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CLINICAL STUDY PROTOCOL

IND No : 2016L07859

A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) in patients with Chronic Obstructive Pulmonary Disease

Version No.: 1.0
Date: 09 November 2017

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

Clinical Study Code No.: CCD-01535AC1-02	Version No.: 1.0
IND No.: 2016L07859	Date: 09 November 2017

GENERAL INFORMATION

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MONITORING CRO	PPD
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Clinical Study Code No.: CCD-01535AC1-02	Version No.: 1.0
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PROTOCOL OUTLINE

Study title	A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) 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 1535 100/6 µg pMDI: Beclometasone dipropionate plus formoterol fumarate)
Centre(s)	Multicenter, in approximatively 45 sites
Indication	Chronic Obstructive Pulmonary Disease (COPD)
Study design	Double-blind, double-dummy, randomized, multicentre, 2-arm parallel-group, active-controlled study
Study phase	III
Objectives	***Primary objective:*** To demonstrate that CHF 1535 pMDI is non-inferior to Symbicort® Turbohaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at week 24) in patients with COPD. ***Secondary objectives:*** •To evaluate the effect of CHF 1535 pMDI on other lung function parameters, and patient reported outcomes (PROs). •To assess the safety and the tolerability of the study treatments.
Treatment duration	A 4-week open-label run-in period with Symbicort® Turbohaler® followed by a 24-week randomised treatment period.
Test product dose/route/regimen	**CHF 1535 100/6 µg pMDI:** Fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg (BDP/FF). **Dose regimen:** BDP/FF, 100/6 µg per inhalation, 2 inhalations in the morning (preferably before 10.00 am) and 2 inhalations in the evening (preferably before 10.00 pm) **Administration:** pressurised metered dose inhaler (pMDI) Patients already using a spacer for drug administration shall continue to use it throughout the duration of the study.
Reference product dose/route/regimen	**Symbicort® Turbohaler®:** Fixed combination of 160 µg budesonide + 4.5 µg formoterol fumarate (BUD/FF). **Dose regimen:** BUD/FF, 160/4.5 µg per inhalation, 2 inhalations in the morning (preferably before 10.00 am) and 2 inhalations in the evening (preferably before 10.00 pm) **Administration:** dry powder inhaler (Turbohaler®, AstraZeneca, Sweden)
Number of subjects	A total of 750 patients (375 patients per group) will be randomised in order to reach a total of 540 evaluable and complete patients at Week 24 (270 per group), considering a drop-out rate of 20% and a non-evaluable rate of 10% Assuming a 30% screen failure rate, a total of 1072 patients will be screened.

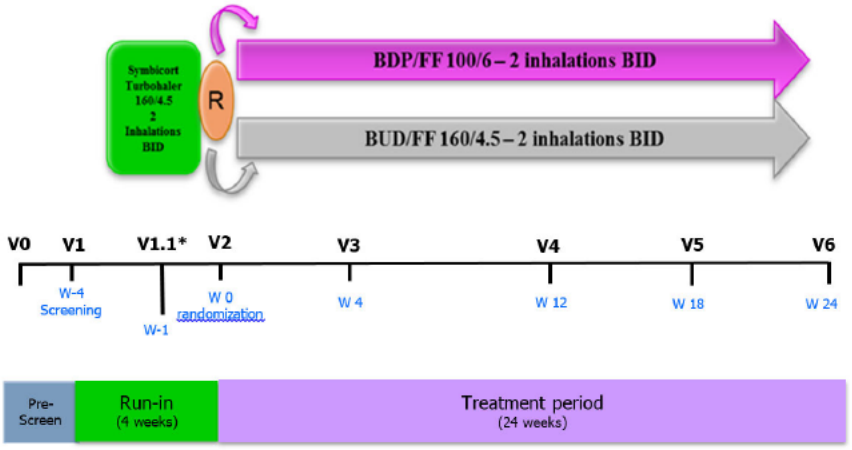
Study population	Patients with moderate to severe COPD
Inclusion/exclusion criteria	**Inclusion criteria** Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study: 1. Male and female adults aged ≥ 40 years, Chinese ethnicity with written informed consent obtained prior to any study-related procedure. 2. Patients with a diagnosis of COPD (according to GOLD document, updated 2017) 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 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI Note: If this criterion is not met at screening, the test can be repeated no more than seven days 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 in treatment 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. *Note: Triple therapy is not allowed 2 months before the screening* 7. A cooperative attitude and ability to be trained to use correctly the study drugs inhalers (pMDI and Turbohaler®). 8. A cooperative attitude and ability to be trained to use correctly the COPD questionnaires.

Exclusion criteria

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

1. 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.
2. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period.
3. 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.
4. 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.
5. 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).
6. 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.
7. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.
8. History of hypersensitivity to β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial.
9. Patients treated with non-cardioselective β-blockers in the 4 weeks preceding the screening visit or during the run-in period.
10. Patients who have clinically significant active 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 or shows QTcF values >450 ms for males or QTcF >470 ms for females. 13. 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, significant hepatic impairment, significant renal impairment or other which may impact the feasibility of the results of the study according to investigator's judgment. 14. 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. 15. Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L). 16. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit. 17. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are using one or more of the following highly effective contraceptive measures: ▪ Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) ▪ Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) ▪ Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) ▪ Bilateral tubal occlusion ▪ Vasectomised partner. Reliable contraception should be maintained throughout the study. Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study. Pregnancy tests will be performed at study entry (a serum test at the screening visit and a urine test at screening and randomisation visits) in all women of childbearing potential. 18. Participation in an interventional clinical trial with intake of the last dose of any investigational drug <12 weeks preceding baseline visit (last dose < 5 half-lives prior to baseline visit for biologics).
Study plan	A maximum of 8 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) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead ECG, spirometric parameters pre/post salbutamol and training for the use of inhalers). - For eligible patients, this visit will be followed by a 4-week open-label run-in period where they will be given Symbicort® Turbohaler® 160/4.5 µg 2 inhalations bid (daily dose 640/18). - At visit 1.1 (V1.1), if the inclusion criterion n.4 was not met at screening (V1) the test (a post-bronchodilator FEV_1 < 50% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio < 0.7 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI) will be repeated and a full physical examination will also be performed. - After the randomisation (V2), patients will be further assessed at 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, to record any new adverse event occurred after the last visit as well as the related concomitant medications. - Inhaled salbutamol will be provided 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.  *Only for patients who didn't meet inclusion criterion 4 at V1
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 and maintained constant during the study 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 (≤10 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 concomitant disease, any appropriate treatment that, according to the Investigator, does not interfere with the study drugs or the study evaluations and is not listed below under the section "forbidden medications" is allowed.
Most relevant forbidden concomitant treatments	1. Depot corticosteroids. 2. Oral/IV/IM corticosteroids (short courses (≤ 10 days) allowed in case of COPD exacerbation). 3. Nebulised β_2-agonists, anticholinergics and/or steroid (short courses (≤ 10 days) allowed in case of COPD exacerbation). 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 (≤ 10 days) allowed in case of COPD exacerbation). 8. Inhaled fixed combinations of a short-acting β_2-agonist and a short-acting muscarinic antagonist (Short course allowed in case of COPD exacerbation). 9. Inhaled short-acting muscarinic antagonists (ipratropium and oxytropium) (Short course (≤ 10 days) allowed in case of COPD exacerbation). 10. Inhaled fixed combinations of a long-acting β_2-agonist and a long-acting muscarinic antagonist 11. Non-cardioselective β-blockers 12. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and other drugs known to prolong the QTc interval. 13. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit. 14. PDE inhibitors (e.g. roflumilast). 15. Leukotriene modifiers. 16. Traditional Chinese Medicines used for respiratory diseases 17. Any medication which can interfere with study drugs and/or affect the

	study outcomes according to investigator's opinion ***Prior to screening (V1), 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 "ultra" long-acting β_2-agonists: 24 hours • Inhaled corticosteroids: 12 hours • Inhaled ICS/LABA fixed combinations: 12 hours • Inhaled LABA/LAMA combinations: 24 hours • Oral xanthines derivatives: 72 hours • Leukotriene modifiers: 72 hours ***Prior to each spirometry, the following wash out periods for concomitant medications must be respected:*** • Salbutamol: 6 hours • Oral xanthines derivatives: 72 hours
Efficacy variables (and/or pharmacokinetics variables)	**Primary efficacy variable** • Change from baseline in pre-dose morning FEV_1 at Week 24. **Secondary efficacy variables** • Change from baseline in pre-dose morning FEV_1 at all the other clinic visits. • Change from baseline in pre-dose morning FVC and IC and Maximal Midexpiratory Flow (MMEF) at all clinic visits. • Change from baseline in the SGRQ total score and domain scores at Week 12 and 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). • Time to first COPD moderate or severe exacerbation. • Rate of moderate and severe COPD exacerbations over 24 weeks of treatment.
Safety variables	• Adverse Events (AEs) and Adverse Drug Reactions (ADRs). • Vital signs (systolic, diastolic blood pressure and pulse rate) at baseline, pre-dose at all visits. • 12-lead ECG parameters: heart rate (HR), PR, QRS, QTcF (pre-dose at screening visit and week 24). ECG will be assessed locally without centralized evaluation.

	• Standard Haematology and Blood Chemistry at screening visit and week 24 (by centralized laboratory)
Sample size calculation	A total of 540 completed and evaluable patients in the PP population (270 per group) will provide 90% power to demonstrate the non-inferiority of CHF 1535 versus Symbicort in pre-dose morning FEV_1 at Week 24, with a non-inferiority margin of -0.07L and a one-sided significance level of 0.025, assuming no difference between treatments and a standard deviation of 250 ml. Estimating a drop-out rate of 20% and a percentage of completed patients with major protocol deviations of 10%, a total of 750 patients (375 per group) will be randomised.
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 (MMRM) including treatment, visit, treatment by visit interaction, site, 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) at Week 24 will be estimated by the model. The non-inferiority of CHF 1535 relative to Symbicort will be demonstrated by a lower confidence limit above -0.07L. **Secondary efficacy variables:** • FEV_1 change from baseline to all other visits will be based on the same model used for the primary analysis. • Mean change in pre-dose morning IC, FVC and Maximal Midexpiratory Flow (MMEF) from baseline to each clinic visit will be based on the same model used for the primary analysis. • The change from baseline in the SGRQ total score and SGRQ domains will be analysed the same model as the one used for the FEV_1 primary analysis. • CAT change from baseline to each clinic visit will be analysed using a similar model as for the primary efficacy variablesThe change from baseline 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 similar models as the one used for the FEV_1. The comparison between treatments on the entire treatment period will be performed using the MMRM, by assigning to inter-visit periods weights proportional to their duration. • The time to first moderate or severe COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, site, number of exacerbation in the previous year and smoking status as factor. A Kaplan-Meier plot will also be

	presented. • The number of moderate and severe COPD exacerbations during the treatment period will be analysed using a negative binomial model including treatment, site, number of COPD exacerbations in the previous year and smoking status as factors, and log-time on study as an offset. Two COPD exacerbations will be considered as a single episode in the statistical analysis if the second exacerbation started less than 10 days after the end of the systemic corticosteroids and/or antibiotics intake for the previous exacerbation. **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, pulse rate) from baseline (Visit 2 pre-dose) to each visit will be calculated with its 95% CI by treatment group. • Mean change from screening to Visit 6 in 12-lead ECG parameters (HR, PR, QRS, QTcF) will be calculated with their 95% CIs by treatment group. • The number and the percentage of patients with a: o QTcF >450 ms, >480 ms and >500 ms o change from screening in QTcF >30 ms and >60 ms at Visit 6 will be presented by treatment group. • Mean changes from screening (V1) to Week 24 (V6) in clinical chemistry and hematology laboratory parameters will be calculated with their 95% CIs by treatment group. • Shift tables from screening (V1) to Week 24 (V6) any visit, with regard to normal range, will be presented by treatment group for the laboratory parameters.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDP	Beclometasone dipropionate
βhCG	Beta-Human Chorionic Gonadotrophin
BID	*Bis In Die* (twice a day)
BUD	Budesonide
Ca	Calcium
CAT	COPD Assessment Test
CFDA	China Food and Drug Administration
CI	Confidence Interval
Cl	Chlore
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DPI	Dry Powder for Inhalation
ECG	Electrocardiogram
ETV	Early Termination Visit
FEV_1	Forced Expiratory Volume in the first second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
γ-GT	Gamma-glutamyl transpeptidase
Hb	Haemoglobin
Hct	Hematocrit
HFA	Hydrofluoroalkane
HR	Heart Rate
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
ID	Identification
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Standards Organization
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
K	Potassium
L	Liter
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
MAOIs	Monoamine Oxidase Inhibitors
MAR	Missing at Random
Max	Maximum

MedDRA	Medical Dictionary for Regulatory Activities
mEq/L	Milliequivalent per Liter
min	Minute
Min	Minimum
MMEF	Mid Maximal Expiratory Flow
mmol/L	Millimol per Liter
MMRM	Mixed Model for Repeated Measures
ms	Millisecond
µg	Microgram
Na	Sodium
NYHA	New York Heart Association
pMDI	pressurised Metered Dose Inhaler
PDE	Phosphodiesterase
PLT	Platelet
PP	Per-Protocol
PR	Time interval between the beginning of the P wave and the beginning of the QRS complex in ECG
PRN	*Pro Re Nova* (as needed)
PRO	Patient reported Outcomes
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)
QTcF	Fridericia – Corrected QTc
RBC	Red Blood Cell
RR	Time interval between two consecutive R waves
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
V	Visit
WBC	White Blood Cell
WHO	World Health Organization

CONTENT

1. BACKGROUNG INFORMATION AND STUDY RATIONALE

1.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [(1)].

According to the latest WHO estimates (2004), 65 million people have moderate to severe chronic obstructive pulmonary disease (COPD) and more than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. In 2000 COPD was the fourth leading cause of death Total deaths from COPD are projected to increase in the next years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. WHO predicts that COPD will become the third leading cause of death worldwide by 2030 [(2)].

The burden of COPD in China is currently greater than that found in developed countries. This is probably due to greater exposure to epidemic risk factors, an imbalance in economic development and health-care disparities between urban and rural areas. A population-based, cross-sectional survey of COPD conducted between 2002 and 2004 showed that the overall prevalence of the disease in people aged > 40 years was 8.2% [(3)]. It has been reported that the prevalence of COPD varied widely among locations across the country, from 5% to 13% [(4)]. According to data published by the Chinese Ministry of Health, COPD ranks as the fourth leading cause of death in urban areas and third leading cause of death in rural areas [(5)].

The Global Initiative for Chronic Obstructive Lung Disease strategic document (GOLD, 2017 update), recommends that the main therapeutic goals of COPD treatment, besides the prevention of disease progression, is to relieve symptoms, improve health status and prevent/treat exacerbations. (GOLD 2017). Bronchodilators are the mainstay of pharmacologic therapy for 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. These drugs have shown to improve lung function and reduce inflammation. The GOLD document highlights that when the disease is not well controlled with bronchodilators alone, combination therapy with a long-acting-β_2-agonist (LABA) and an inhaled corticosteroid (ICS) is recommended to reduce symptoms, prevent exacerbations and improve health status. Therefore the main therapeutic goals in the treatment of COPD should include reduction of exacerbations and relief of other symptoms, prevention of disease progression, improving exercise tolerance and health status, prevention and treatment of complications, and reduction of mortality.

1.2 Rationale

The combination of LABAs and ICSs is supported by a molecular and clinical rationale: Corticosteroids up-regulate β_2 -receptor numbers on the membrane of airway smooth muscle cells and LABAs acts on nuclear uptake of the glucocorticoid receptor/ligand complex in vitro [(6-7-8)].

Corticosteroids can modulate β_2- receptors and their function by several mechanism: protection against desensitization and development of tolerance, increased efficiency of receptor coupling, and protection against inflammation – induced receptor down-regulation and uncoupling. Corticosteroids stimulate the transcription of β_2- receptors via binding to GRE (Glucocorticoid response elements) and increasing in β_2-receptor mRNA. Corticosteroids modulate the efficiency of coupling between the β_2-receptor and Gs protein, this leads to a consequent β_2 receptor-stimulated adenylate cyclase activity and cAMP accumulation [(9)] that triggers PKA with reduction of intracellular calcium levels and final relaxation of airways smooth muscle cells.

LABAs, in turn, may prime the GR (glucocorticoid receptor), by modulating GR phosphorylation, promoting the translocation from the cell cytosol to the nucleus, a fundamental step in the inflammatory activity of corticosteroids. The molecular synergism between ICSs and LABAs may explain the substantial clinical benefits that are observed when they are used together in the treatment of COPD.
Chiesi has been developing a fixed combination of Beclometasone Dipropionate (BDP) and Formoterol Fumarate (FF) pMDI, which has been marketed under the trade name Foster®.
The product was registered in China on February 3, 2013 (IDL No. H20130127) for the following therapeutic indications:

Foster® is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting beta$_2$-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonist or
- patients already adequately controlled on both inhaled corticosteroids and long-acting beta$_2$-agonists.

Note: Foster® is not appropriate for treatment of acute asthma attacks.

The efficacy and safety of Foster® 100/6 µg per actuation has been demonstrated in adult patients with both moderate and severe persistent asthma [(10)] and in severe to very severe COPD patients [(11)]. Both of which represent indications for which Foster® has received marketing authorization in EU.

The aim of this study is to demonstrate the non-inferiority of CHF 1535 pMDI, (fixed combination of Beclometasone dipropionate 100 µg plus Formoterol fumarate 6 µg, 2 inhalations twice daily) vs. Symbicort® Turbohaler® DPI (fixed combination of Budesonide 160 µg plus Formoterol Fumarate 4,5 µg 2 inhalations twice daily) in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at week 24) in patients with COPD. In addition, the effect of CHF1535 pMDI on other lung function parameters, patient reported outcomes (PROs), will also be investigated as well as the safety and tolerability of the study treatments.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), current Good Clinical Practices ICH E6 and all other applicable laws and regulations.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

To demonstrate that CHF 1535 pMDI is non-inferior to Symbicort® Turbohaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at week 24) in patients with COPD.

2.2 Secondary Objectives

- To evaluate the effect of CHF 1535 pMDI on other lung function parameters, and patient reported outcomes (PROs).
- 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, 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 maximum of 8 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, vital signs, a 12-lead ECG, spirometric parameters pre/post salbutamol, and training for the use of inhalers). For eligible patients, this visit will be followed by a 4-week open-label run-in period where they will be given Symbicort® Turbohaler® 160/4.5 µg per inhalation, 2 inhalations bid.
- At visit 1.1 (V1.1), no more than 7 days before the randomisation visit, if the inclusion criteria n.4 was not met at screening (V1) the test (a post-bronchodilator FEV_1 < 50% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio < 0.7 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI) will be repeated and a full physical examination will also be performed.
- After the randomisation (V2), patients will be further assessed at 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, to record any new adverse event occurred after the last visit as well as the related concomitant medications.

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

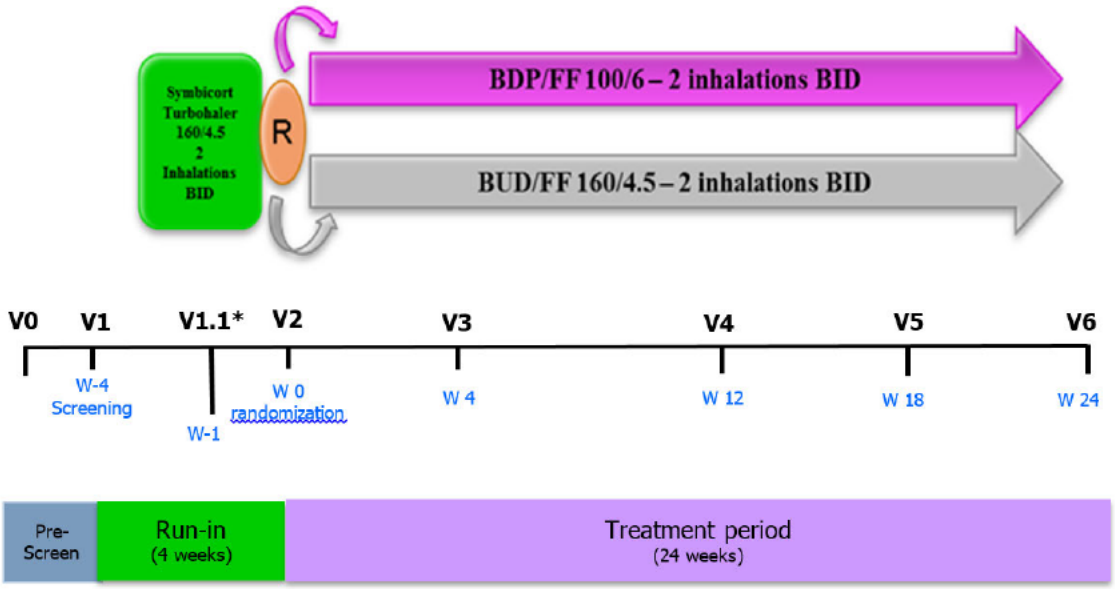
AEs and COPD exacerbations will be monitored throughout the study.

A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6 and -1 to +1 day is allowed for Visit 1.1.

The end of the trial is defined as the last follow-up phone call of the last subject in the trial.

Figure 1. Study design

Clinical Study Code No.: CCD-01535AC1-02	Version No.: 1.0
IND No.: 2016L07859	Date: 09 November 2017



*Only for patients who didn't meet inclusion criterion 4 at V1

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

A total of 750 patients (375 patients per group) will be randomised in order to reach a total of 540 evaluable and complete patients at Week 24 (270 per group), considering a drop-out rate of 20% and a non-evaluable rate of 10%. Assuming a 30% screen failure rate, a total of 1072 patients will be screened.

If a patient is screen failed, he/she can be re-selected at a later stage (one month minimum should elapse), providing the medical conditions of the patient is appropriate with the inclusion in the study according to the investigator and after sponsor approval. In case of re-screening, the patient should sign a new informed consent and will be assigned with a new patient number.

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, Chinese ethnicity with written informed consent obtained prior to any study-related procedure.
2. Patients with a diagnosis of COPD (according to GOLD document, updated 2017) 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 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI.

   Note: If this criterion is not met at screening, the test can be repeated no more than seven days 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 in treatment 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.

Note: Triple therapy is not allowed 2 months before the screening

7. A cooperative attitude and ability to be trained to use correctly the study drugs inhalers (pMDI and Turbohaler®).

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 visit 1.1, the test will be repeated only for patients who have not met the criterion 4 at V1.

At 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. 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.
2. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalization during the run-in period.
3. 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.
4. 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.
5. 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).

6. 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.
7. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia.
8. History of hypersensitivity to β_2-agonist, corticosteroids or any of the excipients contained in any of the formulations used in the trial.
9. Patients treated with non-cardioselective β-blockers in the 4 weeks preceding the screening visit or during the run-in period.
10. Patients who have clinically significant active 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 or shows QTcF values >450 ms for males or QTcF >470 ms for females
13. 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, significant hepatic impairment, significant renal impairment or other which may impact the feasibility of the results of the study according to investigator's judgment.
14. 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.
15. Patients with serum potassium levels < 3.5 mEq/L (or 3.5 mmol/L).
16. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit.
17. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are using one or more of the following highly effective contraceptive measures:
    - Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
    - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Bilateral tubal occlusion
    - Vasectomised partner.

    Reliable contraception should be maintained throughout the study.

    Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study.

Pregnancy tests will be performed at study entry (a serum test at the screening visit and a urine test at screening and randomisation visits) in all women of childbearing potential.

18. Participation in an interventional clinical trial with intake of the last dose of any investigational drug <12 weeks preceding baseline visit (last dose < 5 half-lives prior to baseline visit for biologics).

At screening visit (Visit 1), all exclusion criteria will be checked except criterion 2 that will be checked at Visit 2.

At the randomisation visit (Visit 2), the following criteria will be re-checked: 2, 3, 6, 9, 10, 11, 12, 14, 18.

4.4 Subject 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 subject too unstable to continue the study according to investigator's judgement, the subject 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 non-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 subjects should be avoided. However, should a subject discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible.

All the assessments foreseen at Visit 6 (Week 24) should be done at early termination to the extent possible, providing there is no safety issue for the patient (see section 7.1.9 for more details).

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 subject.

It must be emphasised that after a patient withdraws from a trial, the investigator is still responsible for reporting serious adverse events. The Investigator needs to assure appropriate treatment and follow-up of each adverse event still ongoing at the time of patient's discontinuation. In case of premature discontinuation from the study, a follow-up phone contact will be performed within 7 days after the

last study visit to check the status of any unresolved AEs, to record any new adverse event occurred after the last visit as well as the related concomitant medications.

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

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

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 (≤ 10 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 a concomitant disease any appropriate treatment that, according to the Investigator, does not interfere with the study drugs or the study evaluations and is not listed below under the section "forbidden medications" is allowed.

5.2 Non-permitted concomitant Medications

1. Depot corticosteroids.

2. Oral/IV/IM corticosteroids (short courses (≤ 10 days) allowed in case of COPD exacerbation).

3. Nebulised β_2-agonists, anticholinergics and/or steroid (short courses (≤ 10 days) allowed in case of COPD exacerbation).

4. Inhaled corticosteroids.

5. Inhaled long-acting β_2-agonists or fixed combination of corticosteroids and long-acting β2-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 (≤ 10 days) allowed in case of COPD exacerbation).

8. Inhaled fixed combinations of a short-acting β_2-agonist and a short-acting muscarinic antagonist (Short course (≤ 10 days) allowed in case of COPD exacerbation).

9. Inhaled short-acting muscarinic antagonists (ipratropium and oxytropium) (Short course (≤ 10 days) allowed in case of COPD exacerbation).

10. Inhaled fixed combinations of a long-acting β_2-agonist and a long-acting muscarinic antagonist

11. Non-cardioselective β-blockers

12. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and other drugs known to prolong the QTc interval.

13. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit.

14. PDE inhibitors (e.g. roflumilast).

15. Leukotriene modifiers.

16. Traditional Chinese Medicines for respiratory diseases

17. Any medication which can interfere with study drugs and/or affect the study outcomes according to investigator's opinion

Prior to screening V1, 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 "ultra" long-acting β_2-agonists : 24 hours
- Inhaled corticosteroids: 12 hours
- Inhaled ICS/LABA fixed combinations: 12 hours
- Inhaled LABA/LAMA combinations: 24 hours
- Oral xanthines derivatives: 72 hours
- Leukotriene modifiers: 72 hours.

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

- Salbutamol: 6 hours
- Oral xanthines derivatives: 72 hours

6. TREATMENT(S)

The study medications 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. 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.

6.1 Appearance and Content

Investigational drug:

- **CHF 1535 100/6 µg pMDI - Test product**

  Active ingredient: Fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg.

  Excipients: HFA-134a, Ethanol anhydrous, Hydrochloric acid.

  Presentation: Canister containing 120 doses plus white actuator.

- **CHF 1535 pMDI matched Placebo (*)**

  Excipients: HFA-134a propellant, ethanol anhydrous.

  Presentation: Canister containing 120 doses plus white actuator.

Control drug:

- **Symbicort® Turbohaler® 160/4.5** (AstraZeneca [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® Turbohaler® matched placebo (*)**

  Excipients: Inhalation grade Lactose.

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

(*) The matched placebos pMDI and 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.

Note: **Salbutamol** pMDI 100µg/puff, to be used as rescue medication, will be purchased locally and provided by Investigator site to patients. Patients will take the usual rescue on an as-needed basis. This rescue medication will be reimbursed by the Sponsor.

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

The selection of the dose for CHF 1535 pMDI (100/6 µg per inhalation) is based on the results of previous studies performed by Chiesi in adults with both moderate an severe asthma[10] and in severe to very severe COPD patients[11].

CHF 1535 pMDI (100/6 ug per inhalation) has obtained the Chinese Marketed Authorization for the treatment of patients with asthma.

6.2.2 Dosage

6.2.2.1 Run-in period:

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

6.2.2.2 Randomised Treatment period:

- Test product: CHF 1535 100/6 µg pMDI 2 inhalations b.i.d. plus matched placebo of Symbicort® Turbohaler® 2 inhalations b.i.d (total daily metered dose: BDP 400 µg plus FF 24 µg).
- Control drug: Symbicort® Turbohaler® 160/4.5 µg/unit dose 2 inhalations b.i.d. plus CHF 1535 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 drug.

6.2.3 Administration

6.2.3.1 Run-in period:

At visit 1 (screening), each eligible patient will receive one Run-in kit containing two Symbicort® Turbohaler® 160/4.5µg as run-in medication, in replacement of their current therapy.

The run-in medication will be administered twice a day: **two** inhalations **in the morning** (preferably before 10.00 am) and **two** inhalations **in the evening** (preferably before 10.00 pm). **To the extent possible, the time of dosing must remain constant for each patient for the whole duration of the study**

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.

Note: the first dose of run-in medication must be administered at clinic at the end of Visit 1 (the run-in kit should be dispensed at V1 even if the inclusion criterion 4 must be re-tested before the randomisation).

6.2.3.2 Treatment period:

At visit 2 (randomization), the confirmed eligible patients will be randomised and will receive the **test product** (CHF 1535 100/6µg pMDI) or the **reference product** (Symbicort® Turbohaler® 160/4.5 µg).

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

- 2 refrigerated kits containing each 2 pMDI inhalers of CHF 1535 100/6µg **or** 2 pMDI inhalers of placebo;

  and

- 2 ambient kits containing each 2 dry powder inhalers of Symbicort® Turbohaler® 160/4.5 µg **or** 2 matched placebo Turbohaler® Inhalers.

Each refrigerated kit containing 2 pMDI inhalers covers a period of 6 weeks; patients will be instructed by the investigator to use the second kit after 6 weeks.

Each ambient kit containing 2 dry powder inhalers covers a period of 6 weeks; patients will be instructed by the investigator to use the second kit after 6 weeks.

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

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

In order to ensure the double dummy design of the trial, patients randomised to receive CHF 1535 pMDI will be administered Symbicort® Turbohaler® matched placebo and patients randomised to receive Symbicort® Turbohaler® will be administered pMDI placebo, as detailed in the scheme below:

Treatment Administration scheme	**CHF 1535 pMDI Arm**	**Symbicort® Turbohaler® Arm**
pMDI	Two inhalations in the morning and two inhalations in the evening of CHF 1535 100/6 µg	Two inhalations in the morning and two inhalations in the evening of pMDI matched Placebo
Dry powder for inhalation	Two inhalations in the morning and two inhalations in the evening of Symbicort® Turbohaler® matched placebo	Two inhalations in the morning and two inhalations in the evening of Symbicort® Turbohaler® 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 pMDI inhaler number 1 + 1 from pMDI inhaler number 2 + 1 from Turbohaler® number 1 + 1 Turbohaler® number 2.
- **In the evening**: 1 from pMDI inhaler number 1 + 1 from pMDI inhaler number 2 + 1 from Turbohaler® number 1 + 1 from Turbohaler® 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. For more details regarding the instructions for use of Study Treatments, please refer to patient leaflets.
The first administration of the study drug will take place in the morning at clinic visit under medical supervision.

Then, the study treatments (CHF 1535 pMDI or Symbicort® Turbohaler®) will be administered daily by patients at home.

Note: At the time of drug intake at site, the study drug, stored between 2°C and 8°C, should be removed from the refrigerator and the canister should be taken out of the mouthpiece and warmed with the hands for few minutes before administration to the patient. The canister should never be warmed by artificial means. **The patient should never inhale a cold medication** (see section 6.8).

6.2.3.3 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.
The spacer device to be used in the study is the **AeroChamber Plus™** Flow-Vu antistatic **Valved Holding Chamber** (referred as AeroChamber Plus™ in the rest of the document).
One spacer will be assigned to the patient by the Investigator at visits V1, V2 and V4.
For these patients, **each inhalation** (randomisation period) **must be performed via AeroChamber Plus™. For each puff, the patient must inhale slowly and deeply and** hold his breath as long as possible.

For more details concerning the use of the pMDI with spacer, please refer to the patient leaflet.

6.2.3.4 Use of Rescue Medication

At visit 1 and 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.

The maximum dose allowed is 8 puffs per day. In case the patients' needs exceed 8 puffs/day for more than 2 consecutive days, he/she must contact the investigator.
A minimum period of 6 hours should elapse between the use of rescue salbutamol and the spirometric measurements

6.2.4 Subject Training

During the screening visit, each patient will receive two training kits containing placebo only (see description in section 6.3.1).

Patient will be instructed by the investigator on how to use the pressurised Meter Dose Inhaler and the Symbicort® Turbohaler® inhaler according to the instructions provided along with the study drug.
The proper use of the inhalers will be checked again at randomisation visit (V2) using the same training kits.
These training kits will be kept at the site by the Investigator (will not be dispensed to the patients) and can be re-used for subsequent trainings.

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 spacer (if applicable) will be checked again at randomisation visit (V2).

6.3 Packaging

6.3.1 Training kit

- pMDI Training kit
  One box containing 1 CHF 1535 pMDI placebo.
  - *Primary packaging*: canister plus standard actuator.
  - *Secondary packaging*: box containing 1 canister plus 1 standard actuator.
- DPI Training kit
  One box containing 1 matched placebo Turbohaler® inhaler.
  - *Primary packaging*: Turbohaler® inhaler.
  - *Secondary packaging*: box containing 1 Turbohaler® 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.

One box containing 1 AeroChamber Plus™ Flow-Vu antistatic VHC.
- *Primary packaging:* AeroChamber Plus™ Flow-Vu antistatic VHC.
- *Secondary packaging*: box containing 1 AeroChamber Plus™ Flow-Vu antistatic VHC.

6.3.2 Run-in medication (Symbicort® Turbohaler® 160/4.5 µg)

- *Primary packaging:* 2 Turbohaler® inhalers.
- *Secondary packaging*: box containing 2 Turbohaler® inhalers.

6.3.3 Study treatments (CHF 1535 100/6 µg pMDI or Symbicort® Turbohaler® 160/4.5 µg and matched placebos)

- Refrigerated Treatment Kit:
  - *Primary packaging*: Two canisters plus standard actuators

  The first canister will be labelled with a number 1 sticker and the second canister will be labelled with a number 2 sticker.

  - *Secondary packaging*: box containing 2 canisters plus 2 standard actuators
- Ambient Treatment Kit:
  - *Primary packaging*: Two Turbohaler® inhalers

  The first inhaler will be labelled with a number 1 sticker and the second inhaler will be labelled with a number 2 sticker.

- *Secondary packaging*: box containing 2 Turbohaler® inhalers

6.3.4 AeroChamber Plus™ Spacer

One box containing 1 AeroChamber Plus™ Flow-Vu antistatic VHC.

- *Primary packaging:* Spacer AeroChamber Plus™ Flow-Vu antistatic VHC.
- *Secondary packaging:* One box containing 1 spacer AeroChamber Plus™ Flow-Vu antistatic VHC.

6.4 Labelling

All the supplies will be labelled according to local law and regulatory requirements and will be compliant with Annex 13 to the Volume 4 of the GMP.
All the labels will be in local language.

For all the labels, the patient identification is expressed by the kit number. This number is assigned by the IRT System which allows the full traceability of essential details such as: site identification, investigator's name, visit number, randomization number.

6.5 Treatment allocation

A balanced block randomisation scheme stratified by site will be prepared via a computerised system. Patients will be centrally assigned, in each centre, to one of the two treatment arms with the ratio 1:1. An Interactive Response Technology (IRT) will be used at each visit (from pre-screening to follow-up phone call) to record patient status.

The patient will be identified by a patient number of 8 digits:

- the 3 first digits correspond to the ISO country code (156 for China);
- the 2 second digits to the centre number;
- the 3 last digits to the screening number (chronological in each site).

The IRT will allocate the patient ID, will assign the patient to a certain treatment group using a list-based randomisation algorithm. The investigator, or designee, will call the IRT system to screen, randomise patients and assign the study medication kit number corresponding to the treatment group assigned to the patient. The IRT will also track the screen failures and discontinuations from the study.

In case of re-screening, a new patient number (ID) will be given to the patient by the IRT system.

6.6 Treatment Code

The study medication will be packaged and uniquely numbered. Each primary packaging in the medication kit will have a numbered label that matches the kit number on the label of the outside packaging. The IRT will be used to assign both initial and subsequent kits in order to have an inventory control and patient dosing tracking. The IRT will also maintain quantities, kit numbers, kit status, drug types, batch/code numbers, expiration dates and do not dispense after these dates. The IRT will monitor inventory levels at all sites and manage the study drug re-supply.

The medication list will be provided to the labeling facility but 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, unless in case of emergency.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list nor to the medication list.
In case of emergency, unblinding of the treatment code will be done through IRT. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation to the site for every transaction performed by the Investigators. The Investigator will be provided with usernames and passwords for randomisation purposes and separate usernames and passwords 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.

The Chiesi Farmaceutici S.p.A.'s Global Pharmacovigilance Users will have their own passwords to unblind patients in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees.

6.7 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the patient.
The evaluation of the compliance will be done using the following formula:

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

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.

6.8 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.

Run-in medication:
The boxes containing Symbicort® Turbohaler® 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 1535 100/6 µg or matched placebo***.

pMDI kits must be stored between 2˚C and 8˚C by Pharmacist/Investigator at site. At the time of drug intake at site, the medication kits should be removed from the refrigerator and the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. The canister must never be warmed by artificial means. **The patient should never inhale a cold medication.**

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 actual use-by-date of the pMDI kits will be five months (**150days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the kit labels** once the pMDI kits are removed from the refrigerator, before assigning to the patients. The **use-by-date corresponds to the dispensing date plus 5 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

- ***DPI medication: Symbicort® Turbohaler® 160/4.5 µg or matched placebo***

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

- ***Medication for training*:**

pMDI training kits must be kept at site and **not** dispensed to the patients. pMDI training kits must be stored between 2˚C and 8˚C by Pharmacist/Investigator at site. At the time of the training, the training kits should be removed from the refrigerator and the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. The canister must never be warmed by artificial means. **The patient should never inhale a cold medication.**

After usage, the pMDI training kits must be stored at room temperature (not above 25 ºC) at the clinics. At this temperature condition, the actual use-by-date of the pMDI training kits will be five months (**150 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the kit labels** once the pMDI training kits are removed from the refrigerator, before using them. The **use-by-date corresponds to the dispensing date plus 5 months.** The same training kit will be used by patient at screening and at randomisation.

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

Note: the spacer AeroChamber Plus™ should be stored at room temperature.

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 to the CRA and then to the Sponsor, who shall assess if the affected study medications can still be used.

6.9 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.

6.10 Provision of additional care

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

7. STUDY PLAN

7.1 Study Schedule

The study plan includes a maximum of 8 clinic visits (Visit 0 to Visit 6), 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 (no more than 7 days after V0) to verify the patients' eligibility. For the eligible patients this visit will be followed by a 4-week run-in period, where the patients will receive open-label Symbicort® Turbohaler® treatment;
- *Visit 1.1* (***V1.1***): 7 days before the randomisation visit, inclusion criteria n.4 will be checked if not met at screening (V1);
- *Visit 2 (**V2**)*: randomisation visit when patients will be randomised to one of the two 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*: 1 week after the last visit (V6) or the Early Termination visit to check the status of any unresolved adverse events, to record any new adverse event occurred after the last visit as well as the related concomitant medications.

A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6 and a "window" of -1 to +1 day for V1.1.

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

	Pre-screening	Screening		Treatment Period				
Visits	V 0	V 1	V 1.1*	V 2**	V 3	V 4	V 5	V 6 / ETV
Time (Weeks)	Wk -5	Wk -4 (from 1 to 7 days after V0)	Wk -1 (±1 days)	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	✓							
Inclusion/Exclusion criteria		✓	✓[a]	✓				
Medical history/Previous medications		✓						

Physical examination		✓	✓	✓	✓	✓	✓	✓
Weight and height[1]		✓	✓	✓	✓	✓	✓	✓
Smoking status		✓		✓	✓	✓	✓	✓
Vital signs (SBP/DBP and pulse rate)		✓	✓	✓	✓	✓	✓	✓
12-lead ECG[2]		✓						✓
Lung function post BD[3]		✓	✓					
Lung function measurements at clinic visits: pre-dose[4]		✓	✓	✓	✓	✓	✓	✓
Diary completion		**Daily** ✓						
Diary review[5]			✓	✓	✓	✓	✓	✓
Assessment of COPD exacerbations		✓	✓	✓	✓	✓	✓	✓
Training to the use of Turbohaler®		✓		✓				
Training to the use of pMDI inhaler and of spacer		✓		✓				
COPD Assessment Test (CAT)		✓		✓	✓	✓	✓	✓
St. George's Respiratory Questionnaire (SGRQ)				✓		✓		✓
Haematology – Blood chemistry (Centralized laboratory applied)[6]		✓						✓
Serum pregnancy test[7]		✓						✓
Urinary pregnancy test[7]		✓	✓	✓	✓	✓	✓	
IRT call/connection	✓	✓		✓	✓	✓	✓	✓
Drug dispensing		✓		✓		✓		
Drug returning				✓		✓		✓
Concomitant medications		✓	✓	✓	✓	✓	✓	✓
Adverse events/Serious adverse events		✓	✓	✓	✓	✓	✓	✓

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

***Only** applicable for patients who didn't met the inclusion criterion 4 at V1
**Randomisation
[a] Re-check inclusion criteria n.4 (a post-bronchodilator FEV_1 < 50% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio < 0.7, 10-15 min after 4 puffs (4 x 100 µg) of salbutamol pMDI)

1. Height at Visit 1 only;
2. Triplicate pre-dose ECG – At Investigator's discretion and for safety purpose, ECG can be repeated.
3. Spirometry 10-15 min after 4x100 µg salbutamol;
4. Including IC, FEV_1, FVC, MMEF. Please verify that wash-out of rescue medication (at least 6h), Xanthines (when applicable) or run-in/study medication have been 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 medications;
6. Test can be repeated in case of non-interpretable data or at Investigator's discretion
7. For females of childbearing potential only. Urine pregnancy test performed locally.

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:

- The written informed consent signed by the patient will be collected after the study has been fully explained by the investigator. The investigator or his/her designee should provide them ample 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 in accordance with section 5.2.
- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to allocate a unique patient number.

Before discharge,

- A **patient card** with the phone numbers of Hospital site and Investigator's contact details will be handed out to the patient.
- An **appointment** for the screening visit (V1) will be taken in the morning preferably before 9:00 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 xanthines drug in the 72 hours preceding the next visit if applicable;
  - ➔ 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)

A screening visit (no more than 7 days after V0) will be carried out in the morning preferably before 9:00 am (+/- 2 hours) in order to identify eligible consenting patients for the study.

If any of the wash-out 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-out 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.
- Previous medications in the past 3 months must be collected. Concomitant medications being taken by the patient will be recorded. 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), diastolic (DBP) blood pressure and pulse rate] will be measured before salbutamol administration and after 10 minutes sitting in resting position (see section 7.2.5).
- A triplicate 12-lead ECG will be performed before salbutamol administration after 10 minutes of rest (see section 7.2.6).

  At Investigator's discretion, the ECG can be repeated before V2.
- 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;
- serum pregnancy (β-HCG) test 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 non-interpretable data or at Investigator's discretion, another determination can be performed as soon as possible and prior to Visit 2 to re-assess any parameter.

A urine pregnancy test in women with childbearing potential will be performed locally.

- Pre-bronchodilator spirometry will be carried out: the patients will have to perform a SVC manoeuvre to assess IC followed by FVC manoeuvre to assess parameters (FEV_1, FVC and MMEF) (see section 7.2.1).
- A FEV_1 and FVC test 10-15 minutes after intake of 4 puffs (4 x 100 µg) of salbutamol pMDI will be performed.
- 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 DPI Turbohaler® and pMDI with AeroChamber Plus™ if applicable (see section 6.2.4). The corresponding tear-off label of training kits 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® Turbohaler®) 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 (preferably before 10:00 am) and 2 inhalations in the evening (preferably before 10:00 pm). **The first administration of run-in medication will take place at the clinic visit (preferably before 10:00 am) 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 and the kit number will be recorded in the corresponding electronic CRF (e-CRF). The patients will be instructed to perform 2 inhalations in the morning and 2 inhalations in the evening of Symbicort® Turbohaler® 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.
- **Patient will use a daily diary** for the recording of medication intake (run-in and rescue) until visit 2.
- **An appointment for Visit 1.1** will be made in 3 weeks for patient who has not met the inclusion criterion 4
- **An appointment for Visit 2** will be made in 4 week (± 3 days) from Visit 1, in the morning.

  Patients will be instructed:

  ➔ **Not to take salbutamol in the 6 hours preceding the next visit,** unless absolutely necessary.

  ➔ **Not to take xanthines drug in the 72 hours preceding the next visit** (when applicable)

  ➔ **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) at the next visit.

7.1.3 Visit 1.1 (assessment of inclusion criterion)

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® Turbohaler®) has been taken in the morning of the visit, the visit needs to be re-scheduled within 1 days. A further visit 7 days before the randomisation visit (V2) will be carried out in the morning preferably before 9:00 am (+/- 2 hours) in order to re-assess inclusion criterion 4 if not met at screening visit (V1).
Lung function measurements (FEV_1 and FVC) before and 10-15 minutes after intake of 4 puffs (4 x 100 µg) of salbutamol pMDI will be performed.

- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured, after 10 minutes of rest in sitting position (see section 7.2.5).
- A urine pregnancy test in women with childbearing potential will be performed
- Weight will be recorded.
- A full physical examination will be performed.
- The occurrence of COPD exacerbations will also be evaluated.
- The occurrence of other adverse events will be checked and recorded if any.
- The investigator will check the daily diary where the patient has recorded the 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 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).

7.1.4 Visit 2 (randomisation)

The visit 2 will start in the morning preferably before 9:00 am (+/- 2 hours).

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® Turbohaler®) has been taken in the morning of the visit, the visit needs to be re-scheduled 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 the daily diary where the patient has recorded the 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 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 St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- The occurrence of COPD exacerbations will be evaluated (see section 7.2.8). In case of moderate/severe exacerbation during the run-in, the patient will not be randomised (see also section 4) 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 locally.
- A full physical examination will be performed.
- Weight will be recorded.
- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured, after 10 minutes of rest in sitting position (see section 7.2.5).
- The proper use of pMDI with the Aerochamber Plus™ (if applicable) and DPI Turbohaler® will be checked again using the training kits previously assigned to the patient at V1.
- Eligibility criteria will be reviewed.

For eligible patients:

- A pre-dose spirometry measurement will be performed to assess IC (SVC) and FEV_1, FVC, and MMEF (FVC) 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.

  Note: For patient using a spacer with pMDI, a new spacer will be dispensed.
- The corresponding tear-off labels will be stuck in the dispensation tracking form.

The first administration of the study drug will take place at the clinic visit (preferably before 10:00 am) under supervision of the Investigator.

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 6.2.3. Patient will be instructed to take salbutamol as rescue if necessary. Investigator will dispense also salbutamol if needed.
- **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 9:00 am, +/- 2 hours).

  The patient will be instructed:

  - ➔ To **bring back** the **study medication** (in the box) and the spacer (if applicable) at the next visit.
  - ➔ **To avoid taking salbutamol in the 6 hours preceding the next visit**, unless absolutely necessary.
  - ➔ **Not to take xanthines drug in the 72 hours preceding the next visit** (when applicable)
  - ➔ **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 3 (Week 4 of Treatment Period)

The visit 3 will start in the morning preferably before 9:00 am (+/- 2 hours).

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 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 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 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**.
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The occurrence of COPD exacerbations and other adverse events will be evaluated (see section 7.2.8) (if any).

- 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 locally.
- A full physical examination will be performed.
- Weight will be recorded.
- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured after 10 minutes of rest (see section 7.2.5).
- A pre-dose spirometry measurement will be performed to assess IC (SVC) and FEV_1, FVC, and MMEF (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 (preferably before 10:00 am) under supervision of the Investigator from the two kits dispensed at Visit 2.** For the patient who needs using a spacer with pMDI, medication will be taken via the spacer.
- The Investigator will access IRT to register the status of the patient.

Before discharge

- **Study medication** for the following 8 weeks of treatment will be given back to the patient together with instructions for use.
- **A reminder will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 4 in daily diary.
- **An appointment for Visit 4 will be made within 12 weeks (±3 days) from Visit 2** (at approximately the same time as other visits, before 9:00 am, +/- 2 hours).

  The patient will be instructed:

  - ➔ To **bring back** the **study medication** (in the box) 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 xanthines drug in the 72 hours preceding the next visit** (when applicable)
  - ➔ **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 4 (Week 12 of Treatment Period)

The visit 4 will start in the morning preferably before 9:00 am (+/- 2 hours).

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 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 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 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.**
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- The occurrence of COPD exacerbations and other adverse events will be evaluated (see section 7.2.8) (if any).
- 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 locally.
- A full physical examination will be performed.
- Weight will be recorded.
- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- A pre-dose spirometry measurement will be performed to assess IC (SVC) and FEV_1, FVC, and MMEF (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 kit numbers for the next 12-week treatment period. The corresponding tear-off labels will be stuck in the dispensation tracking form. **The morning dose of study medication will be administered from the kit dispensed at the clinic (preferably before 10.00 am) under supervision of the Investigator** (see section 6.2.3).

Before discharge

- **Study medication** for the following 12 weeks of treatment will be dispensed to the patient together with instructions for use. Patient will be instructed to take salbutamol as rescue if necessary. For patient who is using a spacer with pMDI, the new spacer will be dispensed and

patient will be reminded to use the spacer for each inhalation. Investigator will dispense also salbutamol if needed.

- **A reminder will be given to the patients** for the recording of medication intake (treatment and rescue) in daily diary.
- **An appointment for Visit 5 will be made within 18 weeks (±3 days) from Visit 2** (at approximately the same time as other visits, before 9:00 am, +/- 2 hours).

  The patient will be instructed:

  - ➔ To **bring back** the **study medication** (in the box) and 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 xanthines drug in the 72 hours preceding the next visit (when applicable)**
  - ➔ **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 5 (Week 18 of Treatment Period)

The visit 5 will start in the morning preferably before 9:00 am (+/- 2 hours).

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 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 checked, 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 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 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**.
- The CAT will be completed to evaluate if the patient is symptomatic (see section 7.2.7).

- The occurrence of COPD exacerbations and other adverse events will be evaluated (see section 7.2.8) (if any).
- 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 locally.
- A full physical examination will be performed.
- Weight will be recorded.
- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- Pre-dose measurements will be performed to assess IC (SVC) and FEV_1, FVC, and MMEF (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 (preferably before 10:00 am) under supervision of the Investigator from the kit dispensed at Visit 4.** For the patient who needs using a spacer with pMDI, medication will be taken via the spacer.
- The Investigator will access IRT 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 with pMDI, he/she will be reminded to use the spacer for each inhalation. The investigator will also dispense salbutamol if needed.
- **A reminder will be given to the patients** for the recording of medication intake (treatment and rescue) until visit 7 in daily diary.
- **An appointment for Visit 6 will be made within 24 weeks (±3 days) from Visit 2** (at approximately the same time as other visits, before 9:00 am, +/2 hours).

  The patient will be instructed:

  - ➔ To **bring back** the **study medication** (in the box) 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 xanthines drug in the 72 hours preceding the next visit** (when applicable)
  - ➔ **Not to take the morning dose of the study medication before coming to the clinic visit** (it will be administered at the clinic visit).

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

The visit 6 will start in the morning preferably before 9:00 am (+/- 2 hours).

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 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.
- Changes of concomitant medications 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 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 and other adverse events will be evaluated (see section 7.2.8) (if any).
- The occurrence of other adverse events will be checked and recorded if any.
- A full physical examination will be performed.
- Weight will be recorded.
- The St George's Questionnaire (SGRQ) will be filled in by the patient to check symptoms (see section 7.2.9).
- Pre-dose vital signs (SBP, DBP and pulse rate) will be measured after 10 minutes of rest in the seated position (see section 7.2.5).
- At Investigator's discretion and for safety purpose, the ECG can be repeated.
- Pre-dose triplicate 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;
  - 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 or at Investigator's discretion, another determination must be performed as soon as possible to re-assess any parameter

- A pre-dose spirometry measurement will be performed to assess IC (SVC) and FEV_1, FVC, and MMEF (FVC). For each time point, spirometry consists in three acceptable manoeuvres (see section 7.2.17.2).
- The last intake of study drug is done at Clinic (during the visit).
- The Investigator will access IRT to register the completion of the study for the patient.

- At Investigator's discretion, the pre-study patient's therapy will be resumed or changed if appropriate.
- At the end of the patient's participation in the trial, she/he will be discharged from the unit, providing that all her/his safety assessments are satisfactory.

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

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

The procedures foreseen at Visit 6 (Week 24 / End of Treatment Visit) should be performed to the extent possible, providing there is **no safety issue** for the patient.

The Investigator must fill in the study termination visit in the eCRF. The explanations regarding the reasons of withdrawal and all the assessments performed will be recorded.

7.1.10 Follow-up phone call

One week after the last visit (V6) or the Early Termination visit, the patients will be contacted by phone to check and record in the eCRF:

- The concomitant medications taken by the subjects since last period to treat AEs
- The status of unresolved AEs/SAEs at last period and any new AEs/SAEs which occurred since the last period.

The Investigator will access IRT to record the follow-up phone call for the patient.

7.2 Investigations

7.2.1 Spirometry

Pulmonary function tests (IC, FEV_1, FVC, and MMEF) 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 preferably before 9:00 am (+/- 2 hours), approximately at the same time of the day for each patient.

Lung function measurements and daily calibration of the spirometer will be done in accordance with the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society [(12)]. Predicted values will be calculated according to the formulas reported by Quanjer et al. [(13)]. 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 Body Temperature and Pressure, Saturated (BTPS) conditions.

Calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to any spirometry manoeuvres and the reports must be kept with the source study documents.

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 Mid Maximal Expiratory Flow (**MMEF**, L/sec) will be recorded from a forced vital capacity manoeuver, while a slow manoeuver will be performed for the measurement of Inspiratory Capacity (**IC**, L).

For FEV_1, FVC and IC, **the highest value from three technically satisfactory attempts** will be recorded (irrespective of the curve they come from).
For MMEF, 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.

The ratio **FEV_1/FVC** will be derived from these **highest values** of each parameter [(14)].

FEV_1, **FVC**, **MMEF** and **IC** will be recorded at each clinic visit under medical supervision. At screening, the post-bronchodilator FEV_1 values (within 30 min after administration of 4x100 µg salbutamol) will be considered for eligibility.

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 sections 5.1 and 5.2).

If the wash-out has not been respected the visit needs to be re-scheduled 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, V1.1 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 Diary card

From screening, a 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.

7.2.3 Use of rescue medication

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

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 and Visit 6. The collection will always be done after vital signs and ECG measurements, and before intake of study medication.

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 (Na, K, Ca, Cl), 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.

The urine pregnancy tests will be performed **locally** only for females of childbearing potential and 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 6 in the medical opinion of the investigator will be reported as adverse events in the eCRF.

7.2.5 Vital signs: Blood pressure evaluation and body weight

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

Pre-dose evaluations will be done at all visit from Visit 1.

Body weight must be assessed at each visit preferably using the same weighting scale for a same patient.

7.2.6 12-lead ECG

A local ECG registration will be used. Pre-dose 12-lead ECG measurements will be done at visits 1 and 6.

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 10 minutes before starting the recordings.

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 at visit 1 and visit 6 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 Visit 1 and Visit 6.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at Visit 6 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 ≤ 450 (males) and 470 ms (females) (as per Exclusion Criterion 12).

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 [(15)]. 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 except Visit 1.1. 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 [(16)]:

- **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 pulmonary division, requiring an urgent medical advice or extra visit to physician:

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

The recognition of potential COPD exacerbations will be primarily collected retrospectively during the visits. Data from CAT would also be considered. Investigator will carefully train the patient to recognise the worsening of signs and symptoms associated with COPD exacerbations. The patient will also be instructed on 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. The contact details will be indicated on the patient card distributed to the patient at the pre-screening visit.

During the run-in period: if the patient experienced any moderate or severe COPD exacerbation), he/she will not be randomised in the study (exclusion criteria 2).

After randomisation: 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 an exacerbation 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 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 as drug related.

The assessment of worsening symptoms during any extra unscheduled visit 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.

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 (≤ 10 days) 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:

1. For exacerbation therapy, it is advised to start with an antibiotic 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 the next 5 days.

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. These postponements will not be considered as deviations.

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 [(17)]. 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 site. The information from the SGRQ will be entered into the clinical database by the CRO.

8. EFFICACY ASSESSMENTS

8.1 Primary variables

•Change from baseline in pre-dose morning FEV_1 at Week 24

8.2 Secondary variables

•Change from baseline in pre-dose morning FEV_1 at all the other clinic visits.

•Change from baseline in pre-dose morning FVC and IC at all clinic visits.

•Change from baseline in pre-dose Maximal Midexpiratory Flow (MMEF) at all clinic visits.

•Change from baseline in the SGRQ total score and domain scores at Week 12 and 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).

•Time to first moderate or severe COPD exacerbation.

•Rate of moderate and severe COPD exacerbations over 24 weeks of treatment.

9. SAFETY ASSESSMENTS

•Adverse Events (AEs) and Adverse Drug Reactions (ADRs)

•Vital signs (systolic, diastolic blood pressure and pulse rate) at all visits pre-dose (except V1.1).

•12-lead ECG parameters: heart rate (HR), PR, QRS, QTcF (pre-dose at visit 1 and visit 6). ECG will be assessed locally without centralized evaluation.

•Standard Haematology and Blood Chemistry at visit 1 and visit 6 (by a centralized laboratory)

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a patient or clinical trial subject 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.

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 subject 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 overnight formal admission into 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 or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as a SAE. Complications that occur during the hospitalization are AEs. If a complication prolongs hospitalization, the event is a 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 subject's physical or psychological well-being to the extent that the subject 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 subject'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 (Summary of Product Characteristics for CHF 1535 pMDI and Symbicort® Turbohaler®), 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".
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 subject, 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 subject and is of a sufficient severity to make the subject 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 subject 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.

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;
- Medical history;
- Lack of efficacy/worsening of existing condition;
- Study treatment(s);
- Mechanism of action of the study drug;
- Class effects;
- Other treatments-concomitant or previous;
- Withdrawal of study treatment(s);
- Dechallenge (did the event abate after stopping drug?);
- Rechallenge (did the event reappear after reintroduction?);
- 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
- Not applicable
- Unknown

10.6 Other actions taken

- Specific therapy/medication
- Concomitant procedure
- Not applicable

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

All Adverse Events occurring during the course of the study must be documented in the Adverse Event page of the electronic Case Report Form (eCRF). Moreover, if the Adverse Event is serious, the Serious Adverse Event Form must also be completed.

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings.
The recording period for Adverse Events is the period starting from the Informed Consent signature until the subject's study participation ends.

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 until the subject is lost to follow-up. Follow-up may therefore continue after the subject has left the study. In this case, the follow-up will continue with no timelines for related SAEs, while for unrelated SAEs the type and extent of follow-up undertaken will be determined for each individual case and will depend upon the nature (e.g. events with poor prognosis or which do not resolve), severity and medical significance of the event.

10.9 Reporting Serious Adverse Events to Chiesi

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

The contact persons are:

Name and Title	Telephone no.	Fax no.	E-mail
PPD	PPD	+86 21 2422 8882	PPD
PPD	PPD	+39 05211885003	PPD

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject 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 CFDA and ECs by fax (CFDA 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 together with the Serious Adverse Event form, 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 subject will be immediately withdrawn from the study and she will be followed 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 subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in/rescue medication/background (as applicable), the pregnancy does not need to be reported; it is only required that the subject 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, primary reason for not continuing, adverse

events if any and concomitant medications when taken to treat AEs or when are the reason for failure.

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 and IRT data) will be processed centrally by third party vendors and sent electronically to the designated CRO. External data will be reconciled against data recorded in the eCRF as part of the cleaning activities.

After cleaning of data, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened and the planned statistical analysis will be performed. Only authorised and well-documented updates to the study data are possible after database lock. A CD-ROM of the subject data will be sent after database lock at the investigational site and Chiesi for archiving.

12. STATISTICAL METHODS

12.1 Sample Size

The sample size has been calculated to demonstrate the non-inferiority of CHF 1535 pMDI over Symbicort® Turbohaler® in terms of change from baseline in pre-dose morning FEV_1 at Week 24 in the Chinese population.
A total of 540 completed and evaluable patients in the PP population (270 per group) will provide approximately 90% power to demonstrate the non-inferiority of CHF 1535 versus Symbicort in pre-dose morning FEV_1 at Week 24, with a non-inferiority margin of -0.07L and a one-sided significance level of 0.025, assuming no difference between treatments and a standard deviation of 250 ml. Estimating a drop-out rate of 20% and a percentage of completed patients with major protocol deviations of 10%a total of 750 patients (375 per group) will be randomised.

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.

Since non-inferiority will be tested, for the primary efficacy analysis the ITT and the PP populations will have equal importance. 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 analysis

A detailed statistical analysis plan will be described in a separate document to be completed after having finalized the protocol. The plan might be reviewed and updated as a result of the Blind Review of the data and will be finalized before breaking the blind and locking the database.

12.3.1 Descriptive Statistics

Descriptive statistics will be provided in summary tables by treatment group according to the type of variable summarised:

- Descriptive statistics for quantitative continuous variables will include n (number of observed values), arithmetic mean, standard deviation (SD), median, minimum and maximum.
- Categorical variables will be summarized by using frequency count and percent distribution. . Unless otherwise specified, missing values will not be used in the percentages calculation. The denominator for each percentage will be the number of non-missing observation within the analysis set

  For the analysis within group, 95% CI for the mean changes from baseline will be calculated.

12.3.2 Missing Data

Missing data for efficacy variables measured repeatedly over time will be handled using a likelihood-based approach. These variables will be analysed using linear mixed models for repeated measures. Under the Missing At Random (MAR) assumption, this model provides an unbiased estimate of the treatment effect that would have been observed if all patients had continued on treatment for the full study duration.

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 prior to treatment unblinding during the Blind Review Meeting. Decisions will be fully documented in the Blind Review Document.

12.3.3 Patient demographics and baseline characteristics

The following variables will be summarised by treatment group on the ITT and PP populations:

- Demographic characteristics (age, gender, race, height, weight, bmi);
- Disease specific history (COPD history, smoking habits);
- COPD medication history;
- Pre-study evaluation of COPD (pulmonary function data, pulmonary function as a percentage of predicted, etc)
- Medical and surgical history;
- Concomitant diseases;
- Previous / maintained / concomitant medications (non-COPD / COPD);

12.3.4 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 (MMRM) including treatment, visit, treatment by visit interaction, site, 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) at Week 24 will be estimated by the model. The non-inferiority of CHF 1535 relative to Symbicort will be demonstrated by a lower confidence limit of the difference between test and reference treatment above -0.07L.

12.3.5 Secondary efficacy variables

- FEV_1 change from baseline to all other visits will based on the same model used for the primary analysis.
- The change from baseline in the SGRQ total score and SGRQ domains will be analysed the same model as the one used for the FEV_1 primary analysis.
- Mean change in pre-dose morning IC, FVC and Maximal Midexpiratory Flow (MMEF) from baseline to each clinic visit will be based on the same model used for the primary analysis.
- CAT change from baseline to each clinic visit will be analysed using a similar model as for the primary efficacy variables. The change from baseline 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 similar models as the one used for the FEV_1. The comparison between treatments on the entire treatment period will be performed using the MMRM, by assigning weights to inter-visit periods proportional to their duration.
- The time to first moderate or severe COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, site, number of exacerbation in the previous year and smoking status as factor. A Kaplan-Meier plot will also be presented.
- The number of moderate and severe COPD exacerbations during the treatment period will be analysed using a negative binomial model including treatment, site, number of COPD exacerbations in the previous year and smoking status as factors, and log-time on study as an offset. Two COPD exacerbations will be considered as a single episode in the statistical analysis if the second exacerbation started less than 10 days after the end of the systemic corticosteroids and/or antibiotics intake for the previous exacerbation.

12.3.6 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.Vital signs (systolic and diastolic blood pressure, pulse rate), ECG parameters (HR, PR, QRS, QTcF) and clinical chemistry and haematology laboratory parameters will be described at each visit during treatment period using summary statistics (see section 12.3.1).
- Mean change in vital signs from baseline (Visit 2 pre-dose) to each visit after the first study drug intake will be calculated with its 95% CI by treatment group.

- Mean change from screening to Visit 6 in 12-lead ECG parameters (HR, PR, QRS, 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 screening in QTcF >30 ms and >60 ms at Visit 6 will be presented by treatment group.
- Mean changes from screening (V1) to Week 24 (V6) in clinical chemistry and hematology laboratory parameters will be calculated with their 95% CIs by treatment group.
- Shift tables from screening (V1) to Week 24 (V6), with regard to normal range (low, normal, high), will be constructed for relevant laboratory parameters

12.3.7 Interim analysis

No interim analysis is planned.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Ethics Committee/Institutional Review Board in accordance with the local Chinese requirements.
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 subjects (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 China.

Selection of the subjects 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

It is the responsibility of the Investigator to obtain written consent from each subject or from the subject's legal representative prior to any study related procedures taking place.

If the subject and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the subject.

Consent must be documented by the subject'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 subject's signed informed consent must be kept on file by the Investigator. One copy must be given to the subject

16. DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

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 subject 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 eCRFs for accuracy and completeness
- To validate the contents of the CRFs against the source documents
- 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.

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 subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject'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 subjects' 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.

25. REFERENCES

1. The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2017) (website www.goldcopd.org)
2. http://www.who.int/healthinfo/global_burden_disease/en/
3. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Zhong N. Am J Respir Crit Care Med. 2007
4. COPD in China. The Burden and Importance of Proper Management Xiaocong Fang. Chest 2010
5. Chinese Ministry Of Health. The top-ten disease-specific rates and causes of death among urban and rural residents. The Ministry of Health of the People's Republic of China Web site. http://en.nhfpc.gov.cn/
6. Mak JC, Nishikawa M, Shirasaki H, Miyayasu K, Barnes PJ. Protective effects of a glucocorticoid on downregulation of pulmonary beta-2 adrenergic receptors in vivo. J Clin Invest 1995;96:99e106.
7. Baraniuk JN, Ali M, Brody D, et al. Glucocorticosteroids induce beta2-adrenergic receptor function in human nasal mucosa. Am J Respir Crit Care Med 1997;155:704e10.
8. Eickelberg O, Roth M, Lorx R, et al. Ligand-independent activation of the glucocorticoid receptor by beta2-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. J Biol Chem 1999;274: 1005e10.
9. Johnson M. Interactions between Corticosteroids and β^2 agonists in Asthma and Chronic Obstructive Pulmonary Disease. Proceedings of the American thoracic society 2004
10. Huchon G, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet Lung function and asthma control with beclomethasone and formoterol in a single inhaler. J.Respir Med. 2009; 103(1):41-9.
11. Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, Varoli G, Papi A, Brusasco V. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med. 2010 104(12):1858-68.
12. Miller MR et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-538
13. Quanjer PH, Stanojevic S, Cole TJ et al. Multi-ethnic reference values for spirometry for the 3-95-yr a ge range: the global lung function 1012 equations. Eur Respir J 2012;40:1324-1343.
14. Standardisation of the lung function testing: the author's replies to readers' comments. Eur Respir J;36:1496
15. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009 Sep;34(3):648-5
16. EMA Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf.
17. Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005; 2:75-9.

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

Clinical Study Code No.: CCD-01535AC1-02	Version No.: 1.0
IND No.: 2016L07859	Date: 09 November 2017

A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) in patients with Chronic Obstructive Pulmonary Disease

Product: CHF 1535 100/6 µg pMDI (fixed combination of Beclometasone dipropionate 100µg plus formoterol fumarate 6µg / metered dose)

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

Approval of Clinical Study Protocol by the 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 subjects and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Code of Federal Regulations (21 CFR 50) and the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), Good Clinical Practices ICH E6 and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Coordinating Investigator's Name: _____,MD

Centre No. :_____

_____ _____

Signature Date

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

Clinical Study Code No.: CCD-01535AC1-02	Version No.: 1.0
IND No.: 2016L07859	Date: 09 November 2017

A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) in patients with Chronic Obstructive Pulmonary Disease

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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 and calibration)
- Post-bronchodilator test (when applicable)
- Laboratory reports
- ECG reports
- Questionnaires
- Date and time of medication intake
- Date and time of investigations
- 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 Turbohaler
- 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