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CLINICAL STUDY PROTOCOL

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Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD

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Chiesi Farmaceutici S.p.A.
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GENERAL INFORMATION

SPONSOR:	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
SPONSOR MEDICAL EXPERT (Clinical Research Physician)	PPD Physician PPD Readily available in case of medical questions
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MONITORING CRO	PPD
CENTRAL LABORATORY OF ANALYSIS:	NA
OTHER CENTRAL TECHNICAL LABORATORIES	PPD

VERSION HISTORY

Version	Date	Change History
1.0	24 November 2020	First version
2.0	2 February 2021	Second Version The following substantial changes have been implemented: - Inclusion criteria #6 changed due to feasibility issues; - Run-in period prolonged up to 6 weeks consequently to the change of inclusion criteria #6.
3.0	11 February 2021	Third Version: The following changes have been implemented:

		- IMP storage conditions updated accordingly to EMA requirements; - Typo corrections.
4.0	26 May 2021	Fourth Version: The following substantial changes have been implemented: - Blood chemistry updated considering the creatinine test replacing BUN analysis - RSI is now referred to Summary of Product Characteristics instead of IB - Sponsor medical expert contacts updated - Typo corrections

PROTOCOL OUTLINE

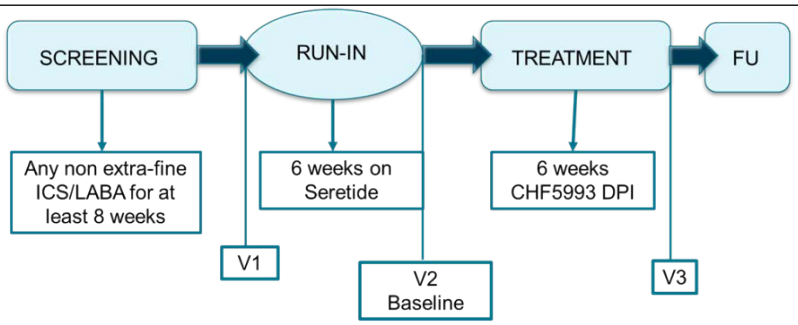
Study title	Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 DPI (fixed combination of Beclometasone Dipropionate (BDP) 100 µg, Formoterol Fumarate (FF) 6 µg, Glycopyrronium Bromide (GB) 12.5 µg)
Centre(s)	~ 8 centres in Europe
Indication	COPD
Study design	Multicentre, open-label, single arm
Study phase	Phase IIIb
Objectives	***Primary Objective*** To assess the effect of stepping-up from SERETIDE™ DISKUS™ (fluticasone propionate/salmeterol or FP/SLM 500/50 µg) DPI to extra fine CHF 5993 (BDP/FF/GB 100/6/12.5 µg) DPI on airway geometry and lung ventilation ***Secondary Objective*** To assess therapeutic aerosol particles deposition, lung function following a switch from FP/SLM 500/50 µg (SERETIDE™ DISKUS™) DPI to extra fine BDP/FF/GB 100/6/12.5 µg (CHF5993) DPI.
Treatment duration	6 weeks
Test product dose/route/regimen	CHF 5993 inhalation powder: (BDP/FF/GB) 100/6/12.5 µg Dose regimen: 2 inhalations bid Administration: via Dry Powder Inhaler (DPI)
Reference product dose/route/regimen	NA
Number of subjects	30 subjects
Study population	Adult subjects with moderate to severe COPD
Inclusion/exclusion criteria	**Inclusion Criteria:** 1. Subject's signed Informed Consent Form obtained prior to any study-related procedure; 2. Male or female ≥ 40 years of age; 3. Current smokers and/or ex-smokers of at least 10 pack-years, calculated as (number of cigarettes/day * number of years)/20. (E-cigarettes smoking cannot be used to calculate pack-year history); 4. Established diagnosis of COPD according to the 2020 GOLD Report, prior to the Screening visit (V1); 5. Post-BD $FEV_1/FVC < 0.7$ and $FEV_1 \leq 60\%$ of predicted at V1 (Note: if the criterion is not met at screening, the measure can be repeated once before run-in day 1);

6. On a stable dose of any non-extra fine ICS/LABA DPI twice daily regimen for at least 8 weeks before screening;
7. Presence of lung hyperinflation based on the increase of Total Lung Capacity (TLC) exceeding either the upper limit of normal (ULN) or an empiric 120% of predicted, and/or a plethysmographic functional residual capacity (FRC) exceeding either ULN or 120 % of predicted;
8. Symptomatic subjects with CAT score ≥ 10 at V1 *and* V2;
9. Documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months prior to V1;
10. To have a cooperative attitude and the ability to be trained and use correctly the Dry Powder Inhalers (DPI);
11. To have a cooperative attitude and the ability to perform the required outcomes measurements (e.g. spirometry manoeuvres in sitting and supine position) and the ability to understand the risks involved;
12. WOCBP fulfilling one of the following criteria:
    a. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up visit *or*
    b. WOCBP with non-fertile male partners (contraception is not required in this case)
13. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile; e.g. amenorrhea for ≥ 12 consecutive months without alternative medical cause). Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

Exclusion Criteria:

1. Pregnant or lactating woman;
2. Exacerbations defined as a sustained and acute deterioration of subject's symptoms and signs (dyspnoea, cough and/or sputum production/purulence) that are either moderate, i.e. require treatment with systemic (oral/IV/IM) corticosteroids and/or antibiotics, or severe, i.e. require hospitalization, if their associated treatment/hospitalization occurred within the 30 days before V1 (or 4 weeks in case the event was treated with just systemic corticosteroids) or if the event is recorded during the run-in period;
3. A current asthma diagnosis;
4. Respiratory disorders other than COPD: subjects with known respiratory disorders other than COPD that in the Investigator's opinion would affect efficacy and safety evaluation or place the subject at risk. This can include but is not limited to known α1-anti-trypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
5. Cardiovascular diseases: subjects who have known clinically significant cardiovascular conditions such as but not limited to:

	unstable or acute ischemic heart disease within one year prior to study entry, NYHA class IV heart failure, history of atrial fibrillation, history of sustained and non-sustained cardiac arrhythmias diagnosed within 6 months prior to study entry and not controlled with therapy according to the investigator's opinion; 6. Evidence or history of other concurrent disease such as but not limited to hyperthyroidism, diabetes mellitus or other endocrine disease; haematological disease; autoimmune disorders (e.g. rheumatoid arthritis), significant renal impairment, significant neurological disease or other disease or condition that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study; 7. Medical history or current diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would have prevented use of anticholinergic agents; 8. History of lung transplant or lung reduction surgery; 9. ECG criteria: any clinically significant abnormal 12-lead ECG that in the investigator's opinion would affect efficacy or safety evaluation or place the subjects at risk. Male subjects with a QTcF >450msec and female subjects with a QTcF > 470msec at V1 are not eligible; 10. Laboratory abnormalities: subjects with clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study; 11. Alcohol/drug abuse: subjects with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening; or having a positive drug test at screening or V2; 12. Participation in investigational trial: subjects who have received any investigational drug within the 30 days or a more appropriate time as determined by the investigator (e.g. approximately 5 half-lives of the investigational drug, whatever is longer); 13. Contra-indications to IMPs, based on investigator judgement; 14. Hypersensitivity: history of hypersensitivity to any of the study medications components or a history of other allergy that in the opinion of the investigator contraindicates the subject's participation; 15. Subjects mentally or legally incapacitated or subjects accommodated in an establishment as a result of an official or judicial order; 16. Documented COVID-19 diagnosis or its complications which have not resolved within 14 days prior to screening; 17. Positive molecular COVID-19 test within the last 72 hours before the remaining of screening activities.
Study plan	Screening visit (Visit 1) will be performed 6 weeks ± 2 days before Visit 2. Eligible subjects will undergo a 6-week run-in period with open-label FP/SLM DPI (SERETIDE™ DISKUS™). At the end of the run-in period (Visit 2), subjects will be switched to open-label treatment with BDP/FF/GB DPI (CHF5993) for 6 weeks (until Visit 3).

	 Please refer to Section 7 for additional details.
Most relevant allowed concomitant treatments	1. Inhaled salbutamol administered as rescue medication. A minimum period of 6 hours has to elapse between the use of rescue salbutamol and the Spirometry measurements; 2. Anti-histamines (oral, intranasal, ocular) and intranasal corticosteroids (INS) for the treatment of allergy or rhinoconjunctivitis symptoms; 3. Oral Xanthine derivatives (e.g. Theophylline) if taken at stable regimen for at least 1 month prior to screening and to be maintained constant during the study; 4. Nocturnal Oxygen Therapy (NOT) with HbO_2 saturation ≥ 90% at rest; 5. Ambulatory Oxygen Therapy (AOT) with HbO_2 saturation ≥ 90% at rest; 6. Non-Invasive Positive Pressure Ventilation (NIPPV) with diurnal HbO_2 saturation ≥ 90% at rest and at Investigator's discretion; 7. Short courses (≤ 10 days) of nasal corticosteroids (maximum 4 courses) are allowed during the treatment period; 8. In case of a concomitant disease any appropriate treatment not interfering with the study evaluation parameters is allowed; 9. Paracetamol (maximum 2 g per day with a maximum of 10 g per 14 days).
Most relevant forbidden concomitant treatments	1. Long Term Oxygen Therapy (LTOT) prescribed for severe arterial hypoxemia, with HbO_2 saturation ≤ 90% at rest; 2. Depot corticosteroids; 3. Oral/parenteral/IM corticosteroids; 4. Nebulized β2-agonists, anti-cholinergic and/or steroids; 5. ICS (pMDI and DPI); 6. Inhaled LABAs or fixed combination of corticosteroids and LABAs other than study treatments (e.g. salmeterol plus fluticasone or Formoterol plus budesonide); 7. Inhaled LAMAs; 8. Inhaled SABAs (other than salbutamol as rescue medication); 9. Inhaled fixed combinations of a SABA and a SAMA; 10. Inhaled SAMAs (ipratropium and oxytropium); 11. Non-cardio-selective β-blockers;

	12. Tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin re-uptake inhibitors and other drugs known to prolong the QTc interval unless already taken at the time of screening; 13. PDE-4 inhibitors (e.g. roflumilast); 14. Leukotriene modifiers; 15. Non-potassium sparing diuretics (unless administrated as a fixed dose combination with a potassium conserving drug); 16. OTC medicines, homeopathic remedies, etc., in the 7 days before the screening visit and until the end of the study.
Efficacy variables	***Primary endpoints:*** The following FRI parameters are used as primary outcome parameters: • Percentage change from baseline (pre-dose V2) to pre-dose in untrimmed specific airway volume (siVaw) upon inspiration (at Total Lung Capacity, TLC) at Visit 3 • Percentage change from baseline (pre-dose V2) to pre-dose in trimmed specific airway resistance (siRaw) upon inspiration (at TLC) at Visit 3 Data for these parameters will be recorded by lobar region and overall distal region. ***Secondary endpoints:*** Evaluation of the percentage change from baseline (V2) to post-dose at Visit 3, the percentage change from pre-dose to post-dose at Visit 2, and the percentage change from pre-dose to post-dose at Visit 3 for the primary endpoints. Values at pre-dose and post-dose for the following FRI parameters: • siVaw upon expiration (at Functional Residual Capacity, FRC) • siRaw upon expiration (at FRC) • ventilation mapping • perfusion mapping • airway wall thickness upon inspiration (at TLC) • imaged lobe and lung volumes at TLC and FRC • air trapping at FRC • low attenuation score at TLC • Percentile 15th at TLC • Regional lung deposition In addition, pre-dose spirometry, body plethysmography and CAT will be assessed at Visit 2 and Visit 3.
Safety variables	• Adverse Events (AEs) and Adverse Drug Reactions (ADRs) • Vital signs (systolic and diastolic blood pressure)
Sample size calculation	No formal sample size calculation has been performed since the nature of the study (i.e., exploratory study). 30 subjects will be enrolled in the study in order to have at least 25 completed subjects.

Statistical methods	**Efficacy variables** Primary and secondary efficacy endpoints will be presented using descriptive statistics at each timepoint. Change from baseline to pre-dose and post-dose at Visit 3 as well as change from pre-dose to post-dose at Visit 2 and Visit 3 will also be presented for primary and secondary efficacy endpoints FRI-related using descriptive statistics, while change from baseline to pre-dose at Visit 3 will be presented for other secondary endpoints. Overall distal region value for primary endpoints will be log-transformed and analysed using an ANCOVA model including the logarithm of baseline (Visit 2) at TLC, logarithm of pre-dose lobar volume at FRC on Visit 3 as covariates. The adjusted % change from baseline to pre-dose at Visit 3 will be calculated with its 95% CI. Multiple data on lobar regions for primary endpoints will be log-transformed and analysed using the same model as for the overall distal region. For the primary FRI parameters, the percentage change from baseline to post-dose at Visit 3 and the percentage change from pre-dose to post-dose at Visit 2 and Visit 3 will be analysed using the same models described for the primary efficacy endpoints. For the other FRI parameters, analysed using the same model as for the primary endpoints, with exclusion of pre-dose lobar volume at FRC on Visit 3 where appropriate. For all FRI parameters, additional analyses using different models (e.g. mixed-effect models) and subgroup analyses will be performed to get better insights in regional effects. These analyses will be pre-specified and described in the statistical analysis plan (SAP). For all other efficacy endpoints, change from baseline to pre-dose at Visit 3 will be analysed presenting 95% CI of the mean change and using a paired t-test. Relevant correlations between variables will be evaluated using Spearman's rank correlation coefficient. **Safety variables** *Adverse Events* All adverse events starting on or after the time of first study drug intake will be classified as treatment emergent adverse event (TEAE). Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. The number of subjects who experienced at least one AE, drug-related AE, non-serious AE, serious AE, serious related AE, AE leading to study discontinuation, and AE leading to death will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events) and by system organ class and preferred term (number and percentage of subjects having at least one occurrence of that event).

	All adverse events will be listed. Pre-treatment adverse event will be listed only. *Vital signs* Vital signs (systolic and diastolic blood pressure) and their changes from pre-dose to post-dose at Visit 2 and Visit 3 will be summarized using descriptive statistics and the 95% CI of the mean. A detailed statistical analysis description will be provided in the SAP.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab-HCV	Hepatitis C Virus Antibody
Ab-HIV	Human Immunodeficiency Virus Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
anti-HBc	hepatitis B core antibody
AOT	Ambulatory Oxygen Therapy
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification
ATS	American Thoracic Society
BD	Bronchodilator
BDP	Beclometasone Dipropionate
BTPS	Body Temperature Pressure Saturated
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CFD	Computational Fluid Dynamics
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DPI	Dry-Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERS	European Respiratory Society
EVC	Expiratory Vital Capacity
FDC	Fixed-Dose Combination
FET	Forced Expiratory Time
FF	Formoterol Fumarate
FEV1	Forced Expiratory Volume in one second
FPD	Fine Particle Dose
FRC	Functional Residual Capacity
FRI	Functional respiratory imaging
FSH	Follicle-Stimulating Hormone
FSFV	First Subject First Visit
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Haemoglobin
HBsAg	Hepatitis B Surface Antigen
Hct	Haematocrit
ICH	International Conference on Harmonization
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroids
IM	Intra Muscular
IMP	Investigational Medical Product
ITGV	Intrathoracic Gas Volume

ITT	Intention to Treat
IV	Intra Venous
iVlob	Lobar Volume
iVlung	Lung Volume
iVaw	Airway Volume
LABA	Long Acting Beta2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LAS	Low Attenuation Score
LSLV	Last Subject Last Visit
LTOT	Long Term Oxygen Therapy
MDCT	Multi-slice with multidetector Compound Tomography
MedDRA	Medical Dictionary for Regulatory Activities
MEF	Maximal expiratory Flow
MEF25	Maximal expiratory flow at 25% of expired vital capacity
MEF50	Maximal expiratory flow at 50% of expired vital capacity
MMAD	Mass Median Aerodynamic Diameter
NIPPV	Non-Invasive Positive Pressure Ventilation
NOT	Nocturnal Oxygen Therapy
NYHA	New York Heart Association
OTC	Over The Counter
PD15	Percentile 15th
PDE-4	phosphodiesterase-4
PEF	Peak Expiratory Flow
PLT	Platelets
pMDI	Pressurized Metered-Dose Inhaler
PP	Per-Protocol
PRN	Pro Re Nata
Raw	Airway resistance
RBC	Red Blood Cells
RV	Residual Volume
SABA	Short Acting Beta Agonist
SAD	Small Airway Disease
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
sGaw	Specific conductance
SGRQ	St. George Respiratory Questionnaire
siRav	Specific Airway Resistance
siVaw	Specific Airway Volume
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TLC	Total Lung Capacity
UA	Upper Airway
ULN	Upper Limit of Normal
VC	Vital Capacity
WBC	White Blood Cells
WOCB	Women Of Childbearing Potential
γ-GT	Gammaglutamyl transpeptidase

CONTENT

1. INTRODUCTION

1.1 Background information

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and airflow limitations that are due to large, small airways and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic air flow limitation that is characteristic of COPD is caused by a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of each vary from person to person. Chronic inflammation causes structural changes, such as narrowing of the small airways, and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil.
The goal of treatment is to slow disease progression and to control symptoms by recourse to both non-pharmacological (e.g., diet, smoking cessation, exercise, pulmonary rehabilitation, oxygen) and pharmacologic therapy.
Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations and improve exercise tolerance and health status. The mainstays of drug therapy used in stable COPD are inhaled bronchodilators (BDs) (β_2-agonists, anticholinergics and less often theophylline). As the disease state progresses and exacerbations become frequent, inhaled corticosteroids (ICS) and oral phosphodiesterase-4 (PDE-4) inhibitors can be used in combination with long-acting bronchodilators. In some subjects who remain symptomatic on ICS/LABA or continue to experience exacerbations despite treatment with an ICS/LABA or a LABA/LAMA, triple therapy with a combination of ICS with a long-acting β_2-agonist (LABA) and a long-acting muscarinic (M3) antagonist (LAMA) is recommended **[1]**.
CHF 5993 is a fixed-dose triple combination (FDC) of three known active substances: an ICS (beclometasone dipropionate [BDP]), a LABA (formoterol fumarate [FF]), and a LAMA (glycopyrronium bromide [GB]), first formulated to be delivered via a pressurised metered dose inhaler (pMDI) **[2]**.
CHF 5993 was first granted marketing authorisation in 2017 by the European Commission for the treatment of COPD (Trimbow® 100/6/12.5 µg pressurised inhalation solution). Following indication extension authorised in January 2019, the current authorised indication is "*maintenance treatment in adult subjects with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA*" **[3]**. The authorised posology is two inhalations twice a day for a total daily dose of 400 µg BDP, 24 µg FF, and 50 µg GB.
Three 12-month Phase III/IIIb studies have formed the basis of the EMA-approved indication, generating evidence of the superior efficacy of CHF 5993 over different comparators that were representative of the main therapeutic classes deployed in the COPD treatment paradigm (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019): TRILOGY, TRINITY, and TRIBUTE, **[4]**, **[5]**, **[6]**.

The NEXThaler® device is currently marketed in Europe for the administration of Chiesi's fixed dose ICS/LABA combination CHF 1535 (BDP/FF) 100 µg/6 µg dry powder inhaler (Foster® NEXThaler® and other tradenames). It contains extra fine formulations of Beclometasone Dipropionate Anhydrous (BDP) at 100 µg, and Formoterol Fumarate Dihydrate (FF) at 6 µg **[3]**.

Chiesi has developed a dry powder formulation of CHF 5993 (BDP/FF/GB) using the same NEXThaler device, and on 29 January 2021 has received a positive CHMP opinion for the same COPD indication as the pMDI.
Currently, the bulk of the clinical evidence with CHF 5993 has been generated with the pMDI formulation, and there is a need for evidence specific to the DPI formulation, especially in patients who are currently using a DPI for their COPD and who may benefit from a step-up to triple therapy using a DPI device.
In this proposed study, the aim is to explore the changes in peripheral airway volume, resistance, lobar ventilation and the regional deposition of BDP/FF/GB DPI in subjects with moderate to severe COPD by means of Functional Respiratory Imaging (FRI), which is a validated technology alternative to the gold standard technology of lung scintigraphy. FRI uses a three-dimensional (3D) airway model and computational fluid dynamics (CFD) to simulate changes within airways and predict delivery of therapeutic aerosols from extra-thoracic all the way to alveolar region by integrating the effects of device characteristics, aerosols formulations (i.e. mass median aerodynamic diameter or MMAD, fine particle dose or FPD), inhalation duration, and specific subject's airway geometry. Upper Airway (UA) CT scan is performed at V2 (pre-dose). The inter-subject small airway variability is also accounted for by this technology by using 4 low dose thorax CT scans obtained at 2 respiratory levels (inspiration and expiration), before and after a treatment **[7]**.

1.2 Study rationale

Chronic obstructive pulmonary disease is an umbrella term for conditions including emphysema, chronic bronchitis, and sometimes prominent small airway disease (SAD). The pathological effects of SAD contribute to the evolution of airway obstruction in subjects with COPD **[8]**, and quantifying the regional bronchodilation effects of therapeutic aerosols at peripheral airway levels, their central and peripheral deposition, and the changes in lung ventilation is key in subjects with COPD and small airways dysfunction.
Unfortunately, spirometry is not suitable to differentiate large from small airway obstruction. Thus, evaluating the small airways has been better achieved by means of morphologic-functional comparisons **[9]**.

Nowadays, quantitative computed tomography (CT) of the chest affords us detailed imaging that enables accurate measurement of airway thickness, diameter, volume, as well as regional (central and distal) ventilation and perfusion patterns. This technology can be highly useful when characterizing the effects of various pharmacotherapies on the lung and enables a pathophysiologic correlation with subjects' perception of respiratory symptoms **[10]**.
Probing the effects of therapeutic aerosols which deliver extra fine particles that target the small airways and the measurement of the therapeutic aerosol regional deposition in individual subject's airway geometry is now possible by implementing dedicated airway modelling and CFD techniques based on CT scan airway geometry measurements **[11]**. Briefly, the 3D reconstruction of the pharynx, trachea, and bronchial tree is obtained after the acquisition of inspiratory and expiratory chest CT scans by using a new generation low dose multi-detector scanner. It also allows measurement of many signatures of airway physiology such as extent of emphysema, airway wall thickness, lobar and segmental volumes and internal airway dimensions. The ensuing CFD analysis provides the ability to simulate flow in the individual subjects' airway geometry, and to estimate the regional deposition of therapeutic aerosols in the lung of subjects based on each aerosol particle's dimensions and subject's outflow boundary

conditions. By repeating measurements after an intervention, this approach yields a personalised assessment of changes in airway volume and CFD-based resistance.
A recently published FRI simulation study **[12]** compared the lung deposition of ICS, LABA and LAMA components from two fixed-dose triple inhaled therapies, Trimbow® (BDP/FF/GB), a pMDI delivering extra fine particles and Trelegy® Ellipta® (FluF/VI/UMEC) a DPI delivering non-extra fine particles. The results showed a higher peripheral (small airways) deposition of all three components (ICS, LABA, and LAMA) with BDP/FF/GB) pMDI than with FluF/VI/UMEC DPI, based on profiles from patients with moderate to very severe COPD. This finding is consistent with the extra fine particle engineering of BDP/FF/GB pMDI. Other studies have shown that FRI could be used to assess the acute bronchodilation effects of therapeutic FDC aerosols delivered via pMDI device in asthma **[13]** and COPD **[14]**, **[15]**, while information available with DPI is limited to date.

Therefore, this study aims to explore the effect of stepping up symptomatic subjects with COPD from non-extra fine ICS/LABA (FP/SLM) fixed-dose combination to extra fine ICS/LABA/LAMA (BDP/FF/GB) fixed-dose combination on peripheral airway bronchodilation and peripheral aerosol deposition. Both products will be delivered via a DPI device (NEXThaler® for BDP/FF/GB and (DISKUS™), for FP/SLM) where spray aerosolization is accomplished by a subject-generated flow rate which induces shear fluidization of the active pharmacological ingredient particles aggregated to carrier particles such as lactose **[16]**.
We chose to use FRI technology to prospectively explore the changes over baseline airway dimensions and resistances, lobar ventilation, and aerosol particle deposition to peripheral airways by allowing for device characteristics and subjects' specific flow boundary conditions in an open label study design **[17]**.
The rationale for the 6-week treatment duration on extra fine BDP/FF/GB DPI is supported by a prospective pharmacology study by Montuschi et al. **[18]**, showing that a short-term (4-week) treatment with extra fine beclomethasone/formoterol (100/6 µg b.i.d) in patients who previously were on an 8-week maintenance treatment with fluticasone dipropionate/salmeterol (500/50 µg b.i.d) was associated with different breath-prints compared with regular fluticasone propionate/salmeterol. This signals that a differential effect on airway inflammation may be detected in as little as a 4-week time following a switch from a fine high-dose ICS regimen to an extra fine medium-dose ICS treatment. The rationale for the total daily dose selection of FP/SLM (1000/100 µg) and BDP/FF/GB (400/24/50 µg) is based on the approved label of SERETIDE™ DISKUS™ and the proposed label for CHF5993 DPI for the treatment of COPD, respectively. This indeed means that treatment with FP/SLM would result in exposure to high-dose of ICS whereas treatment with BDP/FF/GB would deliver exposure to a medium-dose ICS. This approach avoids off-label use of these products and will help to investigate if switching from a maintenance treatment with a high-dose non-extra fine ICS-containing ICS/LABA combination (FP/SLM) to a medium-dose extra fine ICS-containing formulation (BDP/FF/GB) would result in a different bronchodilation effects at peripheral airway level.

Furthermore, the additive effect of the LAMA component to ICS/LABA has been studied in a 52-week randomized controlled trial conducted with pMDI **[4]** device, with peak effect on FEV_1 evident within 4 weeks of treatment initiation. The effect at 4 weeks was consistent also for DPI device **[19]**.

The presence of lung hyperinflation based on the increase of Total Lung Capacity (TLC) exceeding either the upper limit of normal (ULN) or an empiric 120% of predicted, and/or an increase in plethysmographic functional residual capacity (FRC) above either ULN or 120 % of predicted **[20]** are also desirable screening characteristics among the study participants, because the additive effect of a LAMA in combination with LABA in terms of improving hyperinflation is well documented in patients with COPD and lung hyperinflation **[21]**.

1.3 Risk/benefit assessment

Current risks that have been identified for the BDP/FF/GB (100/6/12.5 µg) combination are based on known pharmacology of the individual active components BDP, FF, and GB, and they can be found in the Investigation Brochure (IB). These include risks of pneumonia, oropharyngeal candidiasis, and bone disorders/fractures from ICS-containing combinations, and the risk of adverse cardiovascular effects from LAMA and LABA-containing combinations.

In this study, both FP/SLM (SERETIDE™ DISKUS™), and BDP/FF/GB (CHF5993) are both approved for the maintenance treatment of COPD.

A significant advantage of a single inhaler triple therapy in COPD is convenience for the subjects as this reduces the need for using separate inhalers that are often of a differing type and therefore need to be used differently **[22]**. This is critical since most symptomatic subjects (CAT score >10) with COPD show poor adherence with regular inhaled therapy **[23]**.

The main rationale for the development of CHF 5993 DPI is to make the extra fine single - inhaler triple therapy option (BDP/FF/GB) available for patients who prefer the use of a DPI, or who are unable to use a pMDI correctly.

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

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

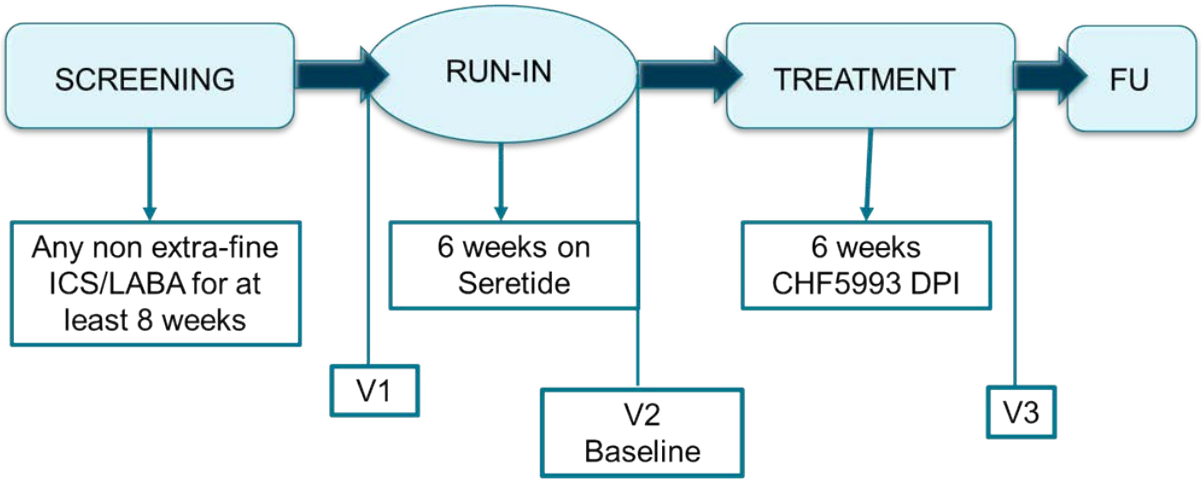
To assess the effect of stepping-up from FP/SLM DPI (SERETIDE™ DISKUS™) to extra fine BDP/FF/GB DPI (CHF5993) on airway geometry and lung ventilation.

2.2 Secondary Objective(s)

To assess therapeutic aerosol particles deposition and lung function following a switch from FP/SLM DPI (SERETIDE™ DISKUS™) to extra fine BDP/FF/GB DPI (CHF5993).

3. STUDY DESIGN

This is a multicenter, open-label, single arm study.
After the screening visit that will be performed 6 weeks ± 2 days before Visit 2, eligible subjects will undergo a 6 weeks run-in period with FP/SLM 500/50 µg (SERETIDE™ DISKUS™).
At the end of the run-in period (Visit 2), subjects will be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks (until Visit 3).



The end of the trial is defined as the last visit/last call of the last subject in the trial.

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

No formal sample size calculation has been performed since the nature of the study (i.e., exploratory study).

30 subjects will be enrolled in the study in order to have at least 25 completed subjects.

4.2 Inclusion Criteria

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

1. Subject's signed Informed Consent Form obtained prior to any study-related procedure;
2. Male or female ≥ 40 years of age;
3. Current smokers or ex-smokers of at least 10 pack-years, calculated as (number of cigarettes/day * number of years)/20. (E-cigarettes smoking cannot be used to calculate pack-year history);
4. Established diagnosis of COPD according to the 2020 GOLD Report, prior to the Screening visit (V1);
5. Post-BD $FEV_1/FVC < 0.7$ and $FEV_1 \leq 60\%$ of predicted at V1 (Note: if the criterion is not met at screening, the measure can be repeated once before run-in day 1);
6. On a stable dose any non-extra fine ICS/LABA DPI twice daily regimen for at least 8 weeks before screening;
7. Presence of lung hyperinflation based on the increase of Total Lung Capacity (TLC) exceeding either the upper limit of normal (ULN) or an empiric 120% of predicted, and/or a plethysmographic functional residual capacity (FRC) exceeding either ULN or 120 % of predicted;
8. Symptomatic subjects with CAT score ≥ 10 at V1 *and* V2;
9. Documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months prior to V1;

10. To have a cooperative attitude and the ability to be trained and use correctly the Dry Powder Inhalers (DPI);
11. To have a cooperative attitude and the ability to perform the required outcomes measurements (e.g. spirometry manoeuvres in sitting and supine position) and the ability to understand the risks involved;
12. WOCBP fulfilling one of the following criteria:
    a. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up visit *or*
    b. WOCBP with non-fertile male partners (contraception is not required in this case).
13. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile; e.g. amenorrhea for ≥12 consecutive months without alternative medical cause). Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

For the purpose of this document, a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

For the purpose of this document, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine hormone-releasing system (IUS)
- intrauterine device
- bilateral tubal occlusion/ligation
- vasectomized partner
- sexual abstinence

Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

For the purpose of this document sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject **[24]**.

4.3 Exclusion Criteria

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

1. Pregnant or lactating woman;
2. Exacerbations defined as a sustained and acute deterioration of subject's symptoms and signs (dyspnoea, cough and/or sputum production/purulence) that are either moderate, i.e. require treatment with systemic (oral/IV/IM) corticosteroids and/or antibiotics, or severe, i.e. require hospitalization, if their associated treatment/hospitalization occurred within the 30 days before V1 (or 4 weeks in case the event was treated with just systemic corticosteroids) or if the event is recorded during the run-in period;
3. A current asthma diagnosis;
4. Respiratory disorders other than COPD: subjects with known respiratory disorders other than COPD that in the Investigator's opinion would affect efficacy and safety evaluation or place the subject at risk. This can include but is not limited to known α1-anti-trypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
5. Cardiovascular diseases: subjects who have known clinically significant cardiovascular conditions such as but not limited to: unstable or acute ischemic heart disease within one year prior to study entry, NYHA class IV heart failure, history of atrial fibrillation, history of sustained and non-sustained cardiac arrhythmias diagnosed within 6 months prior to study entry and not controlled with therapy according to the investigator's opinion;
6. Evidence or history of other concurrent disease such as but not limited to hyperthyroidism, diabetes mellitus or other endocrine disease; haematological disease; autoimmune disorders (e.g. rheumatoid arthritis), significant renal impairment, significant neurological disease or other disease or condition that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study;
7. Medical history or current diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would have prevented use of anticholinergic agents;
8. History of lung transplant or lung reduction surgery;
9. ECG criteria: any clinically significant abnormal 12-lead ECG that in the investigator's opinion would affect efficacy or safety evaluation or place the subjects at risk. Male subjects with a QTcF > 450msec and female subjects with a QTcF > 470msec at V1 are not eligible;
10. Laboratory abnormalities: subjects with clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease that might, in the judgement of

the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study;

11. Alcohol/drug abuse: subjects with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening; or having a positive drug test at screening or V2;
12. Participation in investigational trial: subjects who have received any investigational drug within the 30 days or a more appropriate time as determined by the investigator (e.g. approximately 5 half-lives of the investigational drug, whatever is longer);
13. Contra-indications to IMPs, based on investigator judgement;
14. Hypersensitivity: history of hypersensitivity to any of the study medications components or a history of other allergy that in the opinion of the investigator contraindicates the subject's participation;
15. Subjects mentally or legally incapacitated or subjects accommodated in an establishment as a result of an official or judicial order;
16. Documented COVID-19 diagnosis or its complications which have not resolved within 14 days prior to screening;
17. Positive molecular COVID-19 test within the last 72 hours before the remaining of screening activities.

4.4 Subject Withdrawals

Subjects must 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 subject to continue in the study. In this case, the appropriate measures will be taken
- The subject is lost to follow-up
- The subject withdraws consent
- The subject's safety is affected by violation of inclusion or exclusion criteria or use of not-permitted concomitant medication
- The subject 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 subject
- The subjects experienced a COPD exacerbation
- Positive COVID-19 molecular test
- Pregnancy

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.

In case of early withdrawal (except if the reason is lost to follow-up or consent withdrawal and subject is not willing to perform an early termination visit), an early termination visit will be performed 7 days after the last intake of the study drug.

In case of withdrawal, the Investigator must fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal.

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

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

- Inhaled salbutamol administered as rescue medication. A minimum period of 6 hours has to elapse between the use of rescue salbutamol and the Spirometric measurements
- Anti-histamines (oral, intranasal, ocular) and intranasal corticosteroids (INS) for the treatment of allergy or rhinoconjunctivitis symptoms; Oral Xanthine derivatives (e.g. Theophylline) if taken at stable regimen for at least 1 month prior to screening and to be maintained constant during the study
- Nocturnal Oxygen Therapy (NOT) with HbO_2 saturation ≥ 90% at rest
- Ambulatory Oxygen Therapy (AOT) with HbO_2 saturation ≥ 90% at rest
- Non-Invasive Positive Pressure Ventilation (NIPPV) with diurnal HbO_2 saturation ≥ 90% at rest and at Investigator's discretion
- Short courses (≤ 10 days) of nasal corticosteroids (maximum 4 courses) are allowed during the treatment period
- In case of a concomitant disease any appropriate treatment not interfering with the study evaluation parameters is allowed
- Paracetamol (maximum 2 g per day with a maximum of 10 g per 14 days)

5.2 Non-permitted concomitant Medications

- Long Term Oxygen Therapy (LTOT) prescribed for severe arterial hypoxemia, with HbO2 saturation ≤ 90% at rest
- Depot corticosteroids
- Oral/parenteral/IM corticosteroids
- Nebulized β2-agonists, anti-cholinergic and/or steroids
- ICS (pMDI and DPI)
- Inhaled LABAs or fixed combination of corticosteroids and LABAs other than study treatments (e.g. salmeterol plus fluticasone or Formoterol plus budesonide)
- Inhaled LAMAs
- Inhaled SABAs (other than salbutamol as rescue medication)
- Inhaled fixed combinations of a SABA and a SAMA

- Inhaled SAMAs (ipratropium and oxytropium)
- Non-cardio-selective β-blockers
- Tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin re-uptake inhibitors and other drugs known to prolong the QTc interval unless already taken at the time of screening
- PDE-4 inhibitors (e.g. roflumilast)
- Leukotriene modifiers
- Non-potassium sparing diuretics (unless administrated as a fixed dose combination with a potassium conserving drug)
- OTC medicines, homeopathic remedies, etc., in the 7 days before the screening visit and until the end of the study

Washout period prior to spirometry at Screening Visit:

Oral Xanthine derivates	72 hours
Inhaled ICS/LABA	12 hours
Systemic corticosteroids (oral, IM, IV)	4 weeks
Nasal corticosteroids	24 hours

Washout prior Visit 2 and Visit 3:

Rescue salbutamol	6 hours

6. TREATMENT(S)

The study treatment CHF 5993 DPI and the run-in medication will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity.

6.1 Appearance and Content

- **CHF 5993 DPI NEXThaler® (Test product)**

  Active ingredients: Beclometasone Dipropionate (BDP) 100 µg/inhalation + Formoterol Fumarate (FF) 6 µg/inhalation + Glycopyrronium Bromide (GB) 12.5 µg/inhalation.

  Excipients: Lactose, Magnesium stearate.

  Presentation: NEXThaler® inhaler containing 120 doses.

  Appearance: White inhaler with grey cover.

- **SERETIDE™ DISKUS™ (Run-in)**

  Active ingredients: Fluticasone Propionate (FP) 500 µg/inhalation + Salmeterol Xinafoate (SLM) 50µg/inhalation.

Excipients: Lactose monohydrate.

Presentation: Each Diskus™ contains 60 doses.

Appearance: Moulded purple plastic device with a dose counter.

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

An inhaled dose of CHF 5993 DPI 100/6/12.5 µg (Total daily dose: BDP 400 µg / FF 24 µg / GB 50 µg) was selected for the current study as it corresponds to the therapeutic daily dose.

6.2.2 Dosage

- **CHF 5993 (BDP/FF/GB 100/6/12.5 µg per inhalation) DPI:**

  Two inhalations bid: 4 inhalations; total daily dose of 400/24/50 µg BDP/FF/GB.

6.2.2.1 Run-in period

SERETIDE™ DISKUS™ 500/50 µg
1 inhalation b.i.d (Total daily dose: FP 1 mg / SLM 100 µg)

6.2.2.2 Treatment period:

CHF 5993 DPI 100/6/12.5 µg
2 inhalations b.i.d (Total daily dose: BDP 400 µg / FF 24 µg / GB 50 µg)

6.2.3 Administration

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

All previous COPD medications will have to be withdrawn during the course of the study except as described in section **5**.

6.2.3.1 Run-in period (from Visit 1 to 2):

At Visit 1 (screening visit), each eligible subject will receive the medication to cover the 6-week run-in period:

- Two commercial boxes containing one Diskus™ device of FP 500 µg / SLM 50 µg.

The administration will be b.i.d:

- 1 inhalation in the morning and 1 inhalation in the evening from the same device.

Note: the first dose of run-in medication must be administered at clinic site at the end of Visit 1.

Since the run-in period lasts 6 weeks, the administration will occur using 2 commercial devices: when the first Diskus™ is empty the subject will start to use the second with the same posology.

6.2.3.2 Treatment period (from Visit 2 to Visit 3):

At Visit 2 each subject will receive 1 box with the study drug. The box contains 2 NEXThaler® dry powder inhaler of CHF 5993 100/6/12.5 µg.

The study drug will be administered twice-a-day (in the morning and in the evening):

Morning administration (preferably at 8 am).

- 2 inhalations from NEXThaler® inhaler.

Evening administration (preferably at 8 pm).

- 2 inhalations from the same NEXThaler® inhaler used in the morning.

The first administration of study drug will take place at clinic/hospital during the second visit.

Since the treatment period lasts 6 weeks, the administration will occur using 2 devices of DPI for each subject that will cover the entire period.

Each inhaler and aluminium pouches are numbered 1 or 2 respectively. This indicates the order in which the aluminium pouches and inhalers will be used.

Subject will inhale four puffs a day (two puffs in the morning and two puffs in the evening) from the inhaler numbered 1, until the dose counter shows the number 0. When the first DPI is empty the subject will start to use the inhaler numbered 2 with the same posology.

6.2.4 Subject Training

6.2.4.1 Training with In-check Dial

All subjects should be well trained in the inhalation technique with In-check Dial at screening to familiarize with inhalation technique, in the attempt to yield repeatable inhalations.
During the V1 (screening) all subjects will be trained on the proper use of Seretide Diskus and CHF 5993 NEXThaler® by using In-Check DIAL.
During the training 2 different assessment will be performed: one set for Diskus™ resistance, and the second set for NEXThaler. The obtained successful PIF value (at least 30 L/min) will be recorded in the eCRF.
By comparing the subject's results and the “optimum” results, as reported in figure 10 of Appendix 2, subjects can be trained to use their inhaler properly, continuing to use the same inspiratory flow rate while inhaling the study drug.
See Appendix 2 for instructions on how to use the In-Check Dial.

6.3 Packaging

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

6.3.1 Run-in packaging

The run-in kit will consist of:

- *Primary packaging*: 1 Diskus™ inhaler containing blisters of FP 500 µg / SLM 50 µg as powder for inhalation.
- *Secondary packaging*: 1 commercial box containing 1 Diskus™ inhaler.

6.3.2 Treatment kit packaging

The treatment kit will consist of:

- *Primary packaging*: 2 NEXThaler® inhalers
- *Secondary packaging*: 2 pouches containing 1 NEXThaler® inhaler each
- *Tertiary packaging*: 1 box containing 2 pouches containing 1 NEXThaler® inhaler each

Each inhaler and aluminium pouches are numbered **1** or **2** respectively. This indicates the order in which the aluminium pouches and inhalers will be used.

6.4 Labeling

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

6.5 Treatment allocation

All subjects will be administered with CHF 5993 DPI according to a non-randomized, open-label design.

6.6 Treatment Code

This is an open-label, non-randomized study.

6.7 Treatment compliance

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

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

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

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 box of Seretide™ Diskus™ used as study medication for the run-in period must not be stored above 30°C by Pharmacist/Investigator at the Hospital.

Once dispensed the subjects will be instructed to keep the boxes at home at ambient temperature not above 30°C.

Treatment kits:
NEXThaler® inhaler prepared with CHF 5993:

- *Pouched inhaler*: Store below 25°C;
- *Unpouched inhaler*: A maximum period of 6 weeks and stored in a dry place, below 25°C is considered suitable for the unpouched inhaler.

The use-by date shall therefore correspond to the dispensing date plus 6 weeks (42 days).

Please note that the use-by-date must not exceed the total shelf life of the product.

For pharmacist or investigator:

At clinic visits, remove the inhaler number **1** from the pouch number 1 and write the use-by-date on the appropriate section on the label of pouch number **1.**

For the subject:
The remaining pouched inhaler number **2** must be opened at home. When the pouch number 2 is opened, please write the use-by-date on the appropriate section of the pouch. The handwritten use-by date must not exceed the total shelf life of the product.

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 subject 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 Chiesi or to the designated CRO under Sponsor's responsibility or destroyed directly from the Investigator by the centre. In this case, a destruction certificate must be asked to the investigational centre and filed both at site and at Sponsor. Return and destruction will not occur until authorized by Chiesi.

6.10 Provision of additional care

At completion of subject's study participation, it is under the Investigator's responsibility to prescribe the more appropriate treatment for the subject or to restore the initial therapy or to refer to the General Practitioner.

7. STUDY PLAN

7.1 Study Schedule

	V0	Screening Visit (V1) -6weeks	Visit 2 6 weeks ±2 days	Visit 3 6 weeks ±2 days	Follow-up 2 weeks ±2 days
Informed consent form	✓				
Medical history		✓			
Incl/Excl criteria check and/or confirmation		✓	✓		
Demographic data		✓			
Vital Signs (blood pressure)[1]		✓	✓	✓	✓*
Hematology and Chemistry[2]		✓			
Serology		✓			
COVID-19 test[3]		✓	✓	✓	✓*
Physical examination[4]		✓		✓	✓*
Local safety ECG[5]		✓			
Training with In-check dial		✓			
Urinalysis		✓			
Urine pregnancy test[6]		✓	✓	✓	✓*
Urine sample for drug test[7]		✓	✓		
Body plethysmography[8]		✓	✓	✓	
CAT test		✓	✓	✓	
Spirometry[9]		✓	✓	✓	
Drug intake[10]		✓	✓	✓	
MDCT[11]			✓	✓	
Diary dispensation[12]		✓	✓		
Diary collection[13]			✓	✓	
Concomitant medication		✓	✓	✓	✓
Adverse events assessment		✓	✓	✓	✓

* A follow-up phone call will be done 14 days after Visit 3. For WOCBP the follow-up visit will occur 30 days after Visit 3

Footnotes for schedule of events:

1. **Vital signs (BP)**: duplicate measurements at screening for checking inclusion/exclusion criteria; At Visit 2, Visit 3 and at follow-up visit, if applicable. BP after at least 5 min rest in sitting or supine. Duplicate assessment with at least 5 min in between
2. The **blood samples** will be collected after overnight fasting (i.e. at least 10 h fasting, water allowed).
3. **COVID-19 test**: a molecular swab at screening and serological test at V2, V3 and Follow-up (if applicable). In case a serologic test for COVID-19 antibodies is positive, a molecular test must be performed.
4. **Physical Examination**: Full physical examination at screening visit for checking the inclusion/exclusion criteria; at Visit 3 and follow-up visit (if applicable).
5. **Safety ECG (single ECG)**: At screening visit pre-dose for checking the inclusion/exclusion criteria; ECG will be always recorded after at least 5 minutes of resting in supine position

6. **Pregnancy test**: for WOCBP a urine pregnancy test to be performed at screening, Visit 2, Visit 3 and at Follow-up visit
7. **Urine drug screen:** at screening visit for checking the inclusion/exclusion criteria and at Visit 2.
8. **Body plethysmography**: at screening, at Visit 2 and Visit 3 pre-dose
9. **Spirometry**: at screening pre- and post-bronchodilator, at Visit 2 and Visit 3 pre-dose between 7:00 and 10:00 a.m. preferably
10. **Drug intake**: Run-in medication dispensation at screening, the first dose will be taken at investigational site at Visit 1 in the morning. Study drug dispensation at Visit 2. Morning dose of Visit 2 and Visit 3 will be taken at the investigational site.
11. **MDCT**: multi-slice with multidetector computed tomography (inspiratory at TLC and expiratory at FRC) will be performed pre-dose and within 60– 120 min post-dose at Visit 2 and Visit 3 as detailed in section **7.2.1**. At Visit 2, Upper airway will be also scanned at TLC, pre-dose.
12. **Diary**: the paper subject diary will be dispensed at screening for the run-in medication and at Visit 2 for the IMP. Information on concomitant medications and adverse events occurrences and study drug intake will be recorded. Diaries will be checked by the Investigator at Visit 2 and Visit 3.

7.1.1 Visit 0

During this visit the informed consent form will be obtained and a deep explanation on future screening visit procedures will be performed (such as medication restrictions and fasting conditions).

7.1.2 Visit 1 (screening)

For logistical reason, it is also possible that the screening procedures are spread over different days. The actual date of each assessment will be recorded in the eCRF.
The following procedures will take place at the clinical site:

<u>The following procedures will take place before run-in medication dispensation:</u>

- Pre-dose duplicate vital signs (systolic and diastolic blood pressure) will be evaluated after 5 min in supine position (see section **7.2.2**);
- Pre-dose full physical examination;
- Pre-dose safety ECG (12-lead electrocardiogram) will be recorded after 5 min in supine position;
- Pre-dose training with In-check dial;
- Pre-dose urine pregnancy test on women of childbearing potential;
- Pre-dose urine drug test (see section **7.2.3**);
- Pre-dose urinalysis (see section **7.2.3**);
- Pre-dose blood sampling for hematology and chemistry, and serology (see section 7.2.3);
- Molecular COVID test;
- Pre-dose body plethysmography (panting followed by acceptable and repeatable expiratory vital capacity [EVC]) (see section **7.2.4**);
- Pre-dose COPD Assessment Test (CAT) (see section **7.2.5**);

- Pre- and post-bronchodilator spirometry (3 repeatable and acceptable FVC expiratory-inspiratory maneuvers per the 2019 Standardization of Spirometry Update, An Official ATS and ERS Technical Statement [25] (see section 7.2.6);
- Check of Inclusion/Exclusion Criteria;
- Demographic Data;
- Medical History;
- Run-in medication dispensation. The first morning dose will be taken at the investigational site at Visit 1 (in case spirometry needs to be reperformed to assess inclusion criterion 5, the dispensation and first intake of run-in medication will occur in that occasion);
- Run-in paper Diary delivery to subject and instruction (see section 7.2.7);
- Concomitant medication;
- AEs since the signature of the informed consent will be checked and recorded.

In case of any clinically relevant abnormality revealed during the physical examination or screening procedures, it will be recorded in the subject's medical history, unless its start date is after the informed consent signature date and it is not due to a pre-existing condition. In this case, it will be recorded as an adverse event.
A new appointment will be planned in 6 weeks: subject will be asked to come same time in the morning. Instruction to be given to the subject: bring back run in medication, diary card, and respect the washout prior Visit 2.

7.1.3 Visit 2

For logistical reason, it is also possible that the Visit 2 procedures are spread over different days within the allowed time window.
V2 should occur no more than 44 days after the last assessment for screening visit is completed. The washout period from not allowed concomitant medication should be checked before starting the Visit (Refer to section 5.2). If the washout has not been respected, the Visit can be rescheduled once.

The following procedures will take place at the clinical site before study drug administration:

- Pre-dose Duplicate vital signs (systolic and diastolic blood pressure) will be evaluated after 5 min in supine position;
- Pre-dose urine pregnancy test on women of childbearing potential;
- Pre-dose urine drug test;
- Pre-dose serological COVID test;
- Pre-dose body plethysmography;
- Pre-dose spirometry;
- Return diary check prior to dosing to assess the compliance during run-in and delivery of new diary;
- Check of Inclusion/Exclusion Criteria;
- Pre-dose CAT test;
- Study drug dispensation and morning dose will be taken at the investigational site;
- Multi-slice with multidetector computed tomography (MDCT) (see section 7.2.1);
- AEs and concomitant medications check and recording, if any.

A new appointment will be plan in 6 weeks: subject will be asked to come same time in the morning. Instruction to be given to the subject: bring back medication, diary card, and respect the washout prior Visit 3.

7.1.4 Visit 3

For logistical reason, it is also possible that the Visit 3 procedures are spread over different days (2 days) within the allowed time window.

- Pre-dose duplicate vital signs (systolic and diastolic blood pressure) will be evaluated after 5 min in supine position;
- Pre-dose full physical examination;
- Pre-dose urine pregnancy test on women of childbearing potential;
- Pre-dose Serological COVID test;
- Pre-dose body plethysmography;
- Pre-dose spirometry;
- Pre-dose CAT test;
- Return diary check prior to dosing to assess the compliance during treatment period;
- Study drug morning dose will be taken at the investigational site;
- Return of the dispensed inhalers;
- Multi-slice with multidetector computed tomography (MDCT);
- AEs and concomitant medications check and recording, if any.

7.1.5 Follow-up visit

A follow-up phone call will be done 14 days after Visit 3.
For WOCBP the follow-up visit will occur 30 days after Visit 3; the following procedures will be performed:

- Duplicate vital sign;
- Full physical examination;
- A urine sample collection for pregnancy test;
- Serological COVID test.

For both follow-ups, AEs and related concomitant medications check and recording, if any, including the status of any unresolved AE/SAE.

7.1.6 Early termination visit

During the Early termination visit the following procedures will take place:

- Duplicate vital sign;
- Full physical examination;
- CAT test;
- Spirometry.

7.2 Investigations

The assessment should be performed following the order listed in the table below:

Pre-dose	Post-dose

• Vital signs • Body-plethysmography • Spirometry • CAT • MDCT	• MDCT

The exact time of each activity will be recorded in the eCRF.
For both V2 and V3 assessments can be split over more than 1 day, however, Spirometry, Body plethysmography and MDCT must be performed on the same day.

7.2.1 Multidetector Computed Tomography (MDCT) and FRI endpoints

Scan of the thorax multi-slice with multidetector computed tomography (inspiratory at TLC and expiratory at FRC) will be performed pre-dose and within 60– 120 min post-dose at Visit 2 and Visit 3 At Visit 2, Upper airway will be also scanned at TLC, pre-dose.
Functional Respiratory Imaging (FRI) is a non-invasive quantification imaging methodology that provides detailed measurement, visualization, and evaluation of the lungs and airways, both regionally and in totality. FRI uses low-dose, high-resolution volumetric computerized tomography (CT) scans and quantitative imaging technology based on computational fluid dynamics (CFD) to model airflow and measure structural and functional characteristics of the respiratory system. FRI provides quantifiable measures of drug performance, contributing to clinical proof of concept and dose selection. A relative explanation of the FRI parameters that will be used as endpoints in this study is provided below.

The visible airway generations that comprise the lobes can vary over time. The airway related FRI measurements can thus be performed in two ways: 1) for each segment use all the generations visible at the particular study visit scan (“untrimmed”), or 2) for each segment use only generations of airways that are visible in the baseline scan and in the post scan (“trimmed”). For the two primary endpoints, the following approach will be used:

- siVaw will be “untrimmed”
- siRaw will be “trimmed”

7.2.1.1 Specific Airway Volume (siVaw)

The airways can be segmented up to the point where no distinction can be made between the intraluminal and alveolar air. This is where the airway diameter is around 1-2 mm, typically around the 7^{th}-10^{th} bifurcation, depending mainly on the disease state of the individual subject. From the resulting model, the central and distal airway volumes (iVaw) can be assessed at individual airways or in different regions. The distal airway volume is defined as the segmented airway volume starting from the 3^{rd} bifurcation.
The specific Airway Volume as an FRI parameter is derived from the Airway Volume (iVaw). The specificity is calculated by dividing the airway volume with the lung volume. This way the airway volumes are normalized across subjects and become specific.

7.2.1.2 Specific Airway Resistance (siRaw)

The airway resistance (iRaw) is determined using Computational Fluid Dynamics (CFD). During the CFD calculations, the outflow to each lobe is adjusted iteratively for each subject to match the internal flow rate distributions obtained from the segmentation of the CT scans. As a result, iRaw accounts for the subject specific internal airflow distribution which might be

greatly altered by the lung disease. Hence, the airflow distribution in the CFD calculations reflects the airflow distribution as derived from the expansion of lung lobes from FRC to TLC. The iRaw is defined as the total pressure drop over an airway, divided by the flow rate through that airway.
The specific Airway Resistance as an FRI parameter is derived from the Airway Resistance (iRaw). The specificity is calculated by multiplying the airway resistances with the lung resistances. This way the airway resistances are normalized across subjects and become specific. Generally, when lung volumes (and thus airway volumes) increase, resistances decrease.

7.2.1.3 Ventilation mapping

CT-based surrogates of regional ventilation, often referred to as 'CT-ventilation maps', are derived from pulmonary CT images acquired at different inflation levels, without the use of exogenous contrast, by assuming that regional changes in lung volume relate to regional ventilation.

7.2.1.4 Perfusion mapping

The blood vessel proportion can be measured using two thresholds, ultimately resulting in three categories: vessels less than 5mm^2 in cross sectional area (BV5), vessels bigger than 5mm^2 and less than 10mm^2 in cross sectional area (BV5_10), and finally vessels bigger than 10mm^2 in cross sectional area (BV10). These volumes are the combined volumes of the pulmonary arteries and veins, and because of variations in blood vessel volume based on overall body size, these measures are often expressed using the ratio of either BV5, BV5_10 or BV10 to TBV. This way each of the measures expresses the fraction of blood vessel caliber present in each category. Lower values in small vasculature (BV5 and BV5_10) suggest CT imaging evidence of vascular pruning, i.e. a smaller proportion of the blood vessel volume comprised of small peripheral pulmonary blood vessels. The BVX data is expressed as % of all regional blood vessel volume. BVXvol is the absolute volume, expressed in mL.

7.2.1.5 Airway wall thickness

This parameter consists of all visible tissue in the CT scan that encompasses the airway wall. The airway wall can typically be described to the same generation level as the volume description of the airway lumen. This is where the airway diameter is around 1-2 mm. This parameter will be described in multiple versions: the wall area as a percentage of the sum of wall area and airway area (WA%), as the square root of the wall area for a theoretical airway with an internal perimeter of 10 mm (Pi10), and as the wall area adjusted for BSA (Mosteller's formula).

7.2.1.6 Lung and lobar Volume (iVlung and iVlobe)

Lobar Volume is an FRI-based ventilation parameter obtained by identifying and grouping voxels that represent the air in the lungs. The lung volume (L) can be determined from the scans at both FRC and TLC. During segmentation, identifying the fissure planes on the CT images and using these surfaces as cutting objects can separate lung lobes. This means that not only the total lung volume is determined, but also the volume of each lobe individually.

7.2.1.7 Air trapping

Air trapping, also called gas trapping, is an abnormal retention of air in the lungs. FRI based air trapping is defined as all the intrapulmonary voxels with Hounsfield Units between -1024 and -850 using the expiratory scans at Functional Residual Capacity (FRC).

7.2.1.8 Low attenuation score (LAS)

The low attenuation areas on CT scans have been reported to represent emphysematous changes of the lung. Emphysema is a long-term, progressive disease of the lungs that primarily causes shortness of breath due to over-inflation of the alveoli. FRI-based emphysema calculations are defined as all the intrapulmonary voxels with Hounsfield Units between -1024 and -950 using the inspiratory scans at TLC.

7.2.1.9 Percentile 15th (PD15)

The 15th percentile density (PD15) of the cumulative CT value distribution in HU indicates the HU value below which the lower 15% of all voxels are distributed. The percentile density (PD) can also be used to express emphysema.

7.2.1.10 Regional lung deposition

Regional aerosol deposition is determined by simulating the flow in the subject specific geometries using subject specific boundary conditions by means of CFD. While solving the flow equations, simultaneously particles are released in the flow and the force mass balance of the individual particles is determined through additional discrete phase computations. When a calculated particle trajectory intersects with the airway wall, the particle is trapped in that location. This allows for the determination of the regional concentration of inhaled aerosols and consequently the effective lung dose of inhaled medication as depicted in the figure below.

7.2.2 Vital signs: Blood pressure

Systolic and diastolic blood pressure will be measured after at least 5 min rest in sitting or supine position (for the same subject, the position must be consistent throughout the whole study). Duplicate BP measurements will be performed within a time window of 2 to 5 minutes between each measurement. Vital signs may be repeated at the discretion of the investigator for the purposes of safety or to confirm eligibility. If the investigator performed more assessments than expected a comment in the eCRF must be included.
In eCRF the single measurements and the average of duplicate blood pressure measurements will be recorded.

7.2.3 Blood and urine sample collection for safety laboratory test

The blood samples will be collected after overnight fasting (i.e. at least 10 h fasting, water allowed).
If the subjects attend the screening visit not in fasting conditions, laboratory test will be performed on another day within the allowed time window.
The following blood samples will be collected during the study by venipuncture:

- 5-mL sample at screening for clinical chemistry
- 2-mL sample at screening for clinical haematology

- 2-mL sample at screening for serology

Clinical hematology and chemistry:
The following parameters will be assessed in blood by a local laboratory:

- Routine haematology: red blood cells count (RBC), white blood cells count (WBC) and differential count (absolute value and %), total haemoglobin (Hb), haematocrit (Hct), platelets count (PLT).
- Blood Chemistry: creatinine, BUN (If BUN cannot be assessed it is acceptable that carbamide will be assessed instead), glucose (fasting), phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gammaglutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, total cholesterol, triglycerides and sodium, potassium, calcium.

FSH (if applicable): serum FSH levels may be indicated, as per investigator's request, to confirm the post-menopausal status in female participants

Clinical serology:
The following parameters will be assessed in blood by the local laboratory:

- Human Immunodeficiency Virus Antibody (Ab-HIV1 and 2), Hepatitis B Surface Antigen (HBsAg), hepatitis B core antibody (anti-HBc) and Hepatitis C Virus Antibody (Ab-HCV)
- COVID-19 (IgG, IgM)

Mid-stream urine sample of about 10 mL will be collected at screening for urinalysis, for drug test and pregnancy test (if applicable); at pre-dose on Visit 2 for drug test and pregnancy test (in women of childbearing potential) and at each subsequent Visit for pregnancy test in women of childbearing potential. Urine samples will be done by a local laboratory.

Urinalysis:
The following parameters will be assessed in urine by the local laboratory:

- pH, specific gravity, proteins, glucose, ketones, bilirubin, nitrites and microscopic examination of the sediment (casts, erythrocytes, leucocytes).

Urine drug screen:

- cannabinoids, opiates, cocaine, benzodiazepines, amphetamines, morphine, barbiturates and urine cotinine test.

Blood collection and sample preparation will be performed according to procedures provided by the local laboratory which will be in charge of transmitting the results to the Investigator for entry in the eCRF. The normal ranges will be provided by the local laboratory and included into e CRF.

7.2.4 Body plethysmography

Body plethysmography is a well-established technique of lung function determination, providing measures of the lung that reflect a multitude of functional and structural aspects.
It is an alternative method of measuring lung volume that takes advantage of the principle of Boyle's law, which states that the volume of gas at a constant temperature varies inversely with the pressure applied to it. The primary advantage of body plethysmography is that it can measure the total volume of air in the chest, including gas trapped in bullae. Another advantage

is that this test can be performed quickly. A subject is placed in a sitting position in a closed body box with a known volume.
Body plethysmography allows to determinate functional residual capacity (FRC), lung residual volume (RV) and total lung capacity (TLC), airway resistance (Raw) and intrathoracic gas volume (ITGV).
These measures are recorded during breathing at rest and not by forced maneuvers. All procedures must be in accordance with the international recommendations European Respiratory Society and American Thoracic Society (ERS/ATS).

Calibration of the body plethysmograph will be performed at each visit and the reports will be kept with the source study document. A series of 3 technically satisfactory panting manoeuvres will be recorded. Body plethysmography should meet the ATS/ERS guidelines criteria.
Pre-dose body plethysmography will be performed after the vital signs assessment and before the spirometry.

The following parameters should be obtained from plethysmography [percent predicted values for FRC, RV and TLC will be derived from the ECSC 1993 reference equations [26]

- Airway resistance (Raw), as absolute value
- Specific conductance (sGaw), as absolute value
- Functional Residual Capacity (FRC), as absolute value and percentage of predicted
- Residual Volume (RV), as absolute value and percentage of predicted
- Slow Expiratory Vital Capacity (EVC) maneuver will be performed at the end of panting, as absolute value and percentage of predicted, and measure the linked Inspiratory Capacity
- Inspiratory capacity (IC), as absolute value
- Total Lung Capacity (TLC), as absolute value and percentage of predicted

7.2.5 COPD Assessment Test (CAT)

The COPD Assessment Test is an 8-items unidimensional questionnaire to measure health status impairment in COPD subjects. It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0-40, correlates very closely with the St. George's Respiratory Questionnaire (SGRQ), and has been extensively documented.
It provides measure of symptomatic impact of COPD but does not categorize subjects into symptom severity groups for the purpose of treatment.
At Visit 1, Visit 2, and Visit 3, subjects will complete the CAT test and data collected by the Investigator on paper will be recorded in the eCRF. Only symptomatic subjects with a CAT score ≥10 are eligible.

7.2.6 Spirometry

Pulmonary function tests will be carried out under medical supervision in either a clinic or hospital and will be recorded using a computer-operated spirometer.
Throughout the study, the clinic visits and the lung function measurements will start in the morning approximately between 7:00 and 10:00 a.m., preferably at the same time of the day for each subject, who should have only a light breakfast, refrain from smoking for four hours before the test and respect medication washout times.

Calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to spirometry maneuvers and the reports must be kept at the clinical site and be accessible to the CRA and the Sponsor. Personnel using the spirometer should be adequately trained to follow the commonly accepted procedures. The same make and model of spirometer will be used for all measurements and adjusted for the ATS/ERS standards. The predicted values will be calculated according to the Global Lung Function Initiative, ERS Task Force Lung Function Reference Values.

For the Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC) and Maximal Expiratory Flow (MEF) the highest value (L) from three technically satisfactory attempts (1 minute apart) will be recorded (not necessarily coming from the same curve). In order to be considered as technically satisfactory attempts, measurements should be free from cough and false-start. The two largest FEV_1 measurements must be within 150 mL of each other (or 100 mL, if the FEV_1 value is $\leq$ 1L). If the difference is larger, additional tests will be made until the above criterion is met (up to 8 measurements). If at the end, the tests are not within 150 mL, the highest value of FEV_1 and FVC will be recorded and used for eligibility/continuation criteria. Please refer to the complete summary of acceptability, usability, and repeatability criteria for FEV1 and FVC in the 2019 Standardization of Spirometry Update.

If subjects show a progressive reduction in FEV_1 with each subsequent blow, with cumulative drop above 20% of starting value, the test procedure may be terminated in the interest of the subject safety. Subjects should be at rest before each lung function test. All measurements are to be made with the subjects in sitting position. Values will be corrected for pressure saturation (BTPS) conditions.

At screening, the measurement of post-bronchodilator lung function test will be done starting from 20 to 30 minutes after inhalation of salbutamol pMDI 400 µg.
Lung function tests can be repeated if the investigator deems it necessary to assess safety or to confirm eligibility. If the investigator performed more assessments than expected a comment in the eCRF should be included.
Pre-dose spirometry will be performed after the body plethysmography assessment and before the MDCT and CAT test.

The following parameters should be obtained from spirometry:

- Forced Expiratory Volume in one second (FEV_1);
- Forced Vital Capacity (FVC);
- Peak Expiratory Flow (PEF);
- Maximal expiratory flow at 50% of expired vital capacity (MEF50);
- Maximal expiratory flow at 25% of expired vital capacity (MEF25).

In case the restriction is not respected at screening, the visit should be rescheduled once to be performed within the allowed time window, as applicable.

7.2.7 Diary Card

At screening and at Visit 2, a paper diary card will be handed out to the subject. Return will occur at Visit 2 for run-in diary card and Visit 3 for treatment period diary card.

The subject should follow instructions for recording the study medication intake, concomitant treatments and adverse events. The information from the subject diary card will be entered into the clinical database by the Investigators. Investigator will check the diary for completeness before the subject leaves the centre.

The following information will be recorded on the Diary:

- Study drug intake
- Concomitant treatments
- Adverse events

8. EFFICACY ASSESSMENTS

Primary endpoints:

The following FRI parameters are used as primary outcome parameters:

- Percentage change from baseline (pre-dose V2) to pre-dose in untrimmed specific airway volume (siVaw) upon inspiration (at TLC) at Visit 3
- Percentage change from baseline (pre-dose V2) to pre-dose in trimmed specific airway resistance (siRaw) upon inspiration (at TLC) at Visit 3

Data for these parameters will be recorded by lobar region and overall distal region.

Secondary endpoints:

Evaluation of the percentage change from baseline (V2) to post-dose at Visit 3, the percentage change from pre-dose to post-dose at Visit 2, and the percentage change from pre-dose to post-dose at Visit 3 in primary endpoints.

Values at pre-dose and post-dose for the following FRI parameters:

- siVaw upon expiration (at FRC)
- siRaw upon expiration (at FRC)
- ventilation mapping
- perfusion mapping
- airway wall thickness upon inspiration (at TLC)
- imaged lobe and lung volumes at TLC and FRC
- air trapping
- low attenuation score at TLC
- Percentile 15^{th} at TLC
- Regional lung deposition

In addition, pre-dose spirometry, body plethysmography and CAT will be assessed at Visit 2 and Visit 3.

9. SAFETY ASSESSMENTS

The drug safety will be evaluated in the study as follows:

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure)

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a subject 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 unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **Adverse Drug Reaction** is an "untoward and unintended response to an investigational medicinal product related to any dose administered".
All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.
The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

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

- **Results in death**

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

- **Is life-threatening**

Life-threatening refers to an event in which the 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 hospitalisation**

Hospitalization refers to a situation whereby an AE is associated with unplanned formal overnight 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 an AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other

seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

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

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the 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 (included in the Summary of Product Characteristics for TRIMBOW® DPI), 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 reference safety information would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.
In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

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

- **Mild:** The event causes a minor discomfort or does not interfere with daily activity of the subject or does not lead to either modification of test treatment dosage or 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.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:
- Time relationship between study drug intake and event's onset;
- Dechallenge (did the event abate after stopping drug?);
- Rechallenge (did the event reappear after reintroduction?);
- Medical history;
- Study treatment(s);
- Mechanism of action of the study drug;
- Class effects;
- Other treatments-concomitant or previous;
- Withdrawal of study treatment(s);
- Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study medication (or concomitant);
- Protocol related process.

10.5 Action taken with the study drug due to an AE

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

10.6 Other actions taken

- Specific therapy/Medication
- Concomitant Procedure

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/other time points 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 PPD Safety Contact listed below within 24 hours of awareness. The information must be sent by providing the completed Serious Adverse Event form. At a later date, the PPD Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager and the Clinical Research Physician.

Name and Title	Telephone no.	Fax no.	E-mail
PPD Safety Contact		+32 15 299 394	be.life.saefax-ma@sgs.com
Chiesi Safety Contact PPD	PPD	+39 05211885003	PPD ct_cds@chiesi.com

Global Pharmacovigilance Operations Specialist			

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent/other time points 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

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported in compliance with the timelines and standards for reporting SUSARs set out in the EU Directive 2001/20/EC [Directive 2001/20/EC of the European parliament and of the council of 4/April/2001] and linked guidance [European Commission, Enterprise and Industry Directorate General: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use, latest version]. The EMA and the concerned national health authority (if applicable) will be informed through Eudravigilance, or according to local requirements (as applicable) while the Ethics Committees and the investigators by CIOMS I form or by periodic line- listings produced by Chiesi Global Pharmacovigilance.
With regard to regulations in force for Pharmacovigilance, the Investigator must fulfill his/her obligation according to the law in force in his country.

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.
- All documents provided by the Investigator or site staff to the PPD Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and till the age of one year of the child to detect any congenital anomaly or birth defect. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail 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 CRO 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, but the subject participating to the study should not be discontinued from the study.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.
- Any Adverse Drug Reaction (ADR) occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority according to the applicable laws. The Investigator is also recommended to report all adverse drug reactions to the relevant Marketing Authorisation Holders of the involved medicinal products. Additionally, also conditions of use outside the marketing authorisation of the medicinal products (i.e. off-label, overdose, misuse, abuse and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy should be reported.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her representative designee.
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.
Subject diary and questionnaire will be collected on paper and data will be entered in the database by the sites.
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 (Functional Respiratory Imaging) will be processed centrally, sent to PPD and reconciled with the corresponding information recorded in the CRF.
Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.
After the completion of data collection and cleaning, 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, and the planned statistical analysis will be performed.
If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by Chiesi.
At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The investigators will receive copies of the subject data for retention at the investigational sites

12. STATISTICAL METHODS

12.1 Sample Size

No formal sample size calculation has been performed since the nature of the study (i.e., exploratory study).
30 subjects will be enrolled in the study in order to have at least 25 completed subjects.

12.2 Populations for analysis

- **Safety population:** all randomized subjects who receive at least one dose of study treatment.
- **Per-protocol population (PP):** all subjects from the safety population, except subjects without any valid evaluation of FRI or with major protocol deviations (i.e., wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

The Safety population will be used in the analysis of safety variables, while all the other variables will be analysed in the PP population.

12.3 Statistical analysis

A detailed statistical analysis plan (SAP) will be described in a separate document. The plan might be reviewed and updated as a result of the review of the data and will be finalized before locking the database.

12.4 Descriptive Statistics

Descriptive statistics will be provided in summary tables according to the type of variable summarised.
General descriptive statistics for numeric variables will include the n (number of observed values), the mean, the standard deviation, the median, the minimum, and the maximum values. For categorical variables, the number and percent of subjects with a specific level of the variable will be presented.

12.5 Missing data

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 during the review of the data. Decisions will be fully documented in the Data Review Report.

12.6 Subject demographics and baseline characteristics

The following variables will be summarised for the PP population (and for the Safety population, if relevant): demographic characteristics, medical history and concomitant diseases, previous and concomitant medications, efficacy and safety parameters at screening and/or at baseline.

12.7 Efficacy variables

Primary and secondary efficacy endpoints will be presented using descriptive statistics at each timepoint. Change from baseline to pre-dose and post-dose at Visit 3 as well as change from

pre-dose to post-dose at Visit 2 and Visit 3 will also presented for primary and other secondary efficacy endpoints FRI-related using descriptive statistics, while change from baseline to pre-dose at Visit 3 will be presented for other secondary endpoints.

Overall distal region value for primary endpoints will be log-transformed and analysed using an ANCOVA model including the logarithm of baseline (Visit 2) at TLC and logarithm of pre-dose lobar volume at FRC on Visit 3 as covariates. The adjusted % change from baseline to pre-dose at Visit 3 will be calculated with its 95% CI.

Multiple data on lobar regions for primary endpoints will be log-transformed and analysed using the same model as for the overall distal region.
For the primary FRI variables, the percentage change from baseline to post-dose at Visit 3 and the percentage change from pre-dose to post-dose at Visit 2 and Visit 3 will be analysed using the same models described for the primary efficacy endpoints.

For the other FRI parameters, analysed using the same model as for the primary endpoints, with exclusion of pre-dose lobar volume at FRC on Visit 3 where appropriate.

For all FRI parameters, additional analyses using different models (e.g. mixed-effect models) and subgroup analyses will be performed to get better insights in regional effects. These analyses will be pre-specified and described in the statistical analysis plan.

For all other efficacy endpoints, change from baseline to pre-dose at Visit 3 will be analysed presenting 95% CI of the mean change and using a paired t-test.

Relevant correlations between variables will be evaluated using Spearman's rank correlation coefficient.

12.8 Safety variables

Adverse Events
All adverse events starting on or after the time of first study drug intake will be classified as treatment emergent adverse even (TEAE). Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event.
The number of subjects who experienced at least one AE, drug-related AE, non-serious AE, serious AE, serious related AE, AE leading to study discontinuation, and AE leading to death will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events) and by system organ class and preferred term (number and percentage of subjects having at least one occurrence of that event).
All adverse events will be listed. Pre-treatment adverse event will be listed only.

Vital signs
Vital signs (systolic and diastolic blood pressure) and their changes from pre-dose to post-dose at Visit 2 and Visit 3 will be summarised using descriptive statistics and the 95% CI of the mean.

12.9 Interim analysis

Interim analysis not planned.

13. ETHICS COMMITTEE APPROVAL

The study proposal will be submitted to the Ethics Committee/ in accordance with the requirements of each country.
The EC 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 will be provided to the Sponsor.
The Investigator should provide written reports to the EC 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 each participating country.
Selection of the subjects will not start before the approval of the Ethics Committee has been obtained and the study notified to Health Authorities (or authorized by).

15. INFORMED CONSENT

Informed consent must be written in a language understandable to the subjects. 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, by using the latest EC approved version of the document.
Adequate time shall be given to the subject or his or her legal representative to enquiry the PI about any clarification needed and to consider his or her decision to participate to the trial.
If the 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. SOURCE DOCUMENTS/DATA

16.1 Recording of source data

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

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

16.2 Direct access to source document/data

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

17. STUDY MONITORING

Monitoring will be performed by PPD who 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, 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 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 and the protocol.

19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.
Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.
The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.
The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, and addresses and 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 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/, to the Competent Authority of the EU Member State.

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 and, if they fall under the Chiesi commitments on Clinical Trial Transparency, to make them available on www.chiesi.com website.
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 according to the relevant regulatory requirements.

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

Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD

Product: CHF 5993 BDP 100 µg / FF 6 µg / GB 12,5 µg

Pharmaceutical Form: Dry Powder Inhaler

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 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 Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices 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

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

Open label, prospective study to evaluate the effect of step-up from non-extra fine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD

Product: CHF 5993 BDP 100 µg / FF 6 µg / GB 12,5 µg

Pharmaceutical Form: Dry Powder Inhaler

Approval of Clinical Study Protocol by the Principal Investigator:

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

I understand that this trial will not be initiated without Ethics 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 Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Principal Investigator's Name: _____ , MD

Centre No.: _____

_____ _____
Signature Date

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

APPENDIX 2 - INSTRUCTION FOR USE OF IN-CHECK DIAL

1. Reset the In-Check® Dial before each test

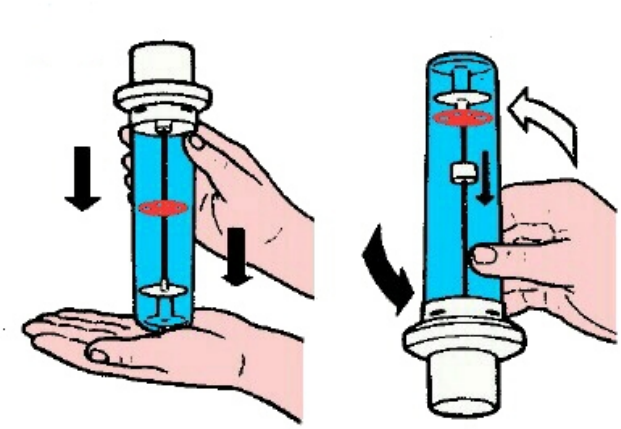

Figure 1

2. Align the scale with the desired inhaler device - an audible "click" should be heard.

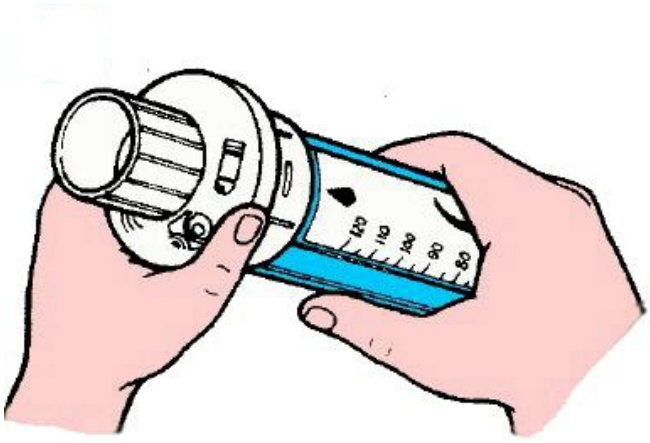

Figure 2

To correctly align the scale, the black arrow shown in the body of the In-check Dial (see red circle line in Figure 3) must be put in correspondence of the “Med Low” and then of the “Med High” symbols (see Figure 4).

Figure 3

It is very important to check that, after alignment, the hole is exactly in the right position as shown in Figure 4 (Diskus Medium-Low resistance and NEXThaler Medium-high resistance**).**

Figure 4

3. After alignment, take one mouthpiece, as shown in Figure 5.

Figure 5

4. Attach the mouthpiece to the In-Check Dial, as shown in Figure 6.

Figure 6

5. Ask the subject to exhale slowly and fully.

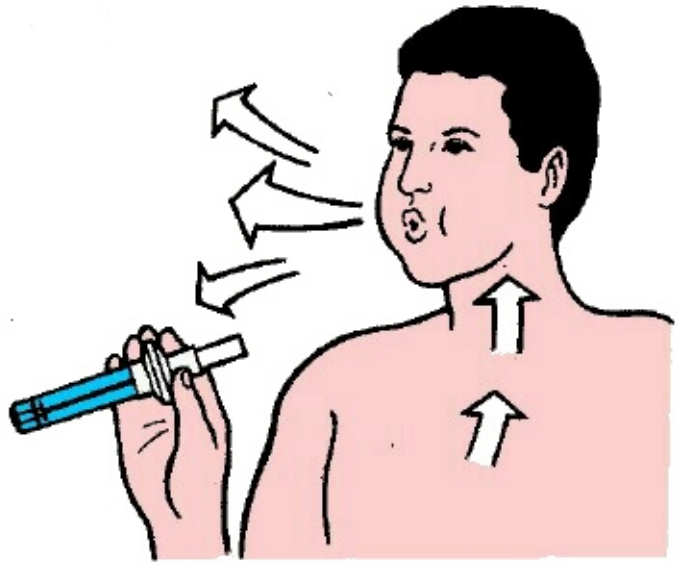

Figure 7

6. Seal lips around the mouthpiece and ask subjects to inhale as quickly as they can.

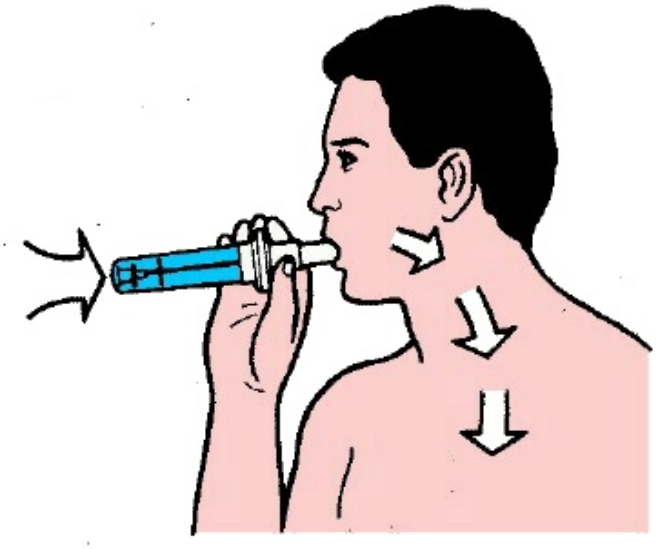

Figure 8

7. Record the inspiratory flow from the position of the red cursor against the scale. Reset, and repeat two more times per each test.

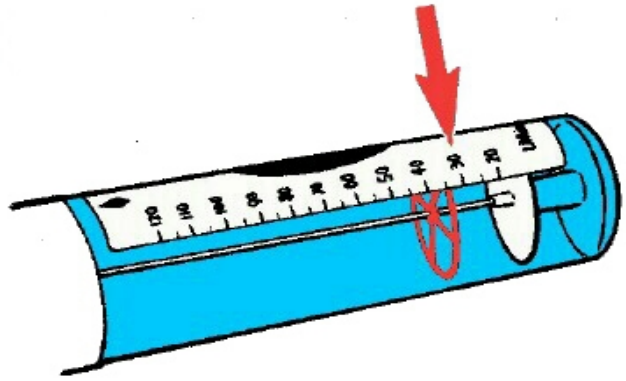

Figure 9

In order to ensure an optimum aerosol dispersion threshold using Plastiape RS-01®, a PIF of at least 30 L/min is required. No upper limit is set.

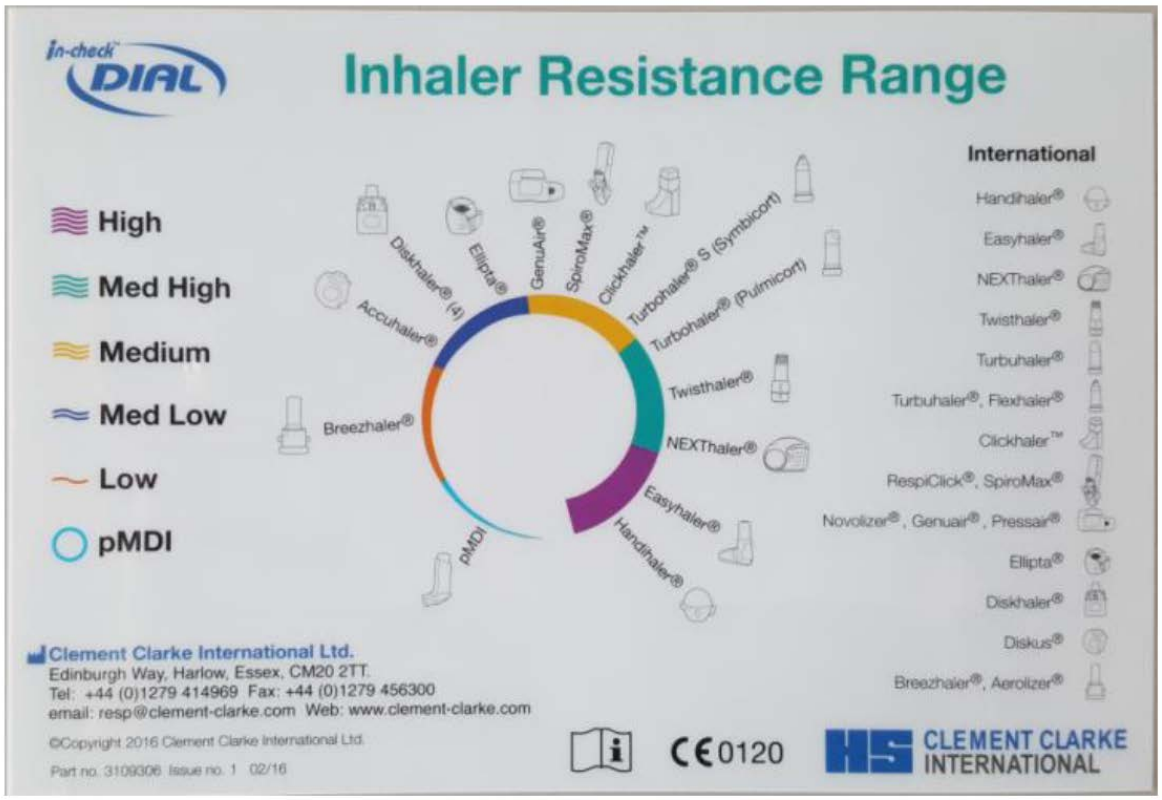

Figure 10