispensed to the patients. pMDI training must be stored between 2˚C and 8˚C by Pharmacist/Investigator at the Hospital. At screening, the training kits should be removed from the refrigerator before patient's administration. If the inhaler has been exposed to severe cold, the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. It must never be warmed by artificial means. The patient should never inhale a cold medication. The canisters contain a pressurised liquid. It must not be exposed to temperatures higher than 50°C. Do not pierce the canister.

Once used, the pMDI training must be kept at site at ambient temperature not above 25°C. At this temperature condition the residual shelf life of the pMDI will be four months (**120 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the kit labels** once the pMDI is removed from the refrigerator, before using it. The **use-by-date corresponds to the dispensing date plus 4 months.** Please note that the use-by-date must not exceed the total shelf life of the product. The same training kit will be used by patient at screening and randomisation.

DPI training must be kept at site and **not** dispensed to the patients. DPI training must be stored at ambient temperature, not above 30°C and protect from moisture by Pharmacist/Investigator at the Hospital.

The site must check the Min/Max temperatures once daily for adequate storage of refrigerated and ambient kits. The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation to the requirement for storage will be promptly reported and Sponsor shall assess if the affected study medications can still be used.

6.8 Drug Accountability

The Investigator, or the designated/authorized representative, is responsible for the management of all the study medications to be used for the study. Study medications that should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study medications.
An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study medication(s) received, dispensed and returned by each patient during the trial.
At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies.

All the study medications supplied, used or unused, will be returned to the designated distribution centre under Sponsor's responsibility for destruction. Return and destruction will not occur until authorized by Chiesi.

6.9 Provision of additional care

At study completion, it is under the Investigator's responsibility to prescribe the most appropriate treatment for the patient or restore the initial therapy.

7 STUDY PLAN

7.1 Study Schedule

The study plan includes a total of 6 clinic visits (Visit 0 to Visit 6) plus a follow up phone call, as follows:

- *Visit 0 (**V0**)*: Pre-screening visit to explain the aim of the study to the patients, to obtain their informed written consent and to prepare patients for V1;
- *Visit 1 (**V1**)*: Screening visit (within 7 days after V0), start of 2-week run-in period, to verify the patients' eligibility. This visit will be followed by a 2-week run-in period, where the patients will receive open-label Symbicort® Turbuhaler®;
- *Visit 2 (**V2**)*: randomisation visit when patients will be randomised to one of the 2 treatment arms;
- *Visit 3 (**V3**)*: after 4 weeks of treatment;
- *Visit 4 (**V4**)*: after 12 weeks of treatment;
- *Visit 5 (**V5**)*: after 18 weeks of treatment;
- *Visit 6 (**V6**)*: after 24 weeks of treatment;
- *Follow-up phone contact (for patients attending Visit 6 and discontinuated patients)*: 7-10 days after last study medication intake or the Early Termination visit in order to check the status of any unresolved AEs at the last visit.

A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6.

Note: unscheduled visits can be performed during the study at the discretion of the Investigator. The relevant information will be collected in the eCRF.

The study plan and scheduled tests are summarized in the following Schedule of events:

Figure 2. Schedule of events

	Pre-screening	Screening	Treatment Period				
Visits	V 0	V 1	V 2*	V 3	V 4	V 5	V6 / ETV**
Time (Weeks)	Wk -3	Wk -2 (within 7 days after V0)	Wk 0 (±3 days)	Wk 4 (±3 days)	Wk 12 (±3 days)	Wk 18 (±3 days)	Wk 24 (±3 days)
Informed consent procedures	✓						
Demographic data	✓						
Instructions for the screening visit	✓						
Patient card	✓						
Inclusion/Exclusion criteria		✓					
Eligibility confirmation for randomisation			✓				
Medical history/Previous medications		✓					
Concomitant medications		✓	✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓	✓
Weight and height		✓					
Smoking status		✓	✓	✓	✓	✓	✓
Vital signs (BP) at pre-dose and 10 min post-		✓[1]	✓	✓	✓	✓	✓
12-lead ECG pre-dose and 10 min post-dose		✓[1]	✓[2]		✓		✓
Post-salbutamol spirometry[3]		✓					
Lung function measurements at clinic visits: pre-dose and 2h post-dose spirometry[4]		✓[1]	✓	✓	✓	✓	✓
Assessment of COPD exacerbations		✓	✓	✓	✓	✓	✓
Training to the use of Turbuhaler inhaler		✓	✓				
Training to the use of pMDI inhaler and of spacer		✓	✓				
COPD Assessment Test (CAT)		✓	✓	✓	✓	✓	✓
EQ-5D-3L Health Questionnaire			✓		✓		✓
Health economic assessment			✓	✓	✓	✓	✓
St. George's Respiratory Questionnaire			✓		✓		✓
Daily diary dispensing[5]		✓	✓	✓	✓	✓	
Daily diary returning[5]			✓	✓	✓	✓	✓
Haematology – Blood chemistry		✓			✓	✓	✓
Serum pregnancy test[6]		✓					✓
Urinary pregnancy test[6]		✓	✓	✓	✓	✓	
IRT call/connection	✓	✓	✓	✓	✓	✓	✓
Drug dispensing		✓	✓	✓[7]	✓	✓[7]	
Drug returning			✓	✓[7]	✓	✓[7]	✓
Adverse events/Serious adverse events		✓	✓	✓	✓	✓	✓

*Randomisation / **ETV: Early Termination Visit for randomised patients withdrawn before Wk 24

1. At screening, only pre-bronchodilator
2. Triplicate pre-dose ECG
3. at least 10-15 min after 4x100 µg salbutamol. It can be repeated once before Visit 2 if the inclusion criterion no. 4 is not met at V1.
4. At V1 pre-bronchodilatator spirometry including FEV_1, FVC, $FEF_{25-75\%}$, IC will be carred out and FEV_1 + FVC will be measured 10-15 minutes after salbutamol intake. From V2 to V6 a pre-dose spirometry including FEV_1, FVC, $FEF_{25-75\%}$and IC will be carried out. Post dose spirometry after 2 hours will only assess FEV_1 and FVC. Wash-out of rescue medication (at least 6h) or run-in/study medication must be respected in the morning of the visit for the pre-dose measurements.
5. For the recording of daily use of study (run-in and treatment period) and rescue medication

6. For females of childbearing potential only
7. Temporary return and re-dispensing of medication dispensed during the previous visit

7.1.1 Visit 0 (Pre-screening visit)

A pre-screening visit will be carried out in order to fully explain the study to potential eligible patient. The following procedures will take place:

- Collection of the written informed consent signed by the patient, after the study has been fully explained by the Investigator. The Investigator or his/her designee should provide the patient enough time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial
- Demographic data will be collected.
- Instructions will be given to the patient for the next screening visit (V1) such as **concomitant medications to be withdrawn** prior to the visit.
- As soon as the informed consent is signed, the Investigator (or his/her designee) will connect to IRT to allocate a 9 digits unique patient's number: the 3 first digits correspond to the ISO country code, the next 3 digits will identify the site incrementally and the 3 last digits will be chronologically be assigned to patients within a centre.

Before discharge,

- A **patient card** with the Investigator's contact details will be handed out to the patient.
- An **appointment** for the screening visit (V1) will be taken in the morning before 10:00 am, **within maximum 1 week**. Patients will be instructed:
  - ➔ To fast overnight (at least 10 hours) for the next visit in order to perform blood sampling (only water is allowed);
  - ➔ Not to take salbutamol or other SABA used as rescue in the 6 hours preceding the next visit, unless absolutely necessary.
  - ➔ Not to take his/her usual medication for COPD (LABA, ICS, LAMA, SAMA …) in accordance with section 5.2.

7.1.2 Visit 1 (Screening visit / Week -2)

A screening visit will be carried out in the morning (before 10:00 am) in order to identify eligible consenting patients for the study.

If any of the wash-outs for COPD medications have not been respected, the visit needs to be re-scheduled within 3 days. This is allowed only once. If any of the relevant wash-outs is not respected again before the rescheduled visit, the patient will be discontinued and recorded in the IRT and eCRF as screen failure.

The following procedures will take place:

- A medical history and smoking status will be recorded. To be eligible, patients must have a smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20]. Current and ex-smokers are eligible.
- Previous medications in the past 3 months must be collected. Concomitant medications being taken by the patient will be recorded. To be eligible, patients must be under therapy

for at least 2 months prior to screening with either: inhaled corticosteroids/long-acting β_2-agonist or inhaled corticosteroids/long-acting muscarinic antagonist or inhaled long-acting β-agonist and inhaled long-acting muscarinic antagonist or long-acting muscarinic antagonist or long-acting β_2-agonist. Intake of non-permitted medication constitutes a non-eligibility criterion for enrolment in the study.

- A full physical examination will be performed.
- Weight and height will be recorded.
- Vital signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before salbutamol administration, after 10 minutes of rest, sitting in resting position (see section 7.2.5).
- A 12-lead ECG will be performed before salbutamol administration, after 10 minutes of rest (see section 7.2.6). A patient will not be eligible in case of QTcF >450 ms for males or QTcF >470 ms for females, or in case of abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgement. In case of tests results beyond the upper limit and upon investigator's opinion, test can be repeated for safety purpose before randomization. If the second tests results are fitting with inclusion criteria this second test will be used for eligibility
- A blood sample will be collected before salbutamol administration, after an overnight fasting (at least 10h), for the assessments of (see section 7.2.4):
  - standard haematology and blood chemistry;
  - a serum and a urinary pregnancy tests will be performed in women of childbearing potential.

  The blood samples must be collected **after vital signs and 12-lead ECG recording**.

In case of serum potassium level falling outside of the allowed range and upon investigator's opinion, test can be repeated for safety purpose before randomization. If the second test results are fitting with inclusion criteria this second test will be used for eligibility determination.

In case of non-interpretable data, another determination must be performed as soon as possible and prior to Visit 2 (randomisation visit).

- Pre-bronchodilator spirometry will be carried out: the patients will have to perform a FVC manoeuvre to assess parameters (FEV_1, FVC, $FEF_{25-75\%}$and IC) (see section 7.2.1).
- A FEV_1 and FVC test at least 10-15 minutes after intake of 4 puffs (4 x 100 µg) of salbutamol pMDI will be performed. To be eligible, post-salbutamol **FEV_1 must be < 50%** of the patient's predicted normal value **and** post-salbutamol **FEV_1/FVC < 0.7**.

  If the criteria are not met, this test can be performed **once more before Visit 2** after an appropriate wash-out from bronchodilators.
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7.)
- The exacerbation assessment will be done. A documented history of at least one exacerbation in the 12 months preceding screening shall be checked (according to Inclusion Criterion 5). Eligible patients shall remain free of exacerbation requiring systemic steroids for 4 weeks prior to screening and of antibiotics for COPD exacerbation for more than 7

days in the 4 weeks prior to screening. If a COPD exacerbation within 4 weeks prior to screening is treated by course of antibiotics no longer than 7 days or with other allowed medications, patient is eligible.

- Any AE occurred since the signature of the informed consent will be checked and recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the patient's medical history, unless its start date is after the informed consent signature date. In this case, it will be recorded as an adverse event.
- If patient is eligible for entry into the run-in, he/she will be trained, with training kits containing placebo, to the proper use of pMDI and Turbuhaler® DPI (see section 6.1.4.) The corresponding tear-off label will be stuck in the patient specific dispensation tracking form.
- Patient will be instructed on how to daily record the medications intake (run-in and rescue) in the daily diary.
- The Investigator will access IRT also in order to obtain the run-in medication (Symbicort® Turbuhaler®) to be dispensed to the patient together with instructions for use. Patient will be instructed to perform 2 inhalations of run-in medication in the morning (before 10:00 am) and 2 inhalations in the evening (before 10:00 pm). **The first administration of run-in medication will take place at the clinic visit (9:00 am ± 2 h) under medical supervision**.
- If the patient is not eligible, the Investigator will access the IRT to record the status of the patient as screen failure.
- Patient will be instructed to stop the non-permitted COPD medications in accordance with section 5.2.
- Rescue salbutamol, for as needed use, will be dispensed by the Investigator. Patients will keep this rescue salbutamol throughout the study period (will be replaced if needed); nevertheless patient will be instructed to bring this medication at each visit in order to check the need for replacement.

Before discharge:

- **Medication for the run-in period** will be dispensed and the corresponding tear-off label will be stuck in the patient specific dispensation tracking form. Patients will be instructed to perform 2 inhalations in the morning and 2 inhalations in the evening of Symbicort® Turbuhaler® of run-in kit **with the exception of the next visit's morning**. Patient will be also instructed to take salbutamol as rescue if necessary.
- **A daily diary will be dispensed.** Patient must complete the daily diary for the recording of medication intake (run-in and rescue) until visit 2.
- **An appointment for Visit 2** will be made in 2 week (± 3 days) time from Visit 1, in the morning (at approximately the same time of the day) before 10:00 am. Patients will be instructed:
  - ➔ **Not to take salbutamol in the 6 hours preceding the next visit,** unless absolutely necessary.
  - ➔ **Not to take run-in medication in the morning of the next visit.**
  - ➔ To **bring back the run-in and rescue medications** (in their boxes) and the **daily diary** at the next visit.

7.1.3 Visit 2 (Randomisation/ Start of Treatment Period /Week 0)

The visit 2 will start in the morning (before 10:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected, or run-in medication (Symbicort®Turbuhaler®) has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. Only one re-schedule is allowed. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or run-in medication intake occurs again in the morning of the re-scheduled visit, the patient will be discontinued and recorded as screen failure in the IRT and eCRF.

The following procedures will be performed:

- Medication for the run-in period will be collected.
- The Investigator will check in the daily diary portal whether patient has taken run-in medication/rescue daily since screening. **In case of lack of compliance, instructions on how to use the daily diary will be given again to the patient.**
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the patient will be withdrawn from the study and recorded as screen failure in the IRT (see section 5.2).
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations will be evaluated (see section 7.2.8) and data recorded in the eCRF. In case of exacerbation during the run-in, the patient will not be randomised (see also section 5) and recorded as screen failure in the IRT.
- The occurrence of other adverse events will be checked and recorded if any.
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest in sitting position (see section 7.2.5).
- A triplicate pre-dose 12-lead ECG (baseline ECG to be done in triplicate at randomisation visit) will be performed after 10 minutes of rest (see section 7.2.6). A patient will not be randomised in case of average QTcF >450 ms for males or average QTcF >470 ms for females, or in case of abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgement.
- The proper use of pressurized metered dose inhaler and DPI Turbuhaler® inhaler will be checked again using the training kits previously assigned to the patient at V1.
- Eligibility criteria will be reviewed.

For eligible patients:

- The EQ-5D-3L questionnaire will be completed by the patient (see section 7.2.10).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- Investigator will collect Health economic information as per section 7.2.11.
- A pre-dose spirometry measurement will be performed to assess FEV_1, FVC, IC and $FEF_{25\ 75\%}$prior to patient randomisation. This measurement will constitute the baseline value (see section 7.2.1).
- The patient will be randomised and the treatment will be allocated according to the central randomisation system. Investigator will access IRT in order to obtain the appropriate kit numbers for the first 12-week treatment period.
- The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the corresponding electronic CRF (e-CRF). For the pMDI study medication, the use-by-date must be filled-in on the labels. Drug administration will be done according to section 6.2.3.
- **The first administration of the study drug will take place at the clinic visit (9:00 am ± 2 h) under supervision of the Investigator.**
- Vital signs (SBP and DBP) will be measured 10 minutes post-dose, after 10 minutes of rest (see section 7.2.5).
- A 10 minutes post-dose single 12-lead ECG (including the evaluation of HR, PR, QRS and QTcF) will be performed after 10 minutes of rest (see section 7.2.6).
- Spirometry to assess FEV1 and FVC will be performed 2 hours (with a +/- 30 minutes window) post-dose: for each time point, spirometry consists of three acceptable manoeuvres (see sections 7.2.1).

Before discharge:

- **Study medication** for the first 12 weeks of treatment will be dispensed to the patient together with instructions for use. Drug administration will be done according to section 6.1.3. Patient will be instructed to take salbutamol as rescue if necessary. For patient who is using a spacer, he/she will be reminded to use the spacer for each inhalation. Investigator will dispense also salbutamol if needed.
- **A new diary will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 3.
- **An appointment for Visit 3** will be made at 4 weeks (±3 days) from Visit 2 (at approximately the same time as Visit 2, before 10:00 am). The patient will be instructed:
  - ➔ To **bring back** the **study medication** (in the box), the daily diary and the spacer (only if applicable) at the next visit.
  - ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.4 Visit 3 (Week 4 of Treatment Period)

The visit 3 will start in the morning (before10:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The Investigator will check in the daily diary where the patient has recorded the study medication/rescue intake daily since randomisation. **In case of lack of compliance, instructions on how to use the daily diary will be given again to the patient** (see section 7.2.3).
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations will be evaluated and recorded in the eCRF (see section 7.2.8) (if any).
- The occurrence of adverse events will be checked and recorded if any.
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Investigator will collect Health economic information as per section 7.2.11.
- Pre-dose (prior to study medication administration) and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest (see section 7.2.5).
- A pre-dose (FEV_1, FVC, IC and $FEF_{25-75\%}$prior to study medication administration) and 2 hours (with a +/- 30 minutes window) post-dose spirometry measurement will be performed to assess FEV_1 and FVC:for each time point, spirometry consists in three acceptable manoeuvres (see section 7.2.1).
- **The morning dose of study medication will be administered at the clinic (9:00 am ± 2 h) under supervision of the Investigator from the two kits dispensed at Visit 2.** For the patient who needs using a spacer, medication will be taken via the spacer.
- The Investigator will access IRT just to register the status of the patient.

Before discharge

- **A new diary will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 4.
- **An appointment for Visit 4** will be made within 8 weeks from Visit 3 (at approximately the same time as other visits, before 10:00 am). **The time window should not exceed 12 weeks (±3 days) from Visit 2**.

  The patient will be instructed:

  - ➔ To **bring back** the **study medication** (in the box), the daily Diary and the spacer (only if applicable)at the next visit.
  - ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.5 Visit 4 (Week 12 of Treatment Period)

The visit 4 will start in the morning (before 10:00 am).
If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the eCRF.

The following procedures will be performed:

- The study medication (in the box) provided at Visit 2 will be collected, as well as the spacer previously provided (if applicable). The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The Investigator will check in the daily diary where the patient has recorded the study medication/rescue intake daily since randomisation. **In case of lack of compliance, instructions on how to use the daily diary will be given again to the patient** (see section 7.2.3).
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations will be evaluated and recorded in the eCRF (see section 7.2.8) (if any).

- The occurrence of adverse events will be checked and recorded if any.
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- The EQ-5D-3L questionnaire will be completed by the patient (see section 7.2.10).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- Investigator will collect Health economic information as per section 7.2.11.
- Pre-dose (prior to study medication administration) and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- Pre-dose (prior to study medication administration) and 10 minutes post-dose 12-lead ECG (including the evaluation of HR, PR, QRS and QTcF) will be performed after 10 minutes of rest (see section 7.2.6).
- A blood sample will be collected prior to study drug administration, after an overnight fasting (at least 10h), for the assessments of standard haematology and blood chemistry (see section 7.2.4). The blood samples must be collected **after vital signs and 12-lead ECG recording**. In case of non-interpretable data, another determination must be performed as soon as possible.
- A pre-dose (FEV_1, FVC, IC and $FEF_{25-75\%}$prior to study medication administration) and 2 hours (with a +/- 30 minutes window) post-dose spirometry measurement will be performed to assess FEV_1 and FVC. For each time point, spirometry consists in three acceptable manoeuvres (see section 7.2.1).
- The Investigator will access the IRT in order to obtain the appropriate subsequent kit numbers for the next 12-week treatment period according to centralised randomisation system.
- **The morning dose of study medication will be administered at the clinic (9:00 am ± 2 h) under supervision of the Investigator from the kit dispensed.** Drug administration will be done according to section 6.1.3. For the patient using a spacer, pMDI medication will be taken via a the spacer dispensed to the patient. The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the corresponding e-CRF. For pMDI, the use-by-date must be filled-in on the labels.

Before discharge

- **Study medication** will be dispensed to the patient together with instructions for use. Patient will be instructed to take salbutamol as rescue if necessary. For the patient who is using a spacer, he/she will be reminded to use the spacer for each inhalation. The Investigator will also dispense salbutamol if needed.
- **A new diary will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 5.
- **An appointment for Visit 5** will be made within 6 weeks from Visit 4 (at approximately the same time as other visits, before 10:00 am). **The time window should not exceed 18 weeks (±3 days) from Visit 2**.

The patient will be instructed:

- ➔ To **bring back** the **study medication** (in the box), the daily diary, the rescue and the spacer (only if applicable) , at the next visit.
- ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.6 Visit 5 (Week 18 of Treatment Period)

The visit 5 will start in the morning (before 10:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the eCRF.

The following procedures will be performed:

- The study medication (in the box) provided at Visit 4 will be collected, as well as the spacer previously provided. The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The Investigator will check in the daily diary where the patient has recorded the study medication/rescue intake daily since randomisation. **In case of lack of compliance, instructions on how to use the daily diary will be given again to the patient** (see section 7.2.3).
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations will be evaluated and recorded in the eCRF (see section 7.2.8) (if any).
- The occurrence of adverse events will be checked and recorded if any.
- A urine pregnancy test in women with childbearing potential will be performed.
- A full physical examination will be performed.
- Investigator will collect Health economic information as per section 7.2.11.

- Pre-dose (prior to study medication administration) and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- A blood sample will be collected prior to study drug administration and **after an overnight fasting** for the assessments of (see section 7.2.4):
  - standard haematology and blood chemistry;

  The blood sample must be collected **after the vital signs and 12-lead ECG recording**.

  In case of non-interpretable data, another determination must be performed as soon as possible.
- A pre-dose (FEV_1, FVC, IC and $FEF_{25-75\%}$prior to study medication administration) and 2 hours (with a +/- 30 minutes window) post-dose spirometry measurement will be performed to assess FEV_1 and FVC. For each time point, spirometry consists in three acceptable manoeuvres (see section 7.2.1).
- **The morning dose of study medication will be administered at the clinic (9:00 am ± 2 h) under supervision of the Investigator from the kit dispensed at Visit 4.** For the patient who needs using a spacer, medication will be taken via the spacer.
- The Investigator will access IRT just to register the status of the patient.

Before discharge

- **Study medication** for the next 6 weeks of treatment will be returned to the patient. Patient will be instructed to take salbutamol as rescue if necessary. For the patient who is using a spacer, he/she will be reminded to use the spacer for each inhalation. The Investigator will also dispense salbutamol if needed.
- **A new diary will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 6.
- **An appointment for Visit 6** will be made within 6 weeks from Visit 5 (at approximately the same time as other visits, before 10:00 am). **The time window should not exceed 24 weeks (±3 days) from Visit 2**.

  The patient will be instructed:

  ➔ To **bring back** the **study medication** (in the box), the daily diary and the spacer (only if applicable), at the next visit.

  ➔ To avoid taking salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.

  ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

7.1.7 Visit 6 (Week 24 / End of Treatment Period)

The visit 6 will start in the morning (before 10:00 am).

If rescue salbutamol has been inhaled in the previous 6 hours, the wash-out for medications permitted for COPD exacerbations has not been respected or the study drug has been taken in

the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If salbutamol intake occurs again in the previous 6 hours before the re-scheduled visit, the wash-out for medications permitted for COPD exacerbations is not respected or study drug intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with wash-out not respected will be recorded in the eCRF.

The following procedures will be performed:

- The study medication (in the box) provided at Visit 4 will be collected, as well as the spacer previously provided. The Investigator will also check whether new rescue shall be provided to the patient.
- Changes of concomitant medications being taken by the patient will be recorded. In case of intake of any non-permitted concomitant medication, the need for the patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest. If the patient is withdrawn, he/she will be recorded as discontinued in the IRT.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The Investigator will check in the daily diary where the patient has recorded the study medication/rescue intake daily since randomisation.
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations will be evaluated and recorded in the eCRF (see section 7.2.8) (if any).
- The occurrence of adverse events will be checked and recorded if any.
- A full physical examination will be performed.
- The EQ-5D-3L questionnaire will be completed by the patient (see section 7.2.10).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- Investigator will collect Health economic information as per section 7.2.11.
- Pre-dose (prior to study medication administration) and 10 minutes post-dose vital signs (SBP and DBP) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- Pre-dose (prior to study medication administration) and 10 minutes post-dose 12-lead ECG (including the evaluation of HR, PR, QRS and QTcF) will be performed after 10 minutes of rest (see section 7.2.6).
- A blood sample will be collected prior to study drug administration and **after an overnight fasting** for the assessments of (see section 7.2.4):
  - standard haematology and blood chemistry;
  - a serum pregnancy test will be performed in women of childbearing potential.

  The blood sample must be collected **after the vital signs and 12-lead ECG recording**.

In case of non-interpretable data, another determination must be performed as soon as possible.

- A pre-dose (FEV_1, FVC, IC and $FEF_{25-75\%}$prior to study medication administration) and 2 hours post-dose spirometry measurement will be performed to assess FEV_1 and FVC. For each time point, spirometry consists in three acceptable manoeuvres (see section 7.2.1).
- The Investigator will access IRT to register the completion of treatment for the patient.
- At Investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate. This will be not recorded in the eCRF
- The patient will be discharged from the unit, providing that all her/his safety assessments are satisfactory.

7.1.8 Early Termination Visit (for a patient withdrawn before Week 24)

In case of early study discontinuation, all the pre-dose procedures scheduled for Visit 6 (Week 24 / End of Treatment Period) will be performed.

If a patient is withdrawn before the end of treatment period, a final evaluation will be done.

The Investigator must fill in the Early Termination visit in the eCRF. The explanations regarding the reasons of withdrawal and all the assessments performed will be inserted.

7.1.9 Follow-up phone contact

For patients attending Visit 6 and discontinued patients, 7-10 days after the last study medication intake or after the Early Termination Visit, the patients will be contacted by phone and the status on all unresolved AEs at the last visit will be checked and recorded.
The Investigator will access IRT to reord the study completion/discontinuation for the patient.

7.2 Investigations

7.2.1 Spirometry

Pulmonary function tests (FEV_1, FVC, $FEF_{25-75\%}$ and IC) will be carried out under medical supervision in either a clinic or hospital and will be recorded using a computer-operated spirometer. Reading will be performed in a centralised laboratory.

Throughout the study, the clinic visits and the lung function measurements will start in the morning preferabily between 7:00 and 10:00 a.m. (**a 1 hour window is acceptable but before 11:00AM**), approximately at the same time of the day for each patient.

Lung function measurements will be done in accordance with the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society [13]. Predicted values will be calculated according to the formulas reported by Quanjer et al. [14]. All sites will be provided with equipments and a central spirometry lab will be used. Investigator sites will be trained to the use of the system during the Investigator meeting. Lung function measurements will be done with patients either standing or sitting (for each patient, this should be consistent throughout the study) with the nose clipped after at least 10 minutes

rest. Values will be corrected for BTPS (Body Temperature and Pressure, Saturated) conditions.

The specific procedures for centralised spirometry will be provided to the Investigator by the centralised spirometry company.
Forced Expiratory Volume in the 1st second (**FEV_1**, L), Forced Vital Capacity (**FVC**, L) and Forced Expiratory Flow at 25-75% (**$FEF_{25-75\%}$**, L/sec) will be recorded at each clinic visit from a forced vital capacity manoeuver, while a slow manoeuver will be performed for the measurement of Inspiratory Capacity (**IC**, L). For FEV_1 and FVC **the highest value from three technically satisfactory attempts** will be recorded (irrespective of the curve they come from) for the IC **the average of at least three manoeuvres should be reported**.
For $FEF_{25-75\%}$, the value will be derived from the best test curve (i.e. greatest sum FEV_1+FVC), The chosen value should not exceed the next one by more than 150mL. If the difference is larger, up to 8 measurements will be made and the largest value be reported.

FEV_1, FVC, $FEF_{25-75\%}$and IC will be recorded at each visit under medical supervision. At screening, the post-bronchodilator FEV_1 values (at least 10-15 min after administration of 4x100 µg salbutamol) will be considered for eligibility. From V2 to V6, FEV_1, FVC, $FEF_{25-75\%}$and IC will be measesured at pre-dose and FEV_1 and FVC will be measured at 2 hours post-dose.

The ratio **FEV_1/FVC** will be derived from these **highest values** of each parameter [15].

The rescue medication (salbutamol) must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit.

Study medication (run-in and after randomisation) should not be taken in the morning of the visits.

The wash-out for medications permitted for COPD exacerbations should be respected (see section 5.15.1 and section 5.25.2).

If the wash-out has not been respected the visit needs to be re-scheduled to take place within 2 days (3 days at V1). If the wash-out for rescue medication or for medications permitted for COPD exacerbations is not respected, or study medication intake occurs again before the re-scheduled visit:

- at V1 and V2, the patient will be discontinued
- from V3 to V6, the visit will be performed anyway and details of the intake (time and quantity) documented.

7.2.2 Use of rescue medication

The use of rescue medication will be recorded in the paper diary. Each day, patient will have to record in the diary the number of puffs taken during the last 24 hours.

7.2.3 Diary Card

At screening and from visit 2 to Visit 5, a new diary card will be handed out to the patient. The patient should follow instructions for recording the intake of run in medication/study medication and the number of puffs of rescue medication taken daily. The information from the patient diary card will be entered into the clinical database by the CRO. Investigator will check the diary for completeness before the patient leaves the centre. COPD Symptoms will also be

recorded in the diary to facilitate the patient interview by the Investigator during the visit and the COPD exacerbation recognition.

7.2.4 Laboratory tests (including pregnancy test)

Standard haematology and blood chemistry

The blood samples for standard haematology and blood chemistry will be collected in the morning after an overnight (at least 10 hours) fasting at Visit 1, Visit 4, Visit 5 and Visit 6. The collection will always be done after vital signs and ECG measurements, and before intake of study medication (salbutamol at V1).

The following parameters will be assessed **by a central laboratory**:

- *Blood Chemistry*: creatinine, BUN, fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, sodium, potassium, calcium, and chloride electrolytes, albumin.
- *Haematology*: red blood cells count (RBC), white blood cells count (WBC) and differential, total haemoglobin (Hb), hematocrit (Hct), platelets count (PLT).
- *Pregnancy test*
    - *serum β-HCG:* only for females of childbearing potential and only at Visit 1 and Visit 6.
    - *Urinary β-HCG:* only for females of childbearing potential from Visit 1 to Visit 5.

  Note: According to local regulation, a urine pregnancy test may be performed on a monthly basis.

Blood collection and sample preparation will be performed according to procedures provided by **the central laboratory** which will be in charge to transmit the results to the Investigator.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at Visit 4, Visit 5 and Visit 6 in the medical opinion of the Investigator will be reported as adverse events in the eCRF.

At visit V1, in case of serum potassium level falling outside of the allowed range and upon investigator's opinion, the test can be repeated for safety purpose before randomization. If the second test results are fitting with inclusion criteria this second test will be used for eligibility determination.

7.2.5 Vital signs: Blood pressure evaluation and body weight

Systolic and Diastolic Blood Pressure (SBP, DBP) will be assessed after 5-10 min in the seated resting position.

Pre-dose and 10 minutes post-dose (acceptable to be performed between 8 and 20 minutes) evaluations will be done at all visit (only pre-bronchodilator evaluation at screening visit).

7.2.6 12-lead ECG

A centralised ECG will be used. Single pre-dose and 10 minutes post-dose (acceptable to be performed between 8 and 20 minutes) 12-lead ECG measurements will be done at visits 1, 2, 4 and 6 (only pre-bronchodilator at screening visit).

Before recording, patients should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and lay in a resting position for 5-10 minutes before each nominal ECG time point.

Only at baseline (**Visit 2**), the pre-dose ECG will be recorded in **triplicate**. The triplicate ECG will consist of 3 ECG recordings in rapid succession (consecutively) and not more than 2 minutes apart. QTc value will be calculated pre-dose and 10 minutes post dose at week 12 and week 24 using the Fridericia formula (Fridericia-corrected $QTc=QT/\sqrt[3]{RR}$). It will be calculated automatically by the ECG recorder. Heart rate (HR), PR and QRS values will be also evaluated from ECG at all visits.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the Investigator will be reported as adverse events in the eCRF.

ECGs with computerized protocol interpretation are considered normal if

- $40 \leq$ Heart rate ≤ 110 bpm,
- 120 ms $\leq$ PR $\leq$ 210 ms,
- QRS $\leq$ 120 ms.

In case of relevant ECG abnormalities, the inclusion of the patient will be judged by the Investigator. The final decision for enrolment would be documented in the Medical File of the patient.

For eligible patients, QTcF values must be QTcF $\leq$ 450 (males) and 470 ms (females) (as per Exclusion Criterion 12) at the screening (V1 and randomisation (V2) visits.

At visit V1, in case of test results beyond the upper limit and upon investigator's opinion, test can be repeated for safety purpose before randomization. If the second tests results are fitting with inclusion criteria this second test will faith to eligibility.

7.2.7 COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a quick and easy to use questionnaire. It was specifically designed to measure candidate items regarding daily symptoms, activity limitations and other manifestations of the COPD [16]. The 8 items which are included in the CAT cover cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy.It has been developed to be self-administered by patients,and is simple enough that nearly all patients should be able to understand and complete it easily by themselves.

The CAT will be filled in at all visits. At each visit, data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.8 COPD exacerbations

A COPD exacerbation is defined as *"A sustained worsening of the patient's condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization."*

The exacerbations will be classified as moderate or severe as per EMA/CMHP guidelines definitions [17]:

- **Moderate:** exacerbations that require treatment with systemic corticosteroids and/or antibiotics;
- **Severe:** exacerbations that require hospitalisation or result in death.

Emergency room (ER) attendance includes any unscheduled visit at any healthcare institution, i.e. at the emergency department or at a pneumological division, requiring an urgent medical advice or extra visit to physician:

- ER visits associated with systemic steroids/antibiotics will be classified as moderate.
- ER visits associated with systemic steroids/antibiotics and at least 24 hours of stay will be considered as hospitalisation and therefore classified as severe.
- ER admission without prescription of systemic steroids/antibiotics will not be considered a moderate/severe exacerbation.

The recognition of COPD exacerbations will be primarily collected retrospectively during the visits. Data from the assessment methods, e.g.: COPD symptoms reported in the diaries, CAT, also would be considered. Investigators will carefully train the patient to recognise the worsening of signs and symptoms associated with COPD exacerbations. The patient will receive instructions how to report these signs and symptoms to the site.

Patients will be regularly reminded to call the investigational site if his/her symptoms worsen and record these contact date and relevant information if any in their diary. The contact details will be indicated on the patient card distributed to the patient at the pre-screening visit.

Based on consistent worsening symptoms/status, actions from the Investigator will be recommended. The physician will be directed to diagnose the cause of the worsening symptoms and decide whether to ask the patient to come to the clinic for an unscheduled visit and whether additional treatment is required.

The physician will record moderate and severe exacerbations in the eCRF.

The duration of treatment for the exacerbation and the duration of hospitalization will be collected and recorded in the eCRF. Patients will be instructed to complete their paper diary, **whenever possible,** in the course of hospitalization/health care utilization.

COPD exacerbations interpreted as due to lack of efficacy (instead of, e.g., to concurrence with acute viral infection), should not be classified drug related.

The assessment of worsening symptoms may include but is not restricted to the following:

- Breathlessness
- Wheeze
- Chest tightness
- Cough
- Fever
- Change in sputum production or purulence
- Unusual increase of use of “rescue” salbutamol

Investigators will use additional diagnostic procedures (e.g. lung function tests, blood oxygen levels, chest X-ray, ECG) at their own discretion to obtain COPD diagnosis.

During the run-in period: if the patient experienced any COPD exacerbation (regardless of whether it is moderate or severe), he/she will be not randomised in the study.

After randomisation: based on worsening symptoms/status, actions from the Investigator will be recommended. The physician will be directed to diagnose the cause of the worsening symptoms and decide whether to ask the patient to come to the clinic for unscheduled assessments and whether additional treatment is required.

The patients will be allowed to receive any medical intervention that is considered necessary for the appropriate control of the symptoms (e.g. oral/iv/im corticosteroids, antibiotics, nebulised bronchodilators/steroids, short courses of oxygen therapy/mechanical ventilation). While the treating physician may use any medicine they deem necessary to treat the exacerbation, a list of medications commonly used to manage exacerbations may be found in section 5.1.

For patients who exhibit worsening COPD disease status while on study treatment, the Investigator is encouraged to maximise the use of therapies in classes different from the ones of the study treatments (e.g. short-acting β_2-agonist).

In case of COPD exacerbation, the following guidelines are provided to the physicians on how to treat the exacerbation, even though they are not mandatory that they be followed:

1. For exacerbation therapy, it is adviced to start with an antibiotic (usually amoxycillin or amoxycillin/clavulanic acid) at standard doses for 7 days when there is increase in sputum purulence or sputum volume.

2. When the patient has symptoms affecting daily living activity, it is advised to start oral prednisolone 30 mg daily for 7 days and then reduce to zero over next 5.

The intake of study medication shall be maintained in case of exacerbation but may be temporarily withdrawn if necessary upon the Investigator's discretion, and the Investigators will carefully annotate in the eCRF all treatments they deem necessary to administer for the most appropriate treatment of the exacerbation. The Investigators will also record in the eCRF in case of extra visits outside of those indicated in the study protocol will be performed to enable continued evaluation of the patient's clinical condition.

In the recovery period after the exacerbation episode, and if the condition of the patient allows, every possible effort should be made to remove all additional medication used in the treatment of the exacerbation, and to restart the treatment of the patient according to the protocol as early as possible.

If a COPD exacerbation occurs close to a study clinic visit, the Investigator may postpone the visit within 5 days if he/she judges it necessary.

A COPD exacerbation is not a reason to withdraw the patient from the study, unless the Investigator deems it necessary.

7.2.9 St. George's Respiratory Questionnaire (SGRQ)

Health Related Quality of Life will be assessed by the St. George's Respiratory Questionnaire, a 76-item questionnaire developed to measure health in chronic airflow limitation [18]. Three component scores are calculated: symptoms, activity and impacts on daily life. Moreover, a total score will be calculated, with lower scores corresponding to better health.

The questionnaire will be completed by patients at visits 2, 4 and 6. The questionnaire will be checked for completeness and collected before the patient leaves the center.

7.2.10 EQ-5D-3L Health Questionnaire

The EQ-5D-3L is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

The questionnaire will be completed by patients at visits 2, 4 and 6. The questionnaire will be checked for completeness and collected before the patient leaves the center.

At each visit, data collected by Investigator on paper will be entered by the Investigator in the eCRF.

7.2.11 Health Economic information

Information on the total use of healthcare resources and absence from work associated with the patients's condition will be collected during the trial.

If the patient has a job, it will be recorded in the eCRF as well as patient work information.

Health Economic information will be collected by the Investigator based on patient interviews at each visit from randomisation visit (Visit 2) until end of treatment (Visit 6).

8 EFFICACY ASSESSMENTS

8.1 Primary variables

- Change from baseline in pre-dose FEV_1 at Week 24.
- Change from baseline in 2-hour post-dose FEV_1 at Week 24.

8.2 Secondary variables:

- Change from baseline in pre-dose and 2-hour post-dose FEV_1 at all the other clinic visits.
- FEV_1 response (change from baseline $\geq$ 100 mL) at Week 24.
- Time to first COPD exacerbation.
- Rate of COPD exacerbations over 24 weeks of treatment.
- Change from baseline in pre-dose FVC and IC at all clinic visits and change from baseline to 2-hour post-dose FVC at all clinic visits.
- Pre-dose FEV_1/FVC at all clinic visits.
- Change from baseline in Forced Expiratory Flow at 25-75% ($FEF_{25-75\%}$).
- Change from baseline in the SGRQ total score and domain scores at all clinic visits.
- SGRQ response (change from baseline in total score $\leq$- 4) at Week 24.
- Change from baseline in COPD Assessment Test (CAT) at all clinical visits.
- 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/day).

Health economic variables:

- EQ-5D-3L VAS score and EQ-5D-3L index at all clinic visits.
- Number of hospital admissions due to COPD and other causes.
- Number of days with oxygen therapy use due to COPD.
- Unplanned diagnostic or instrumental tests performed due to COPD.
- Mortality.

9 SAFETY ASSESSMENTS

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure)
- 12-lead ECG parameters: heart rate (HR), PR, QRS and QTcF (baseline, pre-dose and 10 min post-dose at Week 12 and Week 24)
- Standard Haematology and Blood Chemistry

10 ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

An adverse event can therefore be any unfavourable and unintended sign (including laboratory abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered as related to the investigational medicinal product.

An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".

All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

  Death is not an adverse event but an outcome. It is the cause of death that should be regarded as the adverse event. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the adverse event and "fatal" as its reason for being serious.

- **Is life-threatening**

  Life-threatening refers to an event in which the patient was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalisation or prolongation of existing inpatients' hospitalisation**

  Hospitalization refers to a situation whereby an AE is associated with unplanned formal overnight admission to a hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis should not necessarily be regarded as an AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

- **Results in persistent or significant disability or incapacity**

  The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the patient's physical or psychological well-being to the extent that the patient is unable to function normally.

- **Is a congenital anomaly or birth defect**

- **Is a medically significant adverse event**

  This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the patient's health or may require intervention to prevent one of the above outcomes.
  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.
Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A **Non-Serious Adverse Event/Non-Serious Adverse Drug Reaction** is an adverse event or adverse drug reaction that does not meet the criteria listed above for a serious adverse event/serious adverse drug reaction.

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (Investigator's Brochure for CHF 5993 or Summary of Product Characteristics or approved Package Insert for Symbicort® Turbuhaler®), otherwise it is considered unexpected.
Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.
In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

Each Adverse Event must be rated on a 3-point scale of increasing intensity:

- **Mild:** The event causes a minor discomfort, or does not interfere with daily activity of the patient, or does not lead to neither modification of test treatment dosage nor establishment of a correcting treatment.
- **Moderate:** The event perturbs the usual activity of the patient and is of a sufficient severity to make the patient uncomfortable. The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** The event prevents any usual routine activity of the patient and causes severe discomfort. It may be of such severity to cause the definitive interruption of test treatment.

10.4 Causality Assessment

The following "binary" decision choice will be used by the Investigator to describe the causality assessment:

- Reasonable possibility of a relatedness
- No reasonable possibility of relatedness

The expression "reasonable possibility of relatedness" is meant to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake and event's onset;
- Dechallenge (did the event abate after stopping drug?);
- Rechallenge (did the event reappear after reintroduction?);
  - Medical history;
  - Study treatment(s);
  - Mechanism of action of the study drug;
  - Class effects;
  - Other treatments-concomitant or previous;
  - Withdrawal of study treatment(s);
  - Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study medication (or concomitant);
- Protocol related process.

10.5 Action taken with study drug due to the AE

- Dose not changed
- Drug permanently withdrawn
- Drug temporarily interrupted
- Unknown
- Not applicable

10.6 Other actions taken

- Specific therapy/medication
- Concomitant Procedure/medical procedures

10.7 Outcome

Each Adverse Event must be rated by choosing among:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal

- Unknown

10.8 Recording Adverse Events

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) **derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings** (e.g., how have you felt since I saw you last?; is there anything new that you wish to discuss?).
The recording period for Adverse Events is the period starting from the Informed Consent signature until the patient's study participation ends.

All Adverse Events occurring during the clinical investigation must be documented in the Adverse Event forms on the electronic Case Report Form (eCRF).

Clinically significant abnormalities detected at Visit 1 not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the Investigator must be reported as adverse events in the eCRF.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the patient is lost to follow-up. Follow-up may therefore continue until after the patient has left the study up to 30 days after his/her discontinuation from the study for unrelated SAEs, and without timelines for related SAEs.

10.9 Reporting Serious Adverse Events to Chiesi

The Investigator must report all Serious Adverse Events to the PPD **Safety Contact within 24 hours of awareness.** The information must be sent by providing the **Serious Adverse Event form**. At a later date the PPD Safety Contact will report to Chiesi Global Pharmacovigilance, the Clinical Study Manager and Clinical Research Physician.

The contact persons are:

Name and Title	Telephone no.	Mobile no.	Fax no.	E-mail
PPD	PPD	PPD	+91 40 40188635	PPD
PPD	PPD	NA	+39 0521 1885 003	TriversytiPV@chiesi.com PPD

- Reporting window of SAEs from the investigator site starts from the time of patient's signature of informed consent and until the patient's study participation ends. After this date, even if no active monitoring of patients is required, SAEs occurring to a patient should be reported if the investigator becomes aware of them.

Up to the closure of the site, SAE reports should be reported to the PPD Safety Contact. New serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committees/IRB

In regards to Regulations in force for Pharmacovigilance, the Investigator must also fulfil in his obligation according to the law in force in his country.

Concerning the regulations in force for Pharmacovigilance, the Investigator must report within 24 hours all SAEs to the Competent Authorities and ECs by using the official form.

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the PPD Safety Contact by fax/email together with the Serious Adverse Event form completed in the AE page of the eCRF, retaining a copy on site.
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the PPD Safety Contact as soon as available, retaining a copy on site.
  - In case of pregnancy, the patient will be immediately withdrawn from the study and she will be followed with due diligence until the outcome of the pregnancy is known. The pregnancy must be reported by the Investigator within 24 hours by fax/e-mail/via Monitor to the PPD Safety Contact using the paper Pregnancy Report Form. The PPD Safety Contact will inform Chiesi of the pregnancy within one working day of being notified.
- The first two pages of the Pregnancy Report Form should be completed by the investigator with all the available information and sent to the PPD Safety Contact. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome, together with a follow-up of the first two pages, if necessary (e.g. an update in the medications received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.
- If it is the partner, rather than the patient, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed, but the patient participating to the study should not be discontinued from the study.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in/rescue medication, the pregnancy does not need to be reported; it is only required that the patient is immediately withdrawn from the study

11 DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.
All patients who will sign the informed consent will be databased. For patients who are screened but not randomized a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, prior medications, adverse events and concomitant medications if any.
Questionnaire patient's answers and daily diary will be databased.
Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, adverse events and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug Dictionary and Anatomical Therapeutic Chemical classification (ATC).
External data (spirometry, laboratory, ECG) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities.

Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

After cleaning of data, review meeting will be held to determine the occurrence of any protocol violation and to define the patient populations for the analysis. This process will occur first for the set of patients which will be involved in the interim analysis, and then for all the subsequent patients that will be randomized up to the study recruitment closure.

Once the data of patients included in the interim analysis have been declared to be complete and accurate, the database will be locked (eCRF locked and external data monitored by audit trails to apply data control), the randomization codes will be opened (only for the patients involved in the interim analysis) and shared to the DMC only, which will perform the planned statistical analysis and provide a final recommendation on the study recruitment.

A final database lock will occur once all the data related to the patients enrolled in the study have been declared to be complete and accurate; randomization list will be shared to the Sponsor and final statistical analysis as planned in the SAP will be performed. Only authorised and well-documented updates to the study data are possible after database lock. A CD-ROM of the patient data will be sent after final database lock at the investigational site for archiving.

12 STATISTICAL ANALYSIS

The following describes the statistical analysis as it is foreseen at the time of planning the trial. A detailed statistical analysis plan will be described in a separate document, which will include the statistical methods that will be used for conducting the interim analysis as well as the final analysis, to be finalized before breaking the blind for the interim analysis.

12.1 Sample Size

The sample size has been calculated to demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of change from baseline in pre-dose morning FEV_1 and change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the overall study population and in the Chinese population.

A total of 990 patients (495 patients per group) will be randomised in order to reach a total of 832 evaluable patients at Week 24 (416 per group), considering a non-evaluable rate of approximately 16% at this time point.

The study is planned to recruit 75% of patients in China and 25% of patients in Korea and Taiwan (with at least 96 patients randomized in Taiwan in order to reach at least 80 evaluable Taiwanese patients).

This sample size will provide:

- approximately 93.3% power to detect a mean difference of 60 mL in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 mL;
- approximately 98.1% power to detect a mean difference of 70 mL in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 mL.

An overall study power for the primary efficacy analysis of approximately 91.5% will therefore be ensured.

Under the assumptions of 75% of patients recruited in China (742 randomized, 624 evaluable), this sample size will provide:

- approximately 85% power to detect a mean difference of 60 mL in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 mL;
- approximately 93.8% power to detect a mean difference of 70 mL in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 mL.

An overall power for the primary efficacy analysis in the subgroup of Chinese population of approximately 80% will therefore be ensured.

12.2 Populations for analysis

- **Intention-to-Treat population (ITT):** all randomised patients who receive at least one administration of the study medication and with at least one available evaluation of efficacy after the baseline.
- **Per Protocol population (PP):** all patients from the ITT population without any major protocol deviations (e.g., wrong inclusions, poor compliance, forbidden concomitant medications). Exact definition of major protocol deviations will be discussed by the clinical team case by case during the Blind Review of the data and described in the Blind Review document.
- **Safety population:** all randomised patients who receive at least one administration of the study medication.

The primary efficacy variables will be analyzed both in the ITT and in the PP populations.

The secondary efficacy variables will be analyzed in the ITT population only.

Analysis of safety variables will be performed in the Safety population. In case of deviation between as-randomised treatment and treatment actually received, the treatment actually

received will be used in the analysis of safety variables (i.e. an as-treated analysis will be performed).

12.3 Statistical parameters and tests

12.3.1 Descriptive Statistics

Descriptive statistics will be provided for each variable in summary tables by treatment group. Quantitative variables will be summarized by using n (sample size), mean, 95% confidence interval (CI) of the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by using frequency count and percent distribution.

12.3.2 Patients accountability

Disposition of patients, patient status and patients excluded from analysis sets will be summarized by treatment group.

12.3.3 Description of the population-description of baseline characteristics

Descriptive statistics will be presented at baseline for ITT population (and PP population if relevant). The following parameters will be presented:

- demographics, medical history, previous and concomitant medications;
- efficacy parameters;
- safety parameters.

12.3.4 Missing data

Missing data for efficacy variables measured repeatedly over time will be handled using a likelihood-based approach. These variables will by analysed using linear mixed models for repeated measures.

Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed before breaking the blind for the interim analysis. Decisions will be fully documented in the Blind Review Document.

12.4 Principles of statistical analysis

For quantitative efficacy and safety variables, analysis within treatment groups will be presented. Mean changes from baseline and their 95% CIs will be calculated. Paired t-tests will be performed for efficacy variables only.

The least squares means and their differences obtained from the models will be presented with the respective 95% CIs.

For all inferential analyses, p-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

12.4.1 Primary efficacy variable

- Change from baseline (Visit 2) in pre-dose morning FEV_1 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, number of COPD exacerbations in the previous year (1 or >1), smoking status and severity of airflow limitation (post-bronchodilator FEV_1 at screening <30% or $\geqslant$30% of

predicted normal value) as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) and p-values at Week 24 will be estimated by the model. Superiority of CHF 5993 pMDI over Symbicort®Turbuhaler® ill be demonstrated by a statistically significant difference between treatments at Week 24 (defined as $p<0.05$) favouring CHF 5993 pMDI.

- Change from baseline (Visit 2 pre-dose) to the 2-hour post-dose value of FEV_1 will be analysed using a similar model as for change from baseline in pre-dose morning FEV_1. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs and p-value at Week 24 will be estimated by the model. Superiority of CHF 5993 pMDI over Symbicort®Turbuhaler® will be demonstrated by a statistically significant difference between treatments at Week 24 favouring CHF 5993 pMDI.

The primary efficacy variables will be tested in the overall population first and then in the subgroup of Chinese population.

12.4.2 Secondary efficacy variables

- For change from baseline in pre-dose morning FEV_1 and change from baseline in 2-hours post-dose FEV_1 the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits will be estimated with their 95% CIs by the same model used for the primary efficacy analysis.
- FEV_1 response at Week 24 will be compared between treatment groups using a logistic model including treatment, Country, number of COPD exacerbations in the previous year and smoking status as factors and the baseline value as a covariate.
- At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FEV_1 will be analysed using an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year and smoking status 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 will be analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year and smoking status as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model.
- The time to first COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, country, number of COPD exacerbations in the previous year and smoking status as factors. A Kaplan-Meier plot will also be presented.
- Change from baseline in pre-dose FVC, pre-dose IC and change from baseline in 2-hour post dose FVC at all clinic visits will be analysed using a similar model as for the primary efficacy variables.
- At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FVC will be analysed using a similar model as for FEV_1.
- Pre-dose FEV_1/FVC will be presented by descriptive statistics at all visits.

- Change from baseline in Forced Expiratory Flow ($FEF_{25-75\%}$), the adjusted means in each treatment group and the adjusted mean differences between treatments at all the other clinic visits will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis.
- Change from baseline (Visit 2) in the SGRQ total score and domain scores at all clinic visits will be analysed using a similar model as for the primary efficacy variables.
- SGRQ response at Week 24 will be compared between treatment groups using a similar model as for FEV_1 response.
- Change from baseline (Visit 2) in the CAT score at all clinic visits will be analysed using a similar model as for the primary efficacy variables.
- Change from baseline (run-in period) to each inter-visit period in the percentage of days without intake of rescue medication and in the average use of rescue medication will be analysed using a similar model as for the primary efficacy variables. The inter-visit period will be considered instead of visit in the model. For these variables, the change from baseline to the entire treatment period will be analysed using an ANCOVA model including treatment, country, number of COPD exacerbations in the previous year and smoking status as fixed effects and the baseline value as a covariate.

All secondary efficacy variables will be presented overall and in the subgroup of Chinese population.

Health economic variables

- Health economic variables will be summarised by treatment group using descriptive statistics (overall and by country). The details on other analyses of health economic data will be provided in a separate analysis plan. This health economic analysis will not be part of the Clinical Study Report.

12.4.3 Safety variables

- The number and the percentage of patients experiencing adverse events (AEs), adverse drug reactions (ADRs), serious AEs (SAEs), severe AEs, AEs leading to discontinuation and AEs leading to death will be summarised by treatment group. AEs will also be summarised by System Organ Class and Preferred Term using the MedDRA dictionary.
- Mean change in vital signs (systolic and diastolic blood pressure) from baseline (Visit 2 pre-dose) to each time point after the first study drug intake and from pre-dose to post-dose at each clinic visit will be calculated with its 95% CI by treatment group.
- At each time point after the first study drug intake, the mean absolute values of the 12-lead ECG parameters (HR, PR, QRS and QTcF) will be calculated with their 95% CIs by treatment group.
- The number and the percentage of patients with a
  - QTcF >450 ms, >480 ms and >500 ms
  - change from baseline (Visit 2 pre-dose) in QTcF >30 ms and >60 ms
  - only for post-dose time points: change from pre-dose at the same visit in QTcF >30 ms and >60 ms

at each time point after the first study drug intake and at any time point after the first study drug intake will be presented by treatment group.

- Mean changes from screening in the laboratory parameters will be calculated with their 95% CIs by treatment group.
- Shift tables from screening to any visit, with regard to normal range, will be presented by treatment group for the laboratory parameters.

All safety variables will be presented overall and in the subgroup of patients in the Chinese population.

12.4.4 Interim Analysis

An unblinded interim analysis will be conducted by an independent Data Monitory Committee, testing the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of change from baseline in pre-dose morning FEV_1 and change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the overall study population and in the Chinese population (i.e. primary efficacy variables).

The interim analysis is planned to be based on the following assumptions (reflecting blinded data information collected during the study):

a) mean difference between CHF 5993 pMDI and Symbicort®Turbuhaler® in the change from baseline in pre-dose morning FEV_1 at Week 24: no variation (60 mL);
b) mean difference between CHF 5993 pMDI and Symbicort®Turbuhaler® in the change from baseline in 2-hours post-dose FEV_1 at Week 24: no variation (70 mL);
c) variability (Standard Deviation) for both endpoints: 200 mL;
d) non-evaluable rate, i.e., percentage of patients without evaluable data at Week 24: 13%;
e) about 81% of patients enrolled in China and 19% in Taiwan and South Korea.

To avoid an inflation of the Type I error, the significance level will be adjusted using the Pocock-type error spending function method (considering a two-sided alpha = 0.0372 at interim analysis, and 0.025 at final analysis) [21]. Further details on the alpha correction will be detailed in the statistical analysis plan (SAP) [e.g., in case of different non-evaluable rate or higher number of evaluable patinets].

In order to ensure in the interim analysis a power of approximately 89% for the primary efficacy endpoints in the overall study population, a total of 614 patients should be randomised in order to reach 534 evaluable patients at Week 24.

A total of 499 Chinese patients should be randomized in order to have 434 evaluable Chinese patients that would allow a power of approximately 80% for the primary efficacy endpoints in this population.

The Independent DMC will include experts external to the study (statisticians and clinicians) assessing the study data, with particular focus on the primary endpoints. A DMC Charter will detail the responsibilities of the DMC members, the amount of information expected to undergo DMC evaluation, the endpoints that will be analysed, the level of evidence required to claim superiority. Details on the statistical methods related to the interim analysis will be fully documented in the SAP (which describes the full statistical output); finalization of the document will occur before breaking the blind for the interim analysis.

Only patients who have completed the study or have prematurely discontinued from the study will be included in the interim analysis. In-depth data cleaning activities on patients to be

included in the interim analysis will be performed, with particular attention to the lung function parameters collected during forced spirometry manoeuvres.

It is expected that when the target number of evaluable patients at Week 24 needed for the interim analysis would have completed the study, about 180 additional patients will still be ongoing. These ongoing patients will not be included in the interim analysis.

The full statistical output will be provided to the DMC members for their evaluation by an independent team; particular focus will be given to:

a) primary endpoints: change from baseline in pre-dose morning FEV_1 at Week 24 and change from baseline in 2-hour post-dose FEV_1 at Week 24 in the overall and Chinese populations;
b) safety: summary table of treatment-emergent adverse events.

The DMC members will review unblinded data (i.e., knowing the actual treatment) and will provide final recommendations to the Company (either to stop or to continue the study recruitment), without disclosing the interim study results. The DMC recommendations will be fully documented. The following two scenarios are then possible:

1) ***stop the recruitment***: in case of successful interim analysis, namely
   - the demonstration of superiority of CHF 5993 pMDI over Symbicort®Turbuhaler® for the two primary endpoints in both study main populations (i.e., overall and Chinese populations).
2) ***continue the recruitment***: in case of unsuccessful interim analysis, namely
   - no demonstration of superiority of CHF 5993 pMDI over Symbicort®Turbuhaler® in at least one of the two primary endpoints and in at least one of the study main populations (i.e., overall or Chinese population).

In order to demonstrate superiority of CHF 5993 pMDI over Symbicort®Turbuhaler® in the interim analysis, all the following primary endpoints should show a mean difference between the study medications favouring CHF 5993 pMDI with a two-sided p-value lower than 0.0372:

- change from baseline in pre-dose morning FEV_1 at Week 24 in the overall population;
- change from baseline in 2-hour post-dose FEV_1 at Week 24 in the overall population;
- change from baseline in pre-dose morning FEV_1 at Week 24 in the Chinese population;
- change from baseline in 2-hour post-dose FEV_1 at Week 24 in the Chinese population.

A final analysis will be conducted considering the patients included in the interim analysis and the one which were ongoing at that time. The same statistical models as the interim analysis will be applied, with appropriate correction of the alpha.

13 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Ethics Committee/Institutional Review Board in accordance with the requirements of each country.
The EC/IRB shall give its opinion in writing -clearly identifying the study number, study title and informed consent form approved-, before the clinical trial commences.
A copy of all communications with the EC/IRB will be provided to the Sponsor.

The Investigator should provide written reports to the EC/IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the patients (according to the requirements of each country).

14 REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.
Selection of the patients will not start before the approval of the Ethics Committee/Institutional Review Board has been obtained and the study notified to Health Authorities (or authorized by).
The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

15 INFORMED CONSENT

Informed consent must be written in a language understandable to the patients. It is the responsibility of the Investigator to obtain written consent from each patient or from the patient's legal representative prior to any study related procedures taking place, by using the latest EC/IRB approved version of the document.
Adequate time shall be given to the patient or his or her legal representative to enquiry the PI about any clarification needed and to consider his or her decision to participate to the trial.

If the patient and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, eg., a person independent of the study who will read the informed consent form and the written information for the patient.
Consent must be documented by the patient's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.
Each patient's signed informed consent must be kept on file by the Investigator. One copy must be given to the patient.

16 DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

The Investigators must permit trial-related monitoring, audits, Ethics Committee/Institutional Review Board review or regulatory inspection, providing direct access to source data/documents.

17 STUDY MONITORING

Monitoring will be performed by PPD , which has been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and

source data (source data is any data that is recorded elsewhere to the case report forms), provided that patient confidentiality is respected.

The purposes of these visits are:

- To assess the progress of the study
- To review the compliance with the study protocol
- To discuss any emergent problem
- To check the eCRF for accuracy and completeness
- To validate the contents of the CRFs against the source documents (see APPENDIX 2 – Minimum list of source data required for the minimum list of source data required)
- To assess the status of drug storage, dispensing and retrieval.

Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18 QUALITY ASSURANCE

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with Good Clinical Practices.

19 INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.

Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20 CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.

The Investigator must assure the patient's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the patient's study numbers, names, addresses and (optional) telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21 PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.
The Sponsor should submit a written notification to the Regulatory Authority concerned and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

22 CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to co-ordinating Investigator's for agreement and signature.
At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to the Competent Authority and to Investigators.

23 RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

Regulations require that essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study.

It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact Chiesi before destroying any trial-related documentation. In addition, all patients' medical records and other source documentation will be kept for the maximum time permitted by the institution.

24 PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities. Chiesi furthermore reserves the right to use such data for industrial purposes.
In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation, and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately.
Negative as well as positive results should be published or otherwise made publicly available.

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APPENDIX 1 - Approval of the protocol by clinical investigator(s)

A 24-week, Double Blind, Double dummy, Randomized, 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 the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease

Product: CHF 5993 100/6/12.5 µg: fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrrolate bromide 12.5 µg / metered dose

Pharmaceutical Form: spray aerosol via pMDI HFA-134a propellant

Approval of Clinical Study Protocol by the Coordinating Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating patients and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (attention being drawn to Section concerning freely given consent; copy appended), Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

Coordinating Investigator's Name: PPD

Centre No. : 10601

PPD

Mar 21 2019
Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

A 24-week, Double Blind, Double dummy, Randomized, 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 the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease

Product: CHF 5993 100/6/12.5 µg: fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrrolate bromide 12.5 µg / metered dose

Pharmaceutical Form: spray aerosol via pMDI HFA-134a propellant

Approval of Clinical Study Protocol by the Principal Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Informed written consent will be obtained from all participating patients and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (attention being drawn to Section concerning freely given consent; copy appended), Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in patients.

Principal Investigator's Name: _____, MD

Centre No. : _____

_____ _____

Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma – Italy

APPENDIX 2 – Minimum list of source data required

Patients demography file
Patients medical file (diseases, treatments …)
Study number
Patient identity/number
Randomization number
Medical and surgery history
Previous and concomitant medications
Weight, height
Date of informed consent signature
Date of study visits
Spirometry reports (for test)
Post-bronchodilator test (when applicable)
Laboratory reports
ECG reports
Questionnaires
Date and time of medication intake
Date and time of investigations
Diaries
Kits number for run-in period, treatment period and training kits: attribution comparing to the IRT; labels; kit numbers reported in eCRF ...
Labels of study drugs: Use-by-date completed on the labels, ...
Training with pMDI and Turbuhaler
Examination or assessments carried out during the study
COPD exacerbations
Adverse events / Serious adverse events
If patient is withdrawn, reason
Study end date
Medications on site