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CLINICAL STUDY PROTOCOL

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ClinicalTrials.gov ID: NCT03084796

A 6-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 5259 pMDI (glycopyrronium bromide) in subjects with Chronic Obstructive Pulmonary Disease (COPD)

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

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
CLINICAL PROJECT MANAGER:	[redacted]
SPONSOR MEDICAL EXPERT (Clinical Research Physician)	[redacted], MD, FCCP [redacted] (office) [redacted] (mobile) Readily available in case of medical questions
MONITORING CRO	[redacted]
CENTRAL LABORATORY OF ANALYSIS:	[redacted]
OTHER CENTRAL TECHNICAL LABORATORIES	Spirometry: [redacted] Holter: [redacted]

PROTOCOL OUTLINE

Study title	A 6-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 5259 pMDI (glycopyrronium bromide) in subjects with Chronic Obstructive Pulmonary Disease (COPD)
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5259 pMDI (glycopyrronium bromide)
Center(s)	Multi-center, in approximately 120 sites
Indication	Chronic Obstructive Pulmonary Disease (COPD)
Study design	Randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study
Study phase	II
Objectives	***Primary objective:*** ▪ To evaluate the efficacy of CHF 5259 pMDI by comparison with placebo in terms of change from baseline in FEV_1 AUC_{0-12h} normalized by time at Week 6. ***Secondary objective:*** ▪ To evaluate the effect of CHF 5259 pMDI on other lung function parameters and clinical outcome measures. ▪ To assess the safety and the tolerability of the study treatments.
Treatment duration	6 weeks
Test product dose/route/regimen	▪ **CHF 5259 pMDI: glycopyrronium bromide administered via HFA-pressurized metered dose inhaler (pMDI), available in 6.25µg per inhalation (GB 6.25), 12.5µg per inhalation (GB 12.5) and 25µg per inhalation (GB 25).** Treatment A: GB 12.5µg Total Daily Dose ➢ GB 6.25µg per inhalation, 1 inhalation bid* Treatment B: GB 25µg Total Daily Dose ➢ GB 12.5µg per inhalation, 1 inhalation bid* Treatment C: GB 50µg Total Daily Dose ➢ GB 12.5µg per inhalation, 2 inhalations bid Treatment D: GB 100µg Total Daily Dose ➢ GB 25µg per inhalation, 2 inhalations bid *An adequate number of inhalations from Placebo inhalers will be performed to maintain a double blind design.

Reference product dose/route/regimen	▪ **Matched Placebo for CHF 5259 pMDI** Treatment E: ➢ Matched placebo, 2 inhalations bid ▪ **SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder 18µg). Inhalation Powder (capsules): each capsule contains 18µg tiotropium powder for use with HANDIHALER® device.** Treatment F: ➢ Tiotropium bromide powder 18µg capsule, 2 inhalations qd
Number of subjects	A total of approximately 702 subjects will be randomized in order to reach a total of 594 completed and evaluable subjects, considering a non-evaluable rate of 15%.
Study population	Subjects with moderate COPD
Inclusion/exclusion criteria	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Male or female subjects aged ≥ 40 years who have signed an Informed Consent Form prior to initiation of any study-related procedure; 2. Subjects with a diagnosis of COPD (according to GOLD 2017 Global Strategy for the Diagnosis, Management and Prevention of COPD Report) at least 12 months before the screening visit; 3. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years (pack-years = [number of cigarettes per day x number of years]/20); 4. A post-bronchodilator FEV_1 ≥40% and <80% of the predicted normal value (measured 30 to 45 minutes after administration of 84µg ipratropium pMDI) and, a. a post-bronchodilator $FEV_1/FVC < 0.7$ at screening and, b. a demonstrated partial reversibility to ipratropium defined as $\Delta FEV_1 \geq 5\%$ over baseline 30-45 minutes after inhaling 4 puffs of ipratropium (21µg/actuation). *Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomization;* 5. Subjects under regular COPD therapy for at least 2 months prior to screening with a single or dual LABD with or without an ICS; a. inhaled LAMA b. inhaled ICS/LABA (fixed or free combination) c. inhaled ICS + LAMA d. inhaled LABA e. inhaled LABA/LAMA (fixed or free combination) f. inhaled ICS/LABA/LAMA (fixed or free combination) 6. Symptomatic subjects at screening with a CAT score ≥10. This

criterion must be confirmed at randomization (Visit 2);

7. Symptomatic subjects with a BDI focal score ≤ 10. This criterion must be confirmed at randomization (Visit 2);
8. A cooperative attitude and ability to demonstrate correct use of the pMDI inhalers and e-diary. This criterion must be confirmed at randomization (Visit 2).

If at Visit 1 the inclusion criterion #4 (reversibility) is not met, the subject may return to repeat the procedure once before randomization.

Inclusion criteria # 6-8 should be re-checked at the randomization visit (Visit 2).

Exclusion Criteria:

If a subject meets any of the following criteria, he/she will NOT be enrolled into the study:

1. Pregnant (as evident by a positive urine hCG or serum β-hCG test) or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are willing to use highly effective birth control methods such as:
   a. Placement of an intrauterine device (IUD) or intrauterine releasing system (IUS);
   b. Oral, intravaginal, transdermal combined estrogen and progesterone containing hormonal contraception or oral, injectable, implantable progestogen only hormonal contraception;
   c. Bilateral tubal occlusion;
   d. Partner vasectomy (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success);
   e. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

   Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening, at Visit 4 and at the early termination visit; urinary pregnancy test will be performed at screening, Visit 2 and Visit 3.

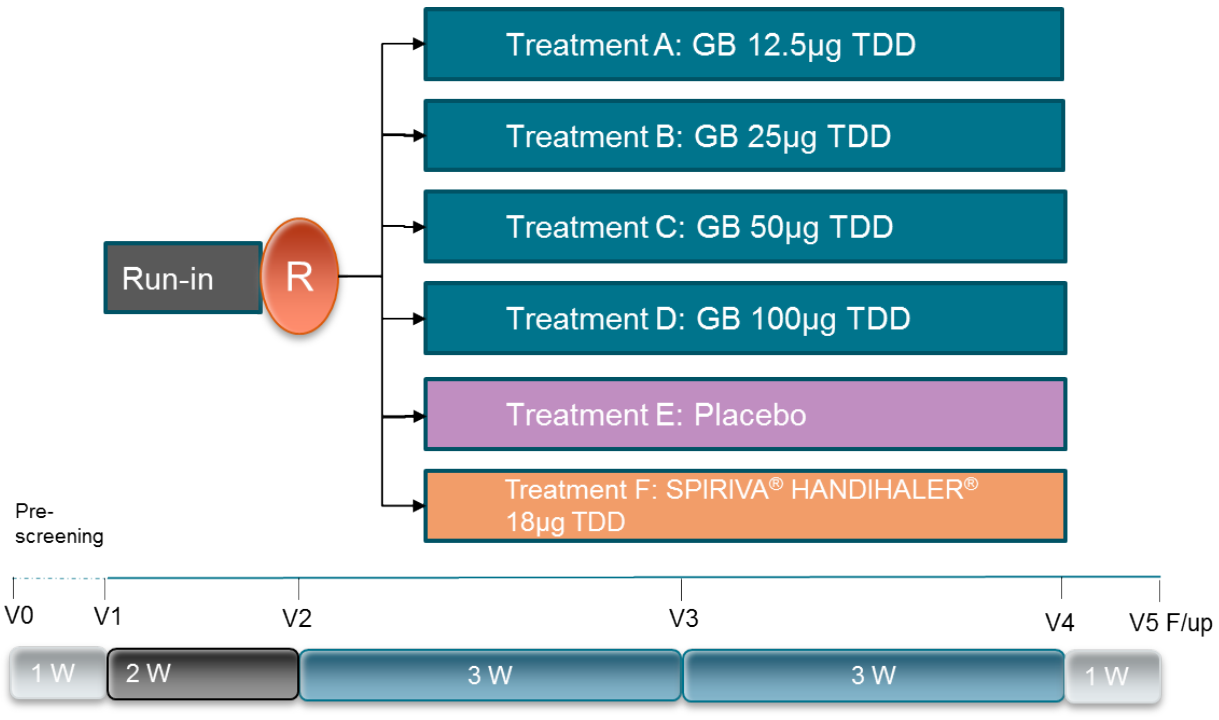
   Women of non-childbearing potential defined as physiologically incapable of becoming pregnant: post-menopausal (defined as no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) are eligible. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy.
2. Diagnosis of asthma or Asthma-COPD Overlap Syndrome (ACOS) as described in GINA Report 2016, history of allergic rhinitis or atopy which may raise contra-indications or impact the efficacy of the study

	treatment according to Investigator's judgment; 3. COPD Exacerbations: a. a moderate or severe COPD exacerbation that has not resolved ≤14 days prior to screening and ≤30 days following the last dose of any oral/intravenous corticosteroid or antibiotic (whichever comes last), and ≤ 3 months of intramuscular depot corticosteroids; b. A Moderate or Severe COPD exacerbation during the run-in period; 4. Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to screening or during run-in; 5. Subjects treated with non-cardio-selective β-blockers in the month preceding screening or during the run-in period; 6. Not applicable; 7. Subjects requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia; 8. Known respiratory disorders other than COPD which may impact the efficacy of the study treatment according to the Investigator's judgment. This can include but is not limited to α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease; 9. Subjects who have a clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV heart failure, acute ischemic heart disease within one year prior to study entry, known history of atrial fibrillation or history of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to screening, not controlled with a rate control strategy; 10. Subjects who have a clinically significant abnormal 12-lead ECG that results in active medical problem which may impact the safety of the subject according to Investigator's judgment; 11. Subjects whose 12-lead ECG shows Fridericia corrected QT interval (QTcF) >450 ms for males or QTcF >470 ms for females at screening or randomization visit (criterion not applicable for subjects with a pacemaker or permanent atrial fibrillation); 12. Medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would prevent use of anticholinergic agents; 13. History of hypersensitivity to M3 receptor antagonists, β2-adrenergic receptor agonist, corticosteroids or any of the excipients contained in any of the formulations used in the study which may raise contra-indications or impact the efficacy of the study treatment according to the Investigator's judgment; 14. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study treatment according to Investigator's judgment; 15. Subjects with serum potassium levels <3.5 mEq/L (or 3.5 mmol/L) at screening; 16. Use of potent cytochrome P450 2D6 and 3A4 inhibitors (e.g. ritonavir,

	ketoconazole, itraconazole) and inducers within 4 weeks prior to screening; 17. Unstable or uncontrolled concurrent disease: e.g. fever, hyperthyroidism, diabetes mellitus or other endocrine disease; gastrointestinal disease (e.g. active peptic ulcer); neurological disease; hematological disease; autoimmune disorders, or other which may impact the feasibility of the results of the study according to Investigator's judgment; 18. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening; 19. Subjects who have received an investigational drug within 1 month or 5 half-lives (whichever is greater) prior to screening visit, or have been previously randomized in this trial, or are currently participating in another clinical trial; 20. Subjects who are mentally or legally incapacitated, or subjects accommodated in an establishment as a result of an official or judicial order; 21. Subjects who have undergone major surgery in the 3 months prior to the screening visit or have a planned surgery during the trial. 22. Subjects using marijuana daily or as needed; Exclusion criteria # 1, 3, 4, 5, 10 and 11 should be re-checked at the randomization visit (V2).
Study plan	The details of the assessments that will be performed during the study are summarized in the study flow diagram in table 1. After a 2-week run-in period, subjects will be randomized to one of the 6 treatment arms and will enter a 6-week treatment period. The study will last approximately 10 weeks for each subject and a total of 5 clinic visits will be performed during the study *(see the flow chart below*) ▪ A pre-screening visit (Visit 0) will be carried out in order to fully explain the study to potential eligible subjects, to obtain their written informed consent and to instruct them on screening visit procedures (such as medication restrictions). ▪ A screening visit (Visit 1) not more than 7 days after Visit 0 will help establish the eligibility of subjects for inclusion in the study (including routine hematology and blood chemistry, vital signs, medical history, weight and height, smoking status, serum and urine pregnancy tests for women of childbearing potential, physical examination, 12-lead ECG, CAT (COPD Assessment Test) and BDI assessment, spirometry testing pre & post-BD, and training on the use of inhalers). Concomitant Medication and Adverse Events will be assessed. Dispensing of subject's diary will be done. This visit will be followed by a 14±2 days run-in period. Treatments that are disallowed by the protocol are to be discontinued at Visit 1. If the subject's treatment includes an inhaled corticosteroid in association with a long-acting β2-agonist or a long-acting anticholinergic, these treatments will be discontinued and the ICS will

	be switched to an equivalent daily dose of Beclomethasone Dipropionate (QVAR® Inhalation Aerosol 80µg/actuation) and this treatment regimen should remain stable for the entire run-in period and the remainder of the study. Subjects will receive rescue medication (albuterol HFA 90µg/actuation) for the treatment or prevention of bronchospasm, with instructions for "on demand" (prn) use for the entire study period. ▪ At randomization visit (Visit 2), inclusion/exclusion criteria, adverse events and concomitant medications will be reviewed. Eligibility recheck will be completed. Smoking status will be checked, urine pregnancy test will be collected if appropriate for women of childbearing potential. 24-hour digital ECG Holter device, that would have been placed the day before the visit, will be kept on. Training on the use of inhalers will be conducted. Pre-dose vital signs, 12-lead ECG, and spirometry testing [FEV_1, FVC, IC (slow vital capacity maneuver)] will be performed. The BDI and CAT questionnaires will be assessed. Subject's e-diary will be checked for daily data transmission. Eligible subjects will then be randomized to one of the treatment groups and will receive the 1st dose of study drug under medical supervision. The subjects will then undergo a 12-hour post-dose serial spirometry assessments and 24-hour digital ECG Holter Monitoring. Lung function (FEV_1, FVC) will be evaluated and recorded at the following time points: T-45 and T-15 min before the 1st dose of study drug and at 15, 30, 45 min and 1, 2, 3, 4, 6, 8, 10, 11.5 and 12h after the 1st dose of study drug. Inspiratory Capacity will be measured at T-45 min before the 1st dose of study drug. Vital signs (SBP, DBP) will also be assessed before and at 30 min, 1.5, 3.5, 7 and 11h after the 1st dose of study drug. A 12-lead ECG will be obtained before and at 1.5h after the 1st dose of study drug. After the last assessment the subjects will then leave the clinical center and will be instructed to return the next day to remove the Holter monitor leads (24h post 1st [morning] dose of study drug), and in 3 weeks' time for Visit 3. Study drug will be dispensed. Subject e- diary will be re-dispensed. ▪ At Week 3 (Visit 3), subjects will undergo pre-dose vital signs assessment and 12-lead ECG. Pre-dose spirometry testing (trough FEV_1, FVC, IC) will be performed and TDI will be assessed. Smoking status, concomitant medication, urine pregnancy test for women of childbearing potential and adverse events will be assessed. Study drug will be returned and accountability will be performed. Study drug will be dispensed. Subject's e-diary will be checked for daily data transmission. The subject will be instructed to return to the clinical center in 3 weeks' time. ▪ At Week 6 (Visit 4), subjects will come to the clinical center and will have the 24-hour digital ECG Holter device, which would have been placed the day before the visit, collected. Physical examination, smoking status, concomitant medications, adverse events, serum pregnancy test will be performed for women of childbearing potential. Routine hematology and blood chemistry will be performed, as well as pre-dose TDI questionnaire, vital signs, 12-lead ECG and spirometry testing [FEV_1, FVC, IC]. The subject will receive the last dose of study

	drug under medical supervision. The subject will then undergo a 12 hours post-dose serial spirometry assessment. Post-dose lung function (FEV_1, FVC) will be evaluated and recorded at the following time points: 15, 30, 45 min and 1, 2, 3, 4, 6, 8, 10, 11.5 and 12h after study drug intake. Vital Signs (DBP/SBP) will be measured at 30 mins, 1.5, 3.5, 7 and 11h post-dose. A 12-lead ECG will also be checked at 1.5h post-dose. Study drug will be returned and accountability will be performed. Subject's e-diary will be returned and checked for daily data transmission. After the last, a follow-up phone call will be scheduled with the subject. ▪ A safety follow-up phone call (Visit 5) will be performed by the investigator or designated staff no later than 1 week after the final visit (Visit 4) or Early Termination Visit to check the status of unresolved AEs and to record any new AEs that may have occurred after Visit 4, as well as related concomitant medications.



Most relevant allowed concomitant treatments

Permitted concomitant medications (from screening visit until the last study visit)

1. Inhaled corticosteroids are permitted in subjects already receiving inhaled corticosteroid at a low-to-medium daily dose in association with a long-acting β2-agonist (LABA) or a long-acting anticholinergic (LAMA) for at least 2 months prior to screening. An equipotent beclomethasone dipropionate (QVAR®) daily dose will be prescribed and will remain constant throughout the study.

ICS*	**Low daily dose**	**Medium daily dose**
BDP extrafine (HFA pMDI) **QVAR®**	80-160µg	>160-320µg
Budesonide (DPI)	200-400µg	>400-800µg
Ciclesonide (HFA pMDI)	80-160µg	>160-320µg
Flunisolide (HFA pMDI)	160-320µg	>320-640µg
Fluticasone Propionate (HFA pMDI/DPI)	100-250µg	> 250-500µg
Fluticasone Furoate (DPI)	100µg	n.a.
Mometasone Furoate (DPI)	110-220µg	>220-440µg

**(Table adapted from GINA Report, 2016).*

Note: ICS monotherapy is not indicated for the treatment of COPD.

ICS/LABA for COPD*	**ICS/LABA Daily Dose**	**QVAR® recommended Daily Dose**
ADVAIR® DISKUS® 250/50	250/50µg bid	160µg bid
BREO® ELLIPTA® 100/25	100/25µg qd	160µg bid
DULERA® 100/5	200/10µg bid	160µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

** Doses of these ICS/LABAs are based on FDA-approved US labels for COPD, except for DULERA®, where doses are suggested based on published clinical trials in COPD. For off-label doses of ICS/LABAs please contact the medical monitor to discuss daily equivalent of QVAR®.*

2. Short-acting β2-agonist (albuterol) as rescue medication. A minimum period of 6 hours should elapse between the use of rescue medication and the spirometric measurements.
3. Mucolytics (e.g. N-acetylcystein) if taken prior to study entry and maintained constant during the study period.
4. Intranasal corticosteroids and oral, intranasal, or ocular antihistamines at FDA-approved doses for the treatment of allergy symptoms will be allowed during the study period.
5. Cardioselective β1-blockers if taken for at least 2 months before screening and to be maintained at a constant dose during the study.

In case of a concomitant disease, appropriate treatment that, according to the investigator, does not interfere with the study evaluation parameters is allowed and if it does not qualify under the section "Non-Permitted Concomitant Medications". All concomitant medications should be noted

<table>
<tr><td></td><td>in the relevant section of the Case Report Form.

In case of exacerbations, subjects will be treated according to the standard clinical practice. This will constitute a reason for withdrawal from the study.</td></tr>
<tr><td>Most relevant forbidden concomitant treatments</td><td>Non-permitted concomitant medications (from screening visit until the last study visit)

The following medications are not permitted during the study:
1. Inhaled long acting β_2-agonists.
2. Inhaled fixed combination of corticosteroids and long-acting β_2-agonists (e.g. salmeterol plus fluticasone or formoterol plus budesonide).
3. Inhaled short acting β_2-agonists (other than study “rescue” medication).
4. Inhaled fixed combinations of a short-acting β_2-agonist (SABA) and a short-acting anticholinergic medication (SAMA).
5. Inhaled short-acting anticholinergics.
6. Inhaled long-acting anticholinergics.
7. Oral/IV/IM corticosteroids.
8. Nebulized bronchodilators or corticosteroids.
9. Inhaled corticosteroids other than study background ICS.
10. Non-cardioselective β-blockers.
11. PDE4 inhibitors (e.g. roflumilast).
12. Leukotriene modifiers.
13. Xanthine derivatives (e.g. theophylline).
14. Any drug with known or possible risk of Torsades de Pointes (TdP) or QT interval prolongation (e.g. quinidine, procainamide, amiodarone).

Prior to screening spirometry (Visit 1), the following washout periods must be respected:

<table>
<tr><td>Caffeinated substances</td><td>6 hours</td></tr>
<tr><td>Inhaled and/or nebulized short-acting β_2-agonists:</td><td>6 hours</td></tr>
<tr><td>Inhaled and/or nebulized short-acting muscarinic antagonists:</td><td>8 hours</td></tr>
<tr><td>Inhaled combination of short-acting β2-agonists /short-acting muscarinic antagonists:</td><td>8 hours</td></tr>
<tr><td>Inhaled corticosteroids (bid):</td><td>24 hours</td></tr>
<tr><td>Inhaled long-acting β_2-agonists (bid):</td><td>24 hours</td></tr>
<tr><td>Inhaled fixed combinations of ICS/LABAs (bid):</td><td>24 hours</td></tr>
<tr><td>Inhaled corticosteroids (qd):</td><td>48 hours</td></tr>
<tr><td>Inhaled "ultra-long-acting" β_2-agonists (qd):</td><td>48 hours</td></tr>
<tr><td>Inhaled fixed combinations of ICS/LABAs (qd):</td><td>48 hours</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Oral leukotriene modifiers:</td><td>72 hours</td></tr><tr><td>Inhaled LAMA:</td><td>7 days</td></tr><tr><td>Xanthine derivatives:</td><td>7 days</td></tr><tr><td>PDE4 inhibitors:</td><td>1 month</td></tr><tr><td>Oral or parenteral (i.v.) corticosteroid:</td><td>1 month</td></tr><tr><td>Intramuscular depot corticosteroid:</td><td>3 months</td></tr></table> ***Prior to other visits with spirometry (V2 → V4) , the following washout periods must be respected:*** <table><tr><td>Inhaled short-acting β_2-agonists:</td><td>6 hours</td></tr><tr><td>Caffeinated substances:</td><td>6 hours</td></tr></table>
Efficacy variables (and/or pharmacokinetics variables)	***Primary efficacy variable*** ▪ Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 6. ***Secondary efficacy variables*** ▪ Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1 ▪ Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time and in FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Week 6 ▪ Change from baseline in FVC $AUC_{0\text{-}12h}$ normalized by time, in FVC $AUC_{0\text{-}4h}$ normalized by time and in FVC $peak_{0\text{-}4h}$ at Day 1 and Week 6 ▪ Time to onset of action (change from baseline in post-dose $FEV_1 \geq 100$ mL) at Day 1 ▪ Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 3 and Week 6 ▪ Change from baseline in pre-dose morning IC at Week 3 and Week 6 ▪ TDI focal score at Week 3 and Week 6 ▪ TDI response (TDI focal score ≥ 1) at Week 3 and Week 6 ▪ Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period ▪ Change from baseline in average use of rescue medication (number of puffs/day) during inter-visit periods and entire treatment period ▪ Change from baseline in average E-RS total score and domain scores during inter-visit periods and entire treatment period
Safety variables	▪ Adverse Events (AEs) and Adverse Drug Reactions (ADRs) ▪ Vital signs (systolic and diastolic blood pressure) ▪ 24-hour digital Holter ECG parameters (HR, QTcF, QRS, PR) ▪ 24-hour HR average, minimum and maximum and hourly average HR ▪ 24-hour digital Holter ECG abnormal findings ▪ Standard blood chemistry and hematology
Sample size calculation	The sample size has been calculated to evaluate the superiority of CHF 5259 pMDI at different doses over placebo in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 6. A total of 594 evaluable subjects (99 per group) will provide 80% power to detect a mean difference of 120 mL between each dose of CHF 5259 pMDI and placebo at a two-sided significance level of 0.0125 (since 4 dose levels will be tested, the Bonferroni adjustment has been taken into account: 0.0125 = 0.05/4), assuming a standard deviation of 250 mL. Since four dose levels will be tested, the Edwards and Berry method will be used to control the family-wise Type I error rate at the 0.05 (two-sided) level. In the sample size calculation, the Bonferroni adjustment of the

	significance level has been taken into account (0.0125 = 0.05/4). This will ensure the required power for each test, since the Edwards and Berry method is uniformly more powerful than the Bonferroni procedure. Considering a non-evaluable rate of 15%, a total of approximately 702 subjects (117 per group) will be randomized.
Statistical methods	***Primary efficacy variable*** Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time will be analyzed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, US regions and smoking status at screening as fixed effects, and the baseline value (average of the pre-dose FEV_1 measurements on Day 1) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 5259 pMDI and placebo at Week 6 will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry. At each dose level, the superiority of CHF 5259 pMDI will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favouring CHF 5259 pMDI. All the other comparisons between treatments will be performed as secondary efficacy analyses with no multiplicity adjustment. ***Secondary efficacy variables*** No multiplicity adjustment will be performed in the secondary efficacy analyses. • For change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1, the adjusted means in each treatment group and the adjusted mean differences between treatments at Day 1 will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis. • Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time and in FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Week 6 and change from baseline in pre-dose morning FEV_1 at Week 3 and Week 6 will be analyzed using the same model as for the primary efficacy variable. • Change from baseline in FVC $AUC_{0\text{-}12h}$ normalized by time, in FVC $AUC_{0\text{-}4h}$ normalized by time and in FVC $peak_{0\text{-}4h}$ at Day 1 and Week 6 will be analyzed using a similar model as the one used for the primary efficacy analysis. • Time to onset of action (i.e., change from baseline in post-dose $FEV_1 \geq$ 100 mL) at Day 1 will be analyzed using a Cox proportional hazard model including treatment, US regions and smoking status at screening as fixed effects, and baseline (average of the pre-dose FEV_1 measurements on Day 1) as covariate. A Kaplan-Meier plot will be presented. • Change from baseline in pre-dose morning IC at Week 3 and Week 6 will be analysed using a similar model as the one used for the primary efficacy analysis. • TDI focal score at Week 3 and Week 6 will be analyzed using a

similar model as the one used for the primary efficacy analysis.

- TDI response at Week 3 and Week 6 will be analyzed using a logistic regression model including treatment, US regions and smoking status at screening as fixed effects and baseline (BDI [Baseline Dyspnea Index] focal score assessed on Day 1) as a covariate.
- Change from baseline to each inter-visit period in percentage of rescue medication-free days, in average use of rescue medication and in average E-RS total score and domain scores will be analyzed using a similar model as the one used for the primary efficacy analysis. The inter-visit period will be considered instead of visit in the model. Comparison between treatments over the entire treatment period will also be derived from this model.

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 Events (TEAEs). Any adverse event started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. Pre-treatment adverse events will be listed only.

The number of TEAEs and the number and percentage of subjects who experienced at least one TEAE will be presented by treatment for all AEs, ADRs, serious AEs, serious ADRs, severe AEs, AEs leading to study discontinuation and AEs leading to death. Summaries will be presented overall and by system organ class and preferred term based on the MedDRA dictionary.

Vital signs

Vital signs (systolic and diastolic blood pressure) and their changes from baseline (pre-dose on Day 1) and from pre-dose on Week 6 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

Holter

ECG parameters extracted from Holter (HR, QTcF, QRS and PR) and their changes from baseline (time-matched on day before V2) will be summarized for all timepoints on Day 1 and Week 6 by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline).

Change from baseline (time-matched on day before V2) in ECG parameters extracted from Holter (HR, QTcF, QRS and PR) will be analyzed using a linear mixed model for repeated measurements including treatment, timepoint, treatment by timepoint interaction, US regions and smoking status at screening as fixed effects, and the baseline value (time-matched on day before V2), baseline by timepoint interaction and time-averaged baseline as covariates. An unstructured covariance matrix will be assumed.

The number and the percentage of subjects with a

- QTcF >450 ms (males only), >470 ms (females only) or >480 ms (males only) and >500 ms (males and females)

	○ change from baseline (time-matched on day before V2) in QTcF >30 ms and >60 ms at each post-dose timepoint and at any post-dose timepoint will be presented by treatment group. 24-hour HR average, minimum and maximum extracted from the Holter and their changes from baseline (day before V2) will be summarized by treatment using descriptive statistics and the 95% CI of the mean. Change from baseline (day before V2) in 24-hour HR average, minimum and maximum extracted from Holter will be analyzed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, US regions and smoking status at screening as fixed effects, and the baseline value (day before V2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. Hourly average HR will be summarized by treatment using descriptive statistics and the 95% CI of the mean. The number and the percentage of subjects with abnormal findings (including supraventricular arrhythmias, ventricular arrhythmias and non-sustained ventricular tachycardia) in the 24-hour Holter will be summarized by treatment group. **Laboratory parameters** Shift tables from screening to the end of treatment, based on normal ranges, will be presented by treatment group for the laboratory parameters.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BD	Bronchodilator
BDI	Baseline Dyspnea Index
BDP	Beclomethasone dipropionate
bid	Bis in die (twice a day)
BTPS	Body Temperature and ambient Pressure Saturated with water vapor
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
(e-) CRF	(Electronic) Case Report Form
CV	Cardiovascular
(e-) Diary	(Electronic) Diary
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	ElectroCardioGram
E-RS	EXACT (Exacerbations of Chronic Pulmonary Disease Tool) – Respiratory Symptoms
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
FPFV	First Patient First Visit
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GCP	Good Clinical Practices
GINA	Global INitiative for Asthma
GMP	Good Manufacturing Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
h	hour
hCG	Human Chorionic Gonadotropin hormone
HR	Heart Rate
HFA	Hydrofluoroalkane
IB	Investigator Brochure
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intention to Treat
IU (D or S)	Intra Uterine (Device or System)
L	Liter

LABA	Long-Acting β_2-adrenergic receptor Agonist
LABD	Long-Acting Bronchodilator
LAMA	Long-Acting Muscarinic Antagonist
LDH	Lactate dehydrogenase
LLN	Lower Limit of Normal
LPLV	Last Patient Last Visit
µg	Microgram
MAOI	Monoamine oxidase inhibitor
MAR	Missing at Random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
mL	Milliliters
mMRC	Modified Medical Research Council
NYHA	New York Heart Association
PEF	Peak Expiratory Flow
PIL	Patient Information Leaflet
pMDI	Pressurized Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval from the beginning of the upslope of the P wave to the beginning of the QRS wave in the ECG
prn	Pro re nata (as-needed)
PRO	Patient-Reported Outcome
Q	Quaque (every so-,any hours)
qd	Quaque die (once a day)
QRS	Time Interval from the end of the PR interval to the end of the S wave in the ECG
QTc	Time interval between the start of the Q wave and the end of the T wave in the ECG (corrected for HR)
QTcF	QT interval corrected for HR using Fridericia's formula
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SABA	Short-Acting Beta Agonist
SABD	Short-Acting Bronchodilators
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
sGAW	Specific Airway Conductance
SGRQ	St. George's Respiratory Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDD	Total Daily Dose
TdP	Torsades de Pointes
TEAE	Treatment Emergent Adverse Event
TDI	Treatment Dyspnea Index
ULN	Upper Limit of Normal
VC (SVC / FVC)	Vital Capacity (Slow /Forced)
WHO	World Health Organization

WOCBP	Woman of Childbearing Potential

CONTENTS

APPENDICES

1. BACKGROUND INFORMATION AND STUDY RATIONALE

Chronic Obstructive Pulmonary Disease (COPD) currently ranks as the 4th leading cause of death in the world, and is expected to be in 3rd place by 2020.[1] COPD is both a preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (e.g. cigarette smoke, biodiesel fumes). A mixture of lung abnormalities are characteristic of COPD, including small airway and parenchymal disease (obstructive bronchiolitis; emphysema), with variable contributions in any given subject.[2]

The NHANES III national survey estimated the U.S. prevalence of COPD to be 10.2% to 20.9% based on whether pre- or post-bronchodilator values were used and which diagnostic criterion (fixed ratio or lower limit of normal {LLN}) was applied.[3] COPD most often occurs in people 45 years of age and older who have a history of smoking (current or former smokers). While not everybody who smokes gets COPD, approximately 80-90% of the individuals who have COPD have smoked.[4]

Smoking cessation can have the greatest influence on stopping the progression of COPD, as well as increasing survival and reducing morbidity.[5] However, long-term quit success rate rarely exceed 25%.[2][6]

Existing pharmacologic therapy is used to improve airflow, symptoms, exercise capacity, health status, and reduce the frequency and severity of exacerbations in stable COPD. To date, there is no conclusive evidence that any available pharmacotherapy for COPD modifies the long-term decline in lung function. The main stay of pharmacotherapies for stable COPD are delivered via inhalation route, and consist of the following:

- **Short acting or long-acting bronchodilators (SABD; LABD)**:
  - ***Short acting and long-acting β2-adrenergic agonists (SABA; LABA)*** improve spirometric measures including FEV_1 by altering airway smooth muscle tone, and tend to reduce dynamic hyperinflation (Residual Lung Volume) at rest and during exercise, and improve exercise performance.
    - Adverse events include sinus tachycardia, rhythm disturbances, and hypokalemia.
    - Despite prior concerns related to the use of LABAs in asthma, no association between the use of this class and loss of lung function and increased mortality has been reported in COPD.[7][8][9]
  - ***Short-acting and long-acting antimuscarinics (SAMA; LAMA).*** These drugs act mainly by blocking the bronchoconstrictor effects of acetylcholine on airway muscarinic receptor M3. Tiotropium is a LAMA that has been shown to improve lung function, symptoms, health status,[10] effectiveness of pulmonary rehabilitation,[11][12] and to reduce exacerbations and related hospitalizations[13] compared to placebo. Studies have shown that the effect of glycopyrronium, another LAMA, versus placebo is similar to that of tiotropium in reducing dyspnea and the risk of exacerbations, as well as improving lung function, exercise tolerance, and health status in subjects with COPD.[14][15][16][17]

- Adverse events of this class of medications are mainly due to their anticholinergic activities, and include dry mouth, constipation, urinary retention and increased intraocular pressure.
- An unexpected small increase in cardiovascular (CV) events in subjects with COPD regularly treated with ATROVENT® (ipratropium bromide) has been reported.[18][19]
- A large, 4-yr long clinical trial in subjects with COPD treated with SPIRIVA® HANDIHALER® (tiotropium) added to other standard therapies reported no effect on CV risk.[20]

- ***Combination Bronchodilators:*** Combining bronchodilators using a LABA and a LAMA increases FEV_1, albeit not to the full additive effect of each individual component; improves PROs and reduces exacerbations vs monotherapy. One study (FLAME trial) in subjects with post-BD FEV_1 ≥25% and < 60% predicted, an mMRC score of ≥2, and a history of ≥1 exacerbation reported an 11% further reduction in COPD exacerbations with fixed combination of once daily indacaterol 110µg + glycopyrronium 50µg (LABA+LAMA) compared to fixed combination twice daily fluticasone propionate 500µg + salmeterol 50µg (ICS+LABA).[21] Combining a SABA and a SAMA or a LABA and LAMA can be done using separate inhalers or using a single inhaler containing a fixed dose combination.

- **Anti-inflammatory agents**
  - **Inhaled Corticosteroids (ICS) alone:** The available evidence does not support a beneficial effect of ICS monotherapy in subjects with COPD.[22]
  - **ICS in combination with LABD:** Most studies in subjects with mod-severe COPD and history of exacerbations found a beneficial effect of ICS+LABA fixed dose combination over either component alone in improving lung function, health status, and in reducing exacerbations. Studies that evaluated withdrawal of ICS have yielded equivocal results.
    - High quality evidence has confirmed an increased rate of pneumonia, oral candidiasis, hoarseness and skin bruising with ICS treatment.[23][24][25][26][27] Factors associated with a higher risk for pneumonia on ICS include: current smokers, age ≥ 55 yrs, have a history of prior exacerbation or pneumonia, a BMI < 25 kg/m^2, a poor MRC dyspnea grade, and/or severe airflow limitation.[28][29] A meta-analysis suggested that subjects with COPD with lower blood eosinophil counts (<2%) had more pneumonia events than did those with higher counts.[30]
    - RCTs have reported variable outcomes regarding ICS effect on decreased bone mineral density (BMD) [31][32] and risk of fractures,[33] and observational studies suggest an increased risk of diabetes / poorly controlled diabetes,[34] cataracts,[35][36] and mycobacterial infections, including tuberculosis.[37]
- **Triple Combination of ICS+LABA+LAMA:** Available evidence from RCTs suggests that adding a LAMA to an ICS+LABA (or vice-versa) further improves lung function, PROs and reduces exacerbations risk.[38][39][40][41][42][43] This step-up therapy can be achieved using various available approaches and products. More studies with this combination are needed to understand the benefits and risks and the target population.

Chiesi Farmaceutici has patented MODULITE®, a technology for the development of pMDI as HFA solution formulations. It currently markets **FOSTER®,** a fixed dose combination of an ICS/LABA (beclomethasone dipropionate 100µg / formoterol fumarate 6µg) for the maintenance treatment of asthma (1-2 inhalations bid, and 1 inhalation prn, not to exceed 8 inhalations/day) and COPD (2 inhalations bid) in subjects 18 yrs and older. The product was launched in Germany in 2006 and is currently available in 35 countries worldwide including Russia and China, but not the US. FOSTER® is dispensed as a Pressurized Inhalation Solution (pMDI, Modulite®) and as a dry powder for inhalation (DPI) by the NEXThaler® device, releasing extra-fine particles.[44] FOSTER® pMDI has been developed with a high "extrafine" (< 1.1µm) BDP particle size fraction, similarly to another HFA BDP marketed formulation (QVAR® Inhalation Aerosol, Teva Respiratory, LLC).

Chiesi Farmaceutici is also developing a **fixed dose triple combination** of an ICS/LABA/LAMA (CHF 5993) with beclomethasone dipropionate (BDP) + formoterol fumarate (FF) + glycopyrronium bromide (GB), and on Sep 29, 2016 became the first company to submit a marketing authorization application with this investigational product to the European Medicine Agency (EMEA) for the treatment of COPD. The product is administered using a single pressurized metered dose inhaler (pMDI), specifically formulated to deliver extra-fine particles efficiently reaching both central and peripheral airways.

The submission of the EMEA dossier is based on the results of a large and comprehensive development program performed by Chiesi since 2009, which included 12 clinical studies involving more than 8,000 subjects.[45]

As part of the US development program of this fixed dose triple combination for COPD, a full characterization of the individual components (BDP, FF, GB) using the same inhaler device is required, including clinical dose-ranging studies at multiple doses, and using appropriate comparators for benchmarking purposes. An inhaled formulation of GB delivered via hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) using the Modulite® technology has been developed by Chiesi for this purpose and will be used in this dose-ranging trial.

Previously, HFA GB pMDI (CHF 5259) has been assessed as a single dose at 12.5 – 200µg/day, and in a multiple dose study over 1 week at 25 – 100µg/day, compared to placebo, in subjects with COPD.[46] This will be a longer (6-week), multi-dose, placebo and active-controlled dose-ranging trial, conducted in subjects with COPD, to satisfy US FDA's recommendations for dose-finding. Since SEEBRI™ NEOHALER® (glycopyrrolate) inhalation powder [47] has not yet been marketed in the US at the time of the development of this protocol, SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder) 18µg once daily was chosen as the active comparator in this study, considering its well characterized efficacy and safety profile.[48]

Glycopyrronium Bromide (Glycopyrrolate):
Description and Mechanism of Action:
Glycopyrronium bromide (GB), also known as glycopyrrolate, is a synthetic quaternary ammonium compound that acts as a competitive antagonist at muscarinic acetylcholine receptors. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, glycopyrrolate exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.[47] The medication, which is the active moiety, is also known as glycopyrronium.[49]

Clinical Efficacy of glycopyrronium bromide:
SEEBRI™ NEOHALER®: In October 2015, the US FDA approved SEEBRI™ NEOHALER® (glycopyrrolate) inhalation powder for oral inhalation use (NOVARTIS Pharmaceutical Corp.), for the long-term, maintenance treatment of airflow obstruction in subjects with COPD. Each capsule contains 15.6µg of glycopyrronium bromide (glycopyrrolate) inhalation powder. Each delivered dose (under standardized in vitro testing at a fixed flow rate of 90 L/min for 1.3 seconds) contains 13.1 µg of glycopyrronium bromide equivalent to 12.5µg of glycopyrronium (ex-mouthpiece).[47]

Dose selection for SEEBRI™ NEOHALER® in COPD was supported by a 28-day, randomized, double-blind, placebo-controlled, 2-period, crossover study evaluating 7 doses of glycopyrrolate (15.6µg, 31.2µg, 62.4µg, and 124.8µg once-daily and 15.6µg, 31.2µg, and 62.4µg twice-daily) or placebo in 388 subjects with COPD. The dose-ranging results supported the evaluation of glycopyrrolate 15.6µg twice-daily in the confirmatory COPD trials for US registration.[50] Two replicate phase III, 12-week, randomized, double-blinded, placebo-controlled, parallel-group trials (GEM1; n=441 and GEM2; n=432) subsequently evaluated and confirmed the efficacy of SEEBRI™ NEOHALER® 15.6µg bid in subjects with moderate-to-severe COPD (30% ≤ predicted FEV_1 > 80%). The primary endpoint was the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ following the morning dose at Day 85 compared with placebo. In both trials, SEEBRI™ NEOHALER® demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0\text{-}12h}$ compared to placebo.[51][52] The mean peak FEV_1 (maximum FEV_1 recorded within 4 hours after the morning dose) improvement from baseline for SEEBRI™ NEOHALER® compared with placebo at Day 1 and at Day 85 ranged between 0.137L and 0.163L. Subjects treated with SEEBRI™ NEOHALER® used less daily rescue albuterol during both trials compared to subjects treated with placebo, and the responder rate to the St. George's Respiratory Questionnaire (SGRQ), defined as an improvement in score of 4 or more as threshold, ranged between 49%-55% in the SEEBRI™ NEOHALER® treatment arm compared to 41%-42% for placebo.

CHF 5259 pMDI – TRIPLE 9 (TRIGON) study: A phase II, multi-center, randomized, double-blind, placebo-controlled, 2-way cross-over study evaluated the efficacy and safety of HFA GB pMDI (CHF 5259), 12.5µg/inhalation (2 inhalations bid, TDD = 50µg) given for 4 weeks in 100 symptomatic subjects (BDI focal score ≤10) with moderate-very severe COPD (post-BD FEV1 < 60% predicted). Subjects were allowed to continue on an ICS (switched to an equivalent dose of QVAR®) if they were receiving it at baseline.[53] HFA GB pMDI was superior to placebo in terms of change from baseline in pre-dose (trough) morning FEV_1 on Day 28 (primary efficacy variable) with a difference in adjusted means (95% CI) between treatments of 0.088L (0.039L; 0.137L) ($p<0.001$), and in FEV_1 $AUC_{0\text{-}12h}$ normalized by time on Day 28 (key secondary efficacy variable) with a difference in adjusted means between treatments of 0.121L (95% CI: 0.079L - 0.162L; $p<0.001$). Superiority was also demonstrated for other lung function parameters (FVC, IC) and clinical outcome measures (TDI, SGRQ, rescue medication use).

Clinical Safety of glycopyrronium bromide:
SEEBRI™ NEOHALER®: The safety database included 3415 subjects with COPD in four 12-week lung function trials and one 52-week long-term safety study.[51][52][54][55] A total of 1202 subjects received treatment with SEEBRI NEOHALER 15.6µg bid.

In the two 12-week trials with SEEBRI™ NEOHALER®, the most common adverse reactions (incidence ≥ 2% and higher than placebo) were upper respiratory tract infection and nasopharyngitis. The proportion of subjects who discontinued treatment due to adverse reactions was 2.4% for the SEEBRI™ NEOHALER®-treated subjects and 3.8% for placebo-treated subjects. Other adverse reactions occurring more frequently with SEEBRI™ NEOHALER® than with placebo, but with an incidence < 1% include rash, pruritus, gastroenteritis, hypersensitivity, atrial fibrillation, insomnia, pain in extremity, dysuria, vomiting, productive cough, and diabetes mellitus/hyperglycemia.

In the 52-week long safety trial comparing glycopyrrolate 15.2µg bid to indacaterol 27.5µg qd, (GEM3; n=507) adverse reactions were consistent with those observed in the 12-week long placebo-controlled trials. Additional adverse reactions that occurred with a frequency ≥ 2% in the group receiving glycopyrrolate that exceeded the frequency seen in the indacaterol 75µg treatment arm were: diarrhea, nausea, upper abdominal pain, fatigue, bronchitis, pneumonia, rhinitis, back pain, arthralgia, dyspnea, and wheezing.[55]

Additional adverse reactions that have been identified during worldwide post-approval use of glycopyrrolate, the active ingredient in SEEBRI™ NEOHALER®, at higher than the recommended dose are angioedema and paradoxical bronchospasm.[47]

CHF 5259 pMDI – TRIPLE 9 (TRIGON) study:[53] Overall, no safety concerns were raised with GB compared to placebo in the clinical trial described above. Twenty (20.6%) patients experiencing 25 TEAEs during treatment with CHF 5259 pMDI and 17 (17.7%) patients experiencing 21 TEAEs during treatment with placebo. Six TEAEs led to study treatment discontinuation: 4 (4.1%) patients due to 4 TEAEs (2 TEAEs of COPD exacerbation, 1 TEAE of bronchial carcinoma and 1 TEAE of death) during treatment with CHF 5259 pMDI and 2 (2.1%) patients due to 2 TEAEs of COPD exacerbation during treatment with placebo. No clinically significant ECG abnormalities were found.

Like other antimuscarinic agents, glycopyrrolate should be used with caution in subjects with narrow-angle glaucoma and in subjects with urinary retention as it may exacerbate these conditions.[56]

More detailed description of the efficacy and safety data available with CHF 5259 pMDI can be found in section 6.2.1 and in the Investigator's Brochure.

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

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

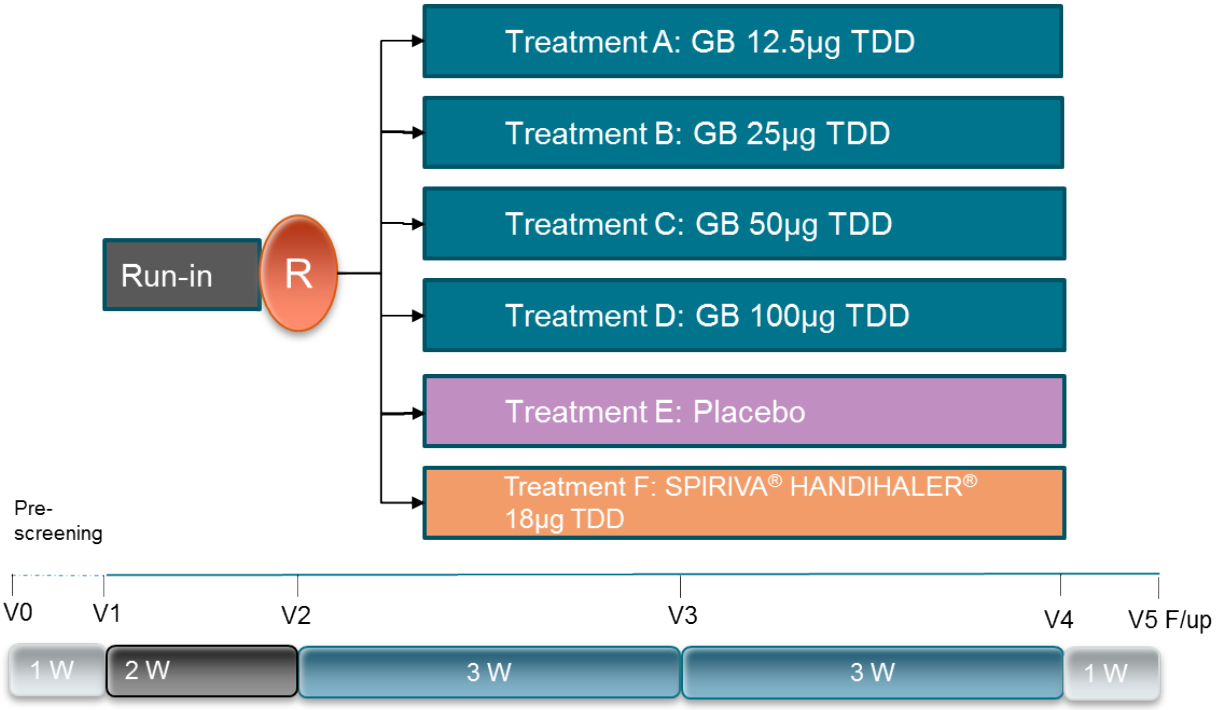
- To evaluate the efficacy of CHF 5259 pMDI by comparison with placebo in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 6.

2.2 Secondary Objective(s)

- To evaluate the effect of CHF 5259 pMDI on other lung function parameters and clinical outcome measures.
- To assess the safety and the tolerability of the study treatments.

3. STUDY DESIGN

This is a phase II, multi-center, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 5259 (glycopyrronium bromide HFA pMDI) delivered twice daily, in adult subjects with COPD. Following a 2-week run-in period, eligible subjects will be randomized to one of 6 study treatments arms (1:1:1:1:1:1) for 6 weeks. A follow-up phone contact for adverse events assessment will be conducted approximately 1 week after the last clinic visit. The study will last approximately 10 weeks for each subject and a total of 5 clinic visits and a follow-up call will be performed during the study.



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

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Assuming a 40% screening failure rate, and a post-randomization non-evaluable rate of 15%, approximately 1170 subjects will be screened and 702 randomized (117 per group) to yield 594 evaluable subjects. Recruitment will occur at approximately 120 participating outpatient study centers within the US.

4.2 Inclusion Criteria

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

1. Male or female subjects aged ≥ 40 years who have signed an Informed Consent Form prior to initiation of any study-related procedure;
2. A diagnosis of COPD (according to GOLD Report, 2017[2]) at least 12 months before the screening visit;
3. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years (pack-years = [number of cigarettes per day x number of years]/20);
4. A post-bronchodilator FEV_1 ≥40% and <80% of the predicted normal value (measured 30 to 45 minutes after administration of 84µg ipratropium pMDI) and,
   a. a post-bronchodilator $FEV_1/FVC < 0.7$ at screening and,
   b. a demonstrated partial reversibility to ipratropium defined as $\Delta FEV_1 \geq 5\%$ over baseline 30-45 minutes after inhaling 4 puffs of ipratropium (21µg/actuation);

   Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomization.
5. Use of regular COPD therapy for at least 2 months prior to screening with a single or dual LABD with or without an ICS;
   a. inhaled LAMA
   b. inhaled ICS/LABA (fixed or free combination)
   c. inhaled ICS + LAMA
   d. inhaled LABA
   e. inhaled LABA+LAMA (fixed or free combination)
   f. inhaled ICS+LABA+LAMA (fixed or free combination)
6. Presence of COPD symptoms at screening with a CAT score ≥10. This criterion must be confirmed at randomization (Visit 2);
7. Presence of dyspnea with a BDI focal score ≤ 10. This criterion must be confirmed at randomization (Visit 2);
8. A cooperative attitude and ability to demonstrate correct use of the pMDI inhalers and the e-diary. This criterion must be confirmed at randomization (Visit 2).

If at Visit 1 the inclusion criterion #4 (reversibility) is not met, the subject may return to repeat the procedure once before randomization.

Inclusion criteria # 6-8 should be re-checked at the randomization visit (Visit 2).

4.3 Exclusion Criteria

If a subject meets any of the following criteria, he/she will NOT be enrolled into the study:

1. Pregnant (as evident by a positive urine hCG or serum β-hCG test) or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are willing to use highly effective birth control methods such as:
   a. Placement of an intrauterine device (IUD) or intrauterine releasing system (IUS);
   b. Oral, intravaginal, transdermal combined estrogen and progestogen containing hormonal contraception or oral, injectable, implantable progestogen only hormonal contraception;
   c. Bilateral tubal occlusion;

d. Partner vasectomy (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success);
e. Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.

Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at screening, at Visit 4 and at the early termination visit; urinary pregnancy test will be performed at screening, Visit 2 and Visit 3. Women of non-childbearing potential defined as physiologically incapable of becoming pregnant: post-menopausal (defined as no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) are eligible. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy.

2. Diagnosis of Asthma, or Asthma-COPD Overlap Syndrome (ACOS) as described in GINA Report, 2016, history of allergic rhinitis or atopy (atopy which may raise contra indications or impact the efficacy of the study treatment according to Investigator's judgment);
3. COPD Exacerbations:
    a. a moderate or severe COPD exacerbation that has not resolved ≤14 days prior to screening and ≤30 days following the last dose of any oral/intravenous corticosteroid or antibiotic (whichever comes last), and ≤ 3months of intramuscular depot corticosteroid;
    b. A moderate or severe COPD exacerbation during the run-in period;
4. Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to screening or during run-in;
5. Subjects treated with non-cardio-selective β-blockers in the month preceding screening or during the run-in period;
6. Not applicable;
7. Subjects requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxemia;
8. Known respiratory disorders other than COPD which may impact the efficacy of the study treatment according to the Investigator's judgment. This can include but was not limited to α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
9. Subjects who have a clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV heart failure, acute ischemic heart disease within one year prior to study entry, known history of atrial fibrillation or history of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to screening, not controlled with a rate control strategy;
10. Subjects who have a clinically significant abnormal 12-lead ECG that results in active medical problem which may impact the safety of the subject according to Investigator's judgment;
11. Subjects whose 12-lead ECG shows Fridericia corrected QT interval (QTcF) >450 ms for males or QTcF >470 ms for females at screening or randomization visit (criterion not applicable for subjects with a pacemaker or permanent atrial fibrillation);

12. Medical diagnosis of narrow-angle glaucoma, clinically relevant prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would prevent use of anticholinergic agents;
13. History of hypersensitivity to M3 antagonists, β2-adrenergic receptor agonist, corticosteroids or any of the excipients contained in any of the formulations used in the study which may raise contra-indications or impact the efficacy of the study treatment according to the Investigator's judgment;
14. Clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease which may impact the efficacy or the safety of the study treatment according to Investigator's judgment;
15. Subjects with serum potassium levels <3.5 mEq/L (or 3.5 mmol/L) at screening;
16. Use of potent cytochrome P450 2D6 and 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening;
17. Unstable or uncontrolled concurrent disease: e.g. fever, hyperthyroidism, diabetes mellitus or other endocrine disease; gastrointestinal disease (e.g. active peptic ulcer); neurological disease; hematological disease; autoimmune disorders, or other which may impact the feasibility of the results of the study according to Investigator's judgment;
18. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening;
19. Subjects who have received an investigational drug within 1 month or 5 half-lives (whichever is greater) prior to screening visit, or have been previously randomized in this trial, or are currently participating in another clinical trial;
20. Subjects who are mentally or legally incapacitated, or subjects accommodated in an establishment as a result of an official or judicial order;
21. Subjects who have undergone major surgery in the 3 months prior to the screening visit or have a planned surgery during the trial.
22. Subjects using marijuana daily or as needed;

Exclusion criteria # 1, 3, 4, 5, 10 and 11 should be re-checked at the randomization visit (Visit 2).

4.4 Subject Withdrawals

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

- An adverse event occurs that, in the opinion of the investigator, makes it unsafe for the subject to continue taking the study drug or undergo study procedures. In this case, the appropriate measures will be taken;
    - COPD Exacerbations: Subjects who experience a moderate or severe COPD exacerbation any time after screening (V1) will be instructed to visit the site as soon as possible for an Early Termination Visit and will be withdrawn permanently from the study. The Adverse Event form will be completed and appropriate medical management of the COPD exacerbation according to standard medical practice will be ensured by the study investigator, with the aim to preserve the research subject's well-being at all times.
        - Definitions of a moderate and a severe COPD exacerbation are provided in section 7.2.12 of the study protocol.
- 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 non-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.

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 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

1. Inhaled corticosteroids are permitted in subjects already receiving them at low-to-medium daily dose in association with a long-acting β2-agonist (LABA) or a long-acting anticholinergic (LAMA) for at least 2 months prior to screening. The subject's current ICS will be discontinued at the screening visit and an equipotent beclomethasone dipropionate (QVAR®) daily dose will be prescribed instead and will remain constant throughout the study.

ICS*	Low daily dose	Medium daily dose
BDP extrafine (HFA pMDI) QVAR®	80-160µg	>160-320µg
Budesonide (DPI)	200-400µg	>400-800µg
Ciclesonide (HFA pMDI)	80-160µg	>160-320µg
Flunisolide (HFA pMDI)	160-320µg	>320-640µg
Fluticasone propionate (HFA pMDI/DPI)	100-250µg	>250-500µg
Fluticasone furoate (DPI)	100µg	n.a.
Mometasone furoate (DPI)	110-220µg	>220-440µg

**(Table adapted from GINA Report, 2016)*

ICS/LABA for COPD*	ICS/LABA Daily Dose	QVAR® recommended Daily Dose
ADVAIR® DISKUS® 250/50	250/50µg bid	160µg bid
BREO® ELLIPTA® 100/25	100/25µg qd	160µg bid

DULERA® 100/5	200/10µg bid	160µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

** Doses of these ICS/LABAs are based on FDA-approved US labels for COPD, except for DULERA®, where doses are suggested based on published clinical trials in COPD. For off-label doses of ICS/LABAs please contact the medical monitor to discuss daily equivalent of QVAR®.*

2. Short-acting β2-agonist (albuterol) as rescue medication. A minimum period of 6 hours should elapse between the use of rescue medication and the spirometric measurements.
3. Mucolytics (e.g. N-acetyl cystein) if taken prior to study entry and maintained constant during the study period.
4. Intranasal corticosteroids and oral, intranasal, or ocular antihistamines at FDA-approved doses for the treatment of allergy symptoms will be allowed during the study period.
5. Cardioselective β1-blockers if taken for at least 2 months before screening and to be maintained at a constant dose during the study.

In case of a concomitant disease, appropriate treatment that, according to the investigator, does not interfere with the study evaluation parameters is allowed and if it does not qualify under the section "Non-Permitted Concomitant Medications". All concomitant medications should be noted in the relevant section of the Case Report Form.

In case of exacerbations, subjects will be treated according to the standard clinical practice. This will constitute a reason for withdrawal from the study.

5.2 Non-Permitted Concomitant Medications

The following medications are not permitted during the total study period, starting from screening visit (V1). Subjects who take any of these medications during the run-in period (V1-V2) should not be randomized into the study. Subjects who take any of these medications during the randomized treatment period (V2-V4) will be carefully evaluated by the investigator for Early Withdrawal on the basis of the potential impact on efficacy or safety evaluations and in the best interest of the subject.

1. Inhaled long acting β_2-agonists.
2. Inhaled fixed combination of corticosteroids and long-acting β_2-agonists (e.g. salmeterol plus fluticasone or formoterol plus budesonide).
3. Inhaled short acting β_2-agonists (other than study "rescue" medication).
4. Inhaled fixed combinations of a short-acting β_2-agonist (SABA) and a short-acting anticholinergic medication (SAMA).
5. Inhaled short-acting anticholinergics.
6. Inhaled long-acting anticholinergics.
7. Oral/IV/IM corticosteroids.
8. Nebulized bronchodilators or corticosteroids.
9. Inhaled corticosteroids other than study background ICS.
10. Non-cardioselective β-blockers.
11. PDE4 inhibitors (e.g. roflumilast).
12. Leukotriene modifiers.
13. Xanthine derivatives (e.g. theophylline).
14. Any drug with known or possible risk of Torsades de Pointes (TdP) or QT interval prolongation (e.g. quinidine, procainamide, amiodarone).

Prior to screening spirometry (Visit 1), the following washout periods must be respected:

Caffeinated substances	6 hours
Inhaled and/or nebulized short-acting β_2-agonists:	6 hours
Inhaled and/or nebulized short-acting muscarinic antagonists:	8 hours
Inhaled combination of short-acting β2-agonists /short-acting muscarinic antagonists:	8 hours
Inhaled corticosteroids (bid):	24 hours
Inhaled long-acting β_2-agonists (bid):	24 hours
Inhaled fixed combinations of ICS/LABAs (bid):	24 hours
Inhaled corticosteroids (qd):	48 hours
Inhaled "ultra long-acting" β_2-agonists (qd):	48 hours
Inhaled fixed combinations of ICS/LABAs (qd):	48 hours
Oral leukotriene modifiers:	72 hours
Inhaled LAMA:	7 days
Xanthine derivatives:	7 days
PDE4 inhibitors	1 month
Oral or parenteral (i.v.) corticosteroid:	1 month
Intramuscular depot corticosteroid:	3 months

Prior to other visits with spirometry (V2 → V4), the following washout periods must be respected:

Inhaled short-acting β_2-agonists:	6 hours
Caffeinated substances:	6 hours

6. TREATMENT(S)

The double-blinded study drug 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

Study drug

Chiesi has patented MODULITE®, a technology for the development of pMDI as HFA solution formulations. Since the non-CFC propellant Norflurane (HFA-134a) has poor solvency properties, ethanol has been included in the formulation to enhance the solubility of the active ingredients (co-solvent). Hydrochloric acid has been added as pH adjuster for the stabilisation of the formulation. All the included excipients are extensively used in pharmaceutical preparations.

- ***CHF 5259 pMDI 6.25µg - Test product***
  Active ingredient: Glycopyrronium bromide 6.25µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: each canister contains 120 doses

- ***CHF 5259 pMDI 12.5µg - Test product***
  Active ingredient: Glycopyrronium bromide 12.5µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: each canister contains 120 doses
- ***CHF 5259 pMDI 25µg - Test product***
  Active ingredient: Glycopyrronium bromide 25µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: each canister contains 120 doses
- ***CHF 5259 pMDI Matched Placebo***
  Active ingredient: None
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: each canister contains 120 doses
- ***QVAR® (HFA beclomethasone dipropionate) Inhalation Aerosol - Background ICS medication for Run in and Treatment Period***
  Active ingredient: beclomethasone dipropionate 80µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: each canister contains 120 doses
- ***SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder) - Reference product***
  Active ingredient: 18µg tiotropium (equivalent to 22.5µg tiotropium bromide monohydrate) per capsule
  Excipient: lactose monohydrate
  Presentation: Blister containing 10 hard capsules

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

An inhaled formulation of glycopyrronium bromide delivered via hydrofluoroalkane (HFA-134a) pressurized metered dose inhaler (CHF 5259 pMDI) under development by Chiesi will be used for the purpose of this phase II dose-ranging study. This formulation uses the Modulite® technology and contains the same excipients as in FOSTER® (fixed combination ICS+LABA available in EU).

The rationale of dose selection in this study is based on the following completed clinical trials and discussions with FDA.

GLYCO study - Part 1 and 2[46]: HFA GB pMDI (CHF 5259) was assessed as a single dose (Part 1) at 12.5, 25, 50, 100 and 200µg/day, and using repeated dosing over 1 week (Part 2) at 12.5, 25 and 50µg bid compared to placebo in 24 and 38 subjects with COPD, respectively.

- In the single dose study, the highest mean FEV_1 and FVC occurred during the first 4h post-inhalation, and for all doses, the mean changes from baseline in FEV_1 were statistically significant at each timepoint up to 6h post-dose, and at some timepoints thereafter. The overall number of patients with at least one TEAE reported was similar across the different doses of CHF 5259 and was lower compared to that observed with placebo. The most frequently reported TEAE was headache. Two subjects were withdrawn from the study due to TEAEs: atrial fibrillation following inhalation of placebo and ventricular extrasystoles

following treatment with 50µg CHF 5259 pMDI. Overall, all doses of GB were safe and well tolerated.

- In the 1-week treatment study, all doses tested demonstrated superiority over placebo (one-sided p <0.001, adjusted for multiplicity) in the primary endpoint of trough FEV_1 at 12h post-dose on Day 7. This difference was clinically significant with the GB 50 and 100µg/day doses (≥ 120mL). Between-dose comparisons revealed statistically significant (p ≤ 0.037) differences in favor of the GB 50 vs the 25µg/day dose on peak and trough FEV_1 on Days 7 and 8; in FEV_1 AUC_{0-12h} on Day 8, in sGAW AUC_{0-12h} and VC AUC_{0-12h} on Day 7. No statistically significant differences were observed between the GB 50 and 100µg/day doses in derived lung function and body plethysmography parameters. Sixteen (44.4%), 12 (35.3%), and 15 (39.5%) subjects had at least one TEAE during treatment with 25, 50, and 100µg/d CHF 5259 pMDI, respectively. Fifteen (42.9%) subjects had at least one TEAE during placebo inhalation and 12 (35.3%) subjects had at least one TEAE during treatment with tiotropium. TEAEs that were reported in more than 2 subjects during any treatment were headache, cough, and back pain, but only headache was reported in more than 2 subjects during any treatment with CHF 5259 pMDI. No SAEs occurred. At Day 1, at 30 minutes time point, the largest mean QTcF increase was 2.4 ms after 12.5µg bid of CHF 5259, and 1.1 ms after 50µg bid. The largest mean QTcF increase was observed at time point 8 h after 50µg bid of CHF 5259 (6.3ms). At Day 7, at 30 minutes time point, the largest mean QTcF increase was 5.8 ms after 12.5µg bid of CHF 5259, but 4.2ms after 50µg bid. The largest mean QTcF increase was observed at time point 3 h after 50µg bid of CHF 5259 (7.9 ms).

TRIPLE 3 study[57]: This multi-center, randomized, double-blind, active controlled, 4-way cross-over, multi-dose study evaluated the efficacy of 3 doses of GB-HFA pMDI 12.5µg (1 inhalation bid) , 25µg (1 inhalation bid) and 25µg (2 inhalations bid) added to FOSTER® (BDP+FF 100/6µg, 2 inhalations bid), compared to FOSTER® alone, in 178 patients with COPD and 30% ≤FEV_1 ,60% and ≥60 mL post-BD (ipratropium, 84µg) partial reversibility. Treatments were for 1 week, separated by 1 week washout period. On the primary endpoint of FEV_1 AUC_{0-12h} normalized by time on Day 7, the addition of HFA GB pMDI at daily doses of 50 and 100µg for 7 days resulted in both a statistically (p<0.001) and clinically significant lung function improvement of 100 and 112mL respectively over FOSTER® alone. The magnitude of improvement with the 25µg/d dose was statistically significant at 87 mL (p<0.001). The difference was statistically significant between the 100µg vs. 25µg/d doses, but not between the 50 and 100µg/d doses. In general, there were no significant advantages with the 100µg over the 50µg daily dose. Overall, TEAEs and TEADRs were reported less frequently during treatment with any FOSTER® + GB combination than in FOSTER® alone. SAEs were reported in 3 patients receiving FOSTER® + GB combination (abscess intestinal on FOSTER® + GB 25µg/d; Bladder transitional cell carcinoma stage II on FOSTER® + GB 50µg/d; and enteritis infectious and acute prerenal failure on FOSTER® + GB 100µg/d. No deaths were reported during the study.

CARSAF study[58]: provided supportive evidence in 191 patients with moderate to severe COPD that HFA GB pMDI 12.5 and 25µg 2 inhalations bid conferred an additional bronchodilator effect when added to FOSTER® (BDP/FF 100/6µg 2 inhalations bid)

TRIPLE 9 (TRIGON study)[53]**:** The efficacy and safety of 4-week treatment with HFA GB pMDI (CHF 5259) 12.5µg/actuation (2 inhalations bid) was investigated in a randomized, double-blind, placebo-controlled, 2-way cross-over study in 100 symptomatic subjects with COPD (post-

BD FEV1 < 60% predicted, BDI focal score ≤10). HFA GB pMDI was superior to placebo in terms of change from baseline in pre-dose (trough) morning FEV_1 on Day 28 (primary efficacy variable), and in FEV_1 AUC_{0-12h} normalized by time on Day 28 (key secondary efficacy variable); and in other lung functions (FVC, IC) and clinical outcome measures (TDI, SGRQ, rescue medication use). No active control was included in this study. Overall, no safety concerns were raised with GB compared to placebo.

These studies supported the conclusion that HFA GB pMDI 50µg/day is the optimal dose to incorporate into the fixed triple inhaler combination program (CHF 5993) that was conducted and filed in Europe.

Following consultation with the US FDA, this planned study will be a longer (6-week), multidose, placebo and active-controlled dose-ranging trial, conducted in subjects with COPD, to satisfy US FDA's recommendations for dose-finding. The study will test 4 doses of CHF 5259 pMDI (6.25, 12.5, 25 and 50µg twice daily) vs placebo and an active comparator SPIRIVA® HANDIHALER® (tiotropium bromide 18µg once daily) in adult subjects with moderate COPD. The chosen doses of glycopyrrolate in CHF 5259 are in close proximity to the doses tested in the US FDA-approved SEEBRI® NEOHALER® inhalation powder development program (15.6µg, 31.2µg, and 62.4µg glycopyrrolate bid; Novartis Pharmaceuticals Corp. East Hanover, NJ),[50] and to the doses tested in a single-dose as part of an on-going investigational program using a co-suspension formulation delivered via pMDI (14.4, 28.8, 57.6, and 115.2µg of glycopyrronium, ex-actuator; Pearl Therapeutics, Inc).[59]

6.2.2 Dosage

6.2.2.1 Background Medication for Run-in and Treatment Periods:

At the screening visit (Visit 1), all eligible subjects who have been receiving an ICS in combination with a LABA or LAMA will be switched to an equipotent dose of QVAR® as run-in / background therapy:

- **QVAR® 80µg *(HFA beclomethasone dipropionate - Teva Respiratory, LLC)***
  1-2 inhalations twice per day (Total daily dose: Beclomethasone dipropionate 160-320µg)

This treatment will be maintained at stable dose and regimen (160-320µg daily) throughout the study from screening until the end of the study.

6.2.2.2 Randomized Treatment Period:

An adequate number of inhalations from Placebo inhalers will be performed to maintain a double blind design:

Treatment A: *CHF 5259 pMDI 6.25µg* – ***CHF 5259 12.5µg Total Daily Dose***

- One inhalation of CHF 5259 pMDI 6.25µg bid plus one inhalation of CHF 5259 pMDI matched placebo bid.

Treatment B: *CHF 5259 pMDI 12.5µg* – ***CHF 5259 25µg Total Daily Dose***

- One inhalation of CHF 5259 pMDI 12.5µg bid plus one inhalation of CHF 5259 pMDI matched placebo bid.

Treatment C: *CHF 5259 pMDI 12.5µg* – ***CHF 5259 50µg Total Daily Dose***

- One inhalation of CHF 5259 pMDI 12.5µg bid plus one inhalation of CHF 5259 pMDI 12.5µg bid.

Treatment D: *CHF 5259 pMDI 25µg* – ***CHF 5259 100µg Total Daily Dose***

- One inhalation of CHF 5259 pMDI 25µg bid plus one inhalation of CHF 5259 pMDI 25µg bid.

Treatment E: *CHF 5259 pMDI Matched Placebo*

- One inhalation of CHF 5259 pMDI matched Placebo bid plus one inhalation of CHF 5259 pMDI matched Placebo bid.

Treatment F (open label arm): SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder), capsules for oral inhalation use, corresponding to 18µg TDD

Two inhalations of the powder contents of a single SPIRIVA capsule (18µg) once daily

6.2.3 Administration

To the extent possible, the time of dosing of study drug 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 *Background ICS Medication Kit for Run-in and Treatment Periods (from Visit 1 to Visit 4):*

At Visit 1 (screening visit), all subjects who have been receiving an ICS in combination with a LABA or LAMA, including those scheduled for Visit 1.1 for a repeat Reversibility test, will be switched to an equipotent dose of QVAR® to cover the 2 week run-in period:

- One commercial pack of QVAR® containing 120 actuations of beclomethasone dipropionate 80µg (total daily dose of 160 or 320µg daily).

At Visit 2 and Visit 3, the Investigator, or designee, will contact the IRT system to dispense to each subject allowed to continue in the study:

- One commercial pack of QVAR® containing 120 actuations of beclomethasone dipropionate 80µg at each of Visit 2 and Visit 3 (total daily dose of 160 or 320µg daily).

QVAR® will be taken only by subjects previously on ICS at time of screening and will be continued during the entire study from Visit 1 to Visit 4. The dose will remain constant throughout the study period.

The run-in/background ICS therapy will be administered daily from Visit 1 to Visit 4 as prescribed by the investigator, immediately after the study drug intake:

- 1-2 inhalations in the morning (between 8-10 am)
- 1-2 inhalations in the evening (between 8-10 pm)

The first dose of run-in/background ICS medication must be administered at hospital/study site at the end of Visit 1.

Subjects issued QVAR® should be instructed to refrain from taking their morning dose of QVAR® before reporting to the study site at V1.1, V2, V3 and V4. During the randomized treatment periods (on visits 2, 3 and 4), QVAR® (if prescribed) should be taken at the clinic immediately after the study drug intake.

6.2.3.2 Randomized Treatment Period (from Visit 2 to Visit 4):

At randomization visit (Visit 2), after the confirmation of the eligibility, the subject will be randomized to one of the following treatment arms.

For Treatment Arms A, B, C, D and E (*CHF-5259 pMDI treatments and placebo*), each subject will receive one box at Visit 2 and one box at Visit 3 containing two pMDI inhalers of randomized medication: one canister plus actuator will be labeled with number 1 and the other one with number 2.

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

Morning administration (between 8-10 am):
- ➔ One inhalation from the inhaler numbered 1
- ➔ One inhalation from the inhaler numbered 2

Evening administration (between 8-10 pm):
- ➔ One inhalation from the inhaler numbered 1
- ➔ One inhalation from the inhaler numbered 2

For Treatment Arm F (*Open Label arm*), each subject will receive one SPIRIVA® HANDIHALER® commercial pack carton at Visit 2 and one commercial pack carton at Visit 3 containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HANDIHALER® inhalation device.
The study drug will be administered once-a-day (in the morning):

Morning administration (between 8-10 am):
- ➔ Two inhalations of the powder contents of a single SPIRIVA® capsule (18µg) once daily

The same kit box will be used for morning and evening administration, where evening administration is applicable.

Administration will be done according to the package instruction leaflets. A package leaflet will be included with study drugs in local language.

The first administration of study drug will take place at the study site on visit 2 (V2) before the background ICS medication intake (if applicable), under medical supervision.

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

On study visit days, study drug should not be taken before coming to the clinic.

6.2.3.3 Rescue Medication

COPD Rescue Medication – Open Label:
Albuterol HFA (a short-acting β2-adrenergic receptor agonist, or SABA): Each canister contains 200 actuations, at 90µg/actuation. At V1, the investigator will prescribe and supply each subject (through local procurement) with 1 canister of albuterol to use as COPD rescue treatment for the treatment of bronchospasm, as 1-2 inhalations Q 4-6h as needed (prn). Albuterol may be re-supplied by the investigator to the subject at subsequent visits during the study as needed, based on assessment of used and remaining doses. The maximum dose allowed is 8 puffs per day. *If the subject's needs exceed 4 puffs/day on ≥ 2 consecutive days during the run-in period, or uses ≥ 4 puffs/day above their run-in average on ≥ 2 consecutive days during the treatment period, or uses ≥8 puffs/day on any given day, he/she must contact the investigator*. A minimum period of 6 hours should elapse between the use of rescue medication and the spirometric measurements. ***Albuterol will not be provided by the study sponsor.***

6.2.4 Subject Training

During the Visit 1 (screening), each subject will receive one training kit containing pMDI placebo (see description in Section 6.3.1). With this kit, the subject will be instructed on how to use the pMDI according to the instructions for use. The training kit will be kept at the site by the Investigator (i.e., will not be dispensed to the subjects) and they will be used again at Visit 2 (randomization) in order to check again the proper use of the inhaler and if needed training can be repeated at following clinical visits.

The Investigator will instruct subjects on how to use QVAR® and SPIRIVA® by reading together and showing the QVAR® and SPIRIVA® leaflets to the subjects. At each visit, the morning administration of QVAR® and SPIRIVA® will be closely supervised by the Investigator to check whether it is conducted in accordance with the leaflet instruction.

6.3 Packaging

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

The Sponsor will supply the background ICS medication (QVAR®, for Run-in and the randomized treatment periods) and study drugs for the randomized treatment period.

6.3.1 Training Kits

The training kit is one box. The box will contain one CHF 5259 pMDI placebo.

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

6.3.2 Background medication kit for run-in and treatment period

- *Primary packaging***:** 1 canister containing 120 actuations, with a beige plastic actuator with a dose counter and gray dust cap[60]
- *Secondary packaging*: 1 commercial box containing 1 canister of QVAR® 80µg Inhalation Aerosol

6.3.3 Treatment period

For Treatment Arms A, B, C, D, and E (CHF 5259 pMDI treatments and placebo), each subject will receive one box at Visit 2 and one box at Visit 3.

Each box will contain 2 pMDI inhalers of CHF 5259 pMDI 6.25µg, 12.5µg, 25µg **or** placebo.

- *Primary packaging*: 1 canister plus standard actuator
- *Secondary packaging*: box containing 2 canisters plus 2 standard actuators

For Treatment F (*Open Label arm treatment*), at randomization (Visit 2) and Visit 3, each subject will be provided with 1 SPIRIVA® inhalation powder commercial box and 1 HANDIHALER® inhalation device.

- *Primary packaging*: blister containing 10 hard capsules
- *Secondary packaging*: box containing 3 blisters

6.3.4 Rescue medication

Starting at Visit 1 the rescue medication (albuterol) will be prescribed and provided by the Investigator to all subjects (purchased locally) for use throughout the study, according to the manufacturer's label.

6.4 Labeling

All the supplies provided by Chiesi will be labeled according to the 21 CFR 312.6 of the GMP as well as to local law and regulatory requirements.

6.5 Treatment Allocation

A balanced block randomization scheme stratified by US Region (based on US Census Bureau Regions: West, Midwest, South, Northeast) will be prepared via a computerized system. Subjects will be centrally assigned to one of the six treatment arms at the end of the run-in period through an IRT system (Interactive Response Technology) with a 1:1:1:1:1:1 ratio.

The IRT will allocate the subject to a certain treatment group using a list-based randomization algorithm and will assign the study drug kit number corresponding to the treatment group assigned to the subject. The IRT will also generate a confirmation after every IRT transaction is performed.
The Investigator will call the IRT at each visit (from pre-screening to follow-up call) to record the subject number at pre-screening, to enroll and randomize the subject, to obtain the medication kit numbers and to register the subject status in the system. Detailed instructions for use of IRT will be provided to the site.

6.6 Treatment Code

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

The medication list will be provided to the labeling facility but will not be available to subjects, Investigators, monitors or employees of the center involved in the management of the trial before unblinding of the data, unless in case of emergency.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list nor to the medication list.

In case of emergency, unblinding of the treatment code will be done through the IRT. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the Investigators. The Investigator will be provided with username and password for randomization purposes and separate username and password to unblind the study drug in case of emergency situation, where he/she considers essential to know what treatment the subject was taking. The IRT will promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.

Users from Chiesi Corporate Pharmacovigilance will have their own passwords to unblind subjects in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees.
The subject will be provided with a card with the phone numbers of study site and Investigator to be called in case of emergency.

6.7 Treatment Compliance

Compliance will be evaluated on the basis of the information recorded daily by the subject on the digital platform (e-diary) as well as the information recorded in the eCRF during the treatment visits.

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 65-135 % will be taken into account for a satisfactory level of compliance.
Subjects with compliance level less than 75% will receive additional coaching during study Visits 2 and 3.

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 and humidity.

Background ICS Medication Kit for Run-in and Treatment Periods:
The boxes of QVAR® must be stored not above 25˚C (77˚F) either by Pharmacist/Investigator at the study site and by subjects at home.

***Study drug for randomized Treatment Period*:**
CHF 5259 pMDI active and matched placebo.

The pMDI kits must be stored between 2˚C (36˚F) and 8°C (46˚F) by Pharmacist/Investigator at the study site. At the clinic visit, the kit to be dispensed must be removed from the refrigerator and the canister(s) should be taken out of the mouthpiece(s) (actuators) and warmed with the hands for a few minutes before administration to the subject. The canister(s) should never be warmed by artificial means.

The subject should never inhale cold medication.

Once dispensed, the subjects will be instructed to keep the boxes at home at ambient temperature not above 25°C (77˚F) but not in the refrigerator. At this temperature condition, the residual shelf life of the pMDI kits will be two months (**60 days**). Therefore, **the Pharmacist/Investigator at the study site must write the use-by-date on the kit labels** once the kits are removed from the refrigerator, before assigning to the subjects. The **use-by-date corresponds to the dispensing date plus 2 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

Open Label arm treatment: Spiriva powder for inhalation

SPIRIVA® HANDIHALER®: Commercial pack must be stored at ambient temperature, **not above 25˚C (77˚F)** either by Pharmacist/Investigator at the study site and by subjects at home.

***pMDI for training*:**
The pMDI training kits must be kept at site and not dispensed to the subjects. The pMDI training kits must be stored between 2˚C (36˚F) and 8°C (46˚F) by Pharmacist/Investigator at the study site.

At the screening visit, the kit to be dispensed must be removed from the refrigerator and the canister(s) should be taken out of the mouthpiece(s) (actuators) and warmed with the hands for a few minutes before administration to the subject. The canister(s) should never be warmed by artificial means.

The subject should never inhale cold medication.

Once used, the pMDI training kit must be kept at site at ambient temperature not above 25°C (77˚F), but not in the refrigerator. At this temperature condition, the residual shelf life of the pMDI will be three months (**90 days**). Therefore, **the Pharmacist/Investigator at the study site must write the use-by-date on the kit labels** once the pMDI is removed from the refrigerator, before using it. The **use-by-date corresponds to the dispensing date plus 3 months.** Please note that the use-by-date must not exceed the total shelf life of the product. Subject will use the same training kit at screening and randomization.

The site must check the Min/Max temperatures once daily for adequate storage of ambient kits.

The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation to the requirement for storage will be promptly reported and Sponsor shall assess if the affected study drugs can still be used.

6.9 Drug Accountability

The Investigator, or the designated/authorized representative, is responsible for the management of all the study drugs to be used for the study. Study drugs that should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study drugs.
An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study drug(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. The study drugs supplied, used or unused, will be returned to the designated distribution center under Sponsor's responsibility. 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 the subject to the General Practitioner.

7. STUDY PLAN

7.1 Study Schedule

Table 1: Study Flow Diagram

	Pre-Screening	Screening	Treatment period			Follow-Up	ET
Visits	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	
Time (Weeks)		-2	0	3	6	7	Early Termination
Window (days)			±2	±2	±2	±2	
Informed consent form	✓						
IRT – visit confirmation call	✓	✓	✓	✓	✓	✓	✓
Demographic data	✓						
BDI questionnaire		✓	✓				
TDI questionnaire				✓	✓		✓
COPD Assessment Test (CAT)		✓	✓				
Vital signs (SBP/DBP) [a]		✓	✓	✓	✓		✓
Weight and Height		✓					
Physical examination		✓			✓		✓
Medical history/Previous medication		✓					
Concomitant medications		✓	✓	✓	✓	✓	✓
Smoking Status		✓	✓	✓	✓		✓
12-lead ECG [b]		✓	✓	✓	✓		✓
Spirometry (pre & post BD) [c]		✓					
Pre-dose spirometry [d]			✓	✓	✓		✓
Post-dose serial spirometry 12h [e]			✓		✓		
Hematology and Blood Chemistry		✓			✓		✓
Serum pregnancy test [f]		✓			✓		✓
Urinary pregnancy test [f]		✓	✓	✓			
Inclusion / exclusion criteria		✓	✓				
Eligibility recheck [g]			✓				
Training for use of pMDI Inhalers and e-diary		✓	✓				
Dispensation of rescue albuterol [h]		✓					
24-hour holter recording [i]			✓		✓		
Schedule next visit	✓	✓	✓	✓	✓		✓
Randomization			✓				
e-diary completion		✓ **(daily)**					
Study drug dispensation (D) / Return (R) and Accountability			D	D/R	R		R
Subject diary dispensation (D) /return (R)		D	D/R	D/R	R		R
Dispensation (D) of background ICS (QVAR®) [j] / return (R)		D	D/R	D/R	R		R
Adverse Events assessment		✓	✓	✓	✓	✓	✓
Check for COPD Exacerbations		✓	✓	✓	✓	✓	✓

[a] At V2 and V4: SBP/DBP will be measured pre-dose and at 30 mins, 1.5h, 3.5h, 7h and 11h post-dose. At V1, V3 and Early Termination: SBP/DBP will be measured before the expected time of study drug administration.

[b] At V2 and V4: Local 12-lead ECG will be done prior to study drug intake and at 1.5h post-dose. At V1, V3 and Early Termination: Local 12-lead ECG will be done before the expected time of study drug administration.

[c] At V1: Spirometry (FVC maneuver) will be carried out before and 30 to 45 minutes after the inhalation of 84µg of ipratropium pMDI.

[d] At V2, V3, V4 and ET: Pre-dose FEV_1, FVC at T -45'and T -15' before the expected time of study drug administration. IC will be measured only once at T-45' using SVC maneuver, before the FVC maneuver.

[e] At V2 and V4: Post-dose serial spirometry (FEV_1, FVC) at T15', T30', T45', T1h, T2h, T3h, T4h, T6h, T8h, T10h, T11.5h, T12h.

[f] In women of childbearing potential only.

[g] Eligibility recheck only for exclusion criteria #1, 3, 4, 5, 10, 11 and inclusion criteria # 6-8.

[h] One commercial albuterol HFA MDI (200 actuations) will be prescribed and supplied by the investigator to each subject at V1, and resupplied as needed at V2-V3 based on assessment of doses used between visits.

[i] At V2: the 24h digital device will be placed the day before the visit and will be removed the day after the visit. At V4: the 24-hour digital device will be placed the day before the visit and will be removed upon arrival to the site (before any assessment).

[j] all subjects who have been receiving an ICS in combination with a LABA or LAMA at V1 will be switched to an equipotent dose of QVAR® and continued on same dose until V4 or Early Termination.

7.1.1 Visit 0 (Pre-screening visit)

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

- The written informed consent signed by the subject will be collected after the study has been fully explained by the investigator. The investigator or his/her designee should provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
- Demographic data will be collected.
- Instructions will be given to the subject for the screening visit (Visit 1) such as **concomitant medications to be withdrawn** prior to the visit.
- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to allocate a unique subject's number before discharge.
- A **subject card** with the Investigator's contact details will be handed out to the subject.
- An **appointment** for the screening visit (Visit 1) will be scheduled in the morning before 9:00 am, **within 1 week**. The appointment day may vary depending on the washout period necessary for the subject prior to the screening visit. Subjects will be instructed:
  - ➔ **To fast overnight (at least 10 hours) for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ **Not to take albuterol or caffeinated substances in the 6 hours preceeding the next visit, and to abstain from all non-permitted medications** in accordance with section 5.2. unless absolutely necessary

7.1.2 Visit 1 (Screening visit /Week -2)

A screening visit will be carried out in the morning (before 9:00 am) in order to identify eligible consenting subjects for the study.

If any of the washouts for non-permitted medications have not been respected, the visit needs to be re-scheduled within 2 days. Only one re-scheduling is allowed. If any of the relevant washouts is not respected again on the rescheduled visit, the subject will be discontinued and recorded in the IRT and eCRF as screen failure.

The following procedures will take place:

- The BDI questionnaire will be completed and BDI focal score will be assessed. Only subjects with a BDI focal score ≤ 10 are eligible (see section 7.2.1).
- The COPD Assessment Test (CAT) will be completed to evaluate if the subject's symptoms burden (see section 7.2.3). Subjects at screening with a CAT score ≥10 are eligible.
- Check for COPD exacerbations.
- Weight and height will be recorded.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator and background ICS (QVAR®) administration, after 5 minutes of rest, in resting position (see section 7.2.4).
- A 12-lead ECG will be performed before spirometry, bronchodilator and background ICS (QVAR®) administration, after 5 minutes of rest (see section 7.2.6). A subject will not be eligible in case of QTcF >450 ms for males or QTcF >470 ms for females, or in case of

abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the subject according to investigator's judgment.

- A medical history and smoking status will be recorded. Previous medications in the past 3 months must be collected.
- Concomitant medications taken by the subject will be recorded. Intake of non-permitted medication constitutes a non-eligibility criterion for enrollment in the study.
- A full physical examination will be performed including assessment of oral candidiasis.
- A urine pregnancy test in women with childbearing potential will be performed.
- A blood sample will be collected before bronchodilator administration, after an overnight fasting (at least 10h), for the assessments of (see section 7.2.9):
  - standard hematology and blood chemistry;
  - a serum β-HCG test will be performed in women of childbearing potential.

  The blood samples must be collected **after vital signs and 12-lead ECG recording**.
  In case of non-interpretable data, another determination must be performed as soon as possible and prior to Visit 2 (randomization visit).
- Pre-bronchodilator spirometry will be performed: the subjects will have to perform a FVC maneuver to assess parameters (FEV_1, FVC) (see section 7.2.8).
- Post-bronchodilator spirometry will be performed: FEV_1 and FVC test within 30-45 minutes after intake of 4 puffs (4 x 21µg) of ATROVENT® HFA (ipratropium bromide HFA) will be performed. To be eligible, the following 3 criteria must be met:
  - post-bronchodilator FEV_1 must be ≥40% and <80% of the subject's predicted normal value, and
  - $FEV_1/FVC < 0.7$, and
  - a post-bronchodilator increase in FEV1 ≥5% from baseline (reversibility)

  If the reversibility criterion is not met, this test can be performed **once more before Visit 2** after an appropriate washout from bronchodilators.
- Any AE occurred since the signature of the informed consent will be checked and recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the subject's medical history, unless its start date is after the informed consent signature date. In this case, it will be recorded as an adverse event.
- Conduct a review of all Inclusion and Exclusion criteria. If the subject is not eligible, the investigator will access the IRT to record the status of the subject as a screen failure. At the discretion of the investigator, a subject who fails to meet all inclusion/exclusion criteria (screening failure) at V1 may be re-screened again, up to one additional time, after 1 month from the date of the initial screening failure. A re-screened subject will be treated as a new subject.
- If the subject is eligible for entry into the run-in period, he/she will be trained, with training kits containing placebo, to the proper use of pMDI (see section 6.2.4). The corresponding tear-off label will be placed in the subject specific dispensation tracking form.
- Subject will be instructed on how to record the medications intake (background ICS and rescue), respiratory symptoms, and adverse events in the electronic Diary (see section 7.2.11).

- The investigator will access IRT also in order to obtain the background ICS medication (one commercial box containing 1 canister of QVAR®) to be dispensed to the subject (previously on ICS at time of screening), together with instructions for use. Subject will be instructed to inhale 1 or 2 puffs (depending on the equipotent dose to previous ICS therapy, see section 5.1) of run-in medication in the morning (before 10:00 am) and 1 or 2 puffs in the evening (before 10:00 pm). **The first administration of background ICS medication (QVAR®) will take place at the clinic visit (before 10:00 am) under medical supervision**.
- Subject will be instructed to stop the non-permitted COPD medications in accordance with section 5.2.
- Rescue albuterol, for as needed use, will be dispensed by the Investigator. Subjects will keep this rescue medication throughout the study period (will be re-supplied if needed); nevertheless subject will be instructed to bring this medication at each visit in order to check the need for replacement.

Before discharge

- **Background ICS medication for the run-in period** (QVAR®) will be dispensed for those subjects previously receiving an ICS and the corresponding tear-off label will be placed in the subject specific dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (eCRF). The subjects will be instructed to inhale 1 or 2 puffs in the morning and 1 or 2 puffs in the evening of the canister in the run-in kit **with the exception of the morning of the next clinic visit (Visit 2)**. Subject will be also instructed to take albuterol as rescue if necessary.
- **An electronic diary will be dispensed.** Subject must complete the Diary each day, until Visit 2. It is important to ensure good compliance of the subject to the use of the diary during the run-in period.
- **An appointment for the day before Visit 2 (in order to place the 24hr Holter) will be scheduled.**
- **An appointment for Visit 2** will be made within 2 weeks (±2 days) time from Visit 1, in the morning (at approximately the same time of the day) before 9:00 am. Subjects will be instructed:
  - ➔ **Not to take albuterol or caffeinated substances in the 6 hours preceding the next visit, and to abstain from all non-permitted medications in accordance with section 5.2** unless absolutely necessary.
  - ➔ **For those subjects prescribed QVAR® : Not to take background ICS medication (QVAR®) in the morning of the next visit.**
  - ➔ To **bring back the run-in and rescue medications** (in their boxes), and the **electronic Diary.**

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

Reminder: Subject must visit clinic one day prior to Visit 2, in order to have the ambulatory 24-hour digital Holter placed and activated. On Visit 2, the Holter recording will continue for

24-hours after morning study drug administration (until the following morning). Subject will return to the clinic the day after Visit 2 in order to have the Holter removed.

The Visit 2 will start in the morning (before 9:00 am).

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, the washout for non-permitted medications has not been respected, or run-in ICS medication (QVAR®) has been taken in the morning of the visit (prior to spirometry), the visit needs to be re-scheduled to take place within 2 days. Only one re-scheduling is allowed. If any of these relevant washouts is not respected again on the morning of the re-scheduled visit, the subject will be discontinued and recorded as screen failure in the IRT and eCRF.

The following pre-dose procedures will be performed:

- The BDI questionnaire will be completed and BDI focal score will be assessed. Only subjects with a BDI focal score ≤ 10 are eligible (see section 7.2.1).
- The COPD Assessment Test (CAT) will be completed to evaluate if the subject's burden of COPD symptoms (see section 7.2.3). Subjects at screening with a CAT score ≥10 are eligible.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.4).
- 12-lead ECG will be measured before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.6)
- Changes of concomitant medications being taken by the subject will be recorded. In case of intake of any non-permitted concomitant medication, the subject will be withdrawn from the study and recorded as screen failure in the IRT. (see section 5.2).
- A urine pregnancy test in women with childbearing potential will be performed.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Background ICS medication dispensed for the run-in period (QVAR®) will be collected.
- The investigator will check the electronic Diary to confirm compliance. **In case of lack of compliance, instructions on how to complete the diary will be given again to the subject** (see section 7.2.11)**.**
- The occurrence of COPD exacerbations will be evaluated (see section 7.2.12) and data recorded in the eCRF. In case of exacerbation during the run-in, the subject will not be randomized (see also sections 5) and recorded as screen failure in the IRT.
- The occurrence of other adverse events will be checked and recorded if any.
- The proper use of pressurized metered dose inhaler will be checked and subject will be retrained on the usage of the pMDI using the Training kit previously assigned at Visit 1 (see section 6.2.4).
- Eligibility criteria will be rechecked: (Inclusion criteria # 6-8 and Exclusion criteria # 1, 3, 4, 5, 10 and 11). At the discretion of the investigator, a subject who fails to meet all inclusion/exclusion criteria (screening failure) at V2 may be re-screened again, up to one

additional time, after 1 month from the date of the initial screening failure. A re-screened subject will be treated as a new subject.

For eligible subjects:

- The subject will be randomized and the study treatment will be allocated according to the central randomization system. Investigator will access IRT in order to obtain the appropriate kit number for the first 3-week treatment period.
- Pre-dose spirometry: pre-dose spirometry measurements will then be performed to assess FEV_1, FVC and IC at -45 min and to assess FEV1 and FVC also at -15 min prior to first dose of study drug. These measurements will constitute the baseline values (see section 7.2.8).
- For subjects randomized to receive open-label **SPIRIVA® HandiHaler®**, the Investigator will instruct subjects on how to use SPIRIVA® by reading together and showing the FDA-approved Patient Information Leaflet to the subjects, in accordance with section 6.2.4.
- **The administration of the 1st dose of study drug will take place at the clinic visit (before 10:00 am) under supervision of the Investigator.** The corresponding tear-off labels will be placed in the dispensation tracking form and the kit number will be recorded in the corresponding electronic CRF (eCRF). The use-by-date must be filled-in on the labels. Drug administration will be done according to section 6.2.3. For those receiving background ICS, the morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at Visit 1.
- Post-dose Vital signs (SBP and DBP) will be measured after 5 minutes of rest at 30 minutes, 1.5h, 3.5h, 7h, 11h post-dose (see section 7.2.4).
- Post-dose 12-lead ECG will be measured after 5 minutes of rest at 1.5h post-dose (see section 7.2.6)
- Post-dose spirometry (FEV_1, FVC) will be performed at T15', T30', T45', T1h, T2h, T3h T4h, T6h, T8h, T10h, T11.5h, T12h. For each time point, spirometry consists of three acceptable maneuvers (see sections 7.2.8).

Before discharge

- **Study drug** will be dispensed to the subject together with instructions for use. Drug administration will be done according to section 6.2.3. Subject will be instructed to take albuterol as rescue if necessary. Investigator will also dispense albuterol if needed.
- **The electronic Diary will be returned to the subject.** Subject will be reminded to continue to complete the electronic Diary each day until Visit 3.
- **An appointment for Visit 3** will be made at 3 weeks (±2 days) from Visit 2 (at approximately the same time as Visit 2, before 9:00 am). The subject will be instructed:
  - ➔ To **bring back** the **study drug** (in the box) and the Diary at the next visit.
  - ➔ **Not to take albuterol or caffeinated substances in the 6 hours preceding the next visit**, **and to abstain from all non-permitted medications in accordance with section 5.2** unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study drug before coming to the next clinic visit** (it will be administered at the clinic visit).

➔ For those subjects prescribed **QVAR®** at Visit 1: **Not to take the morning dose of QVAR® before coming to the next clinic visit** (it will be administered at the clinic visit, immediately after the dose of study drug).

- The Investigator will access IRT in order to record completion of the study visit.

7.1.4 Visit 3 (Week 3 of Treatment Period)

The Visit 3 will start in the morning (before 9:00 am).

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, or the washout for non-permitted medications has not been respected or the study drug has been taken on the morning of the visit (prior to spirometry), the visit needs to be re-scheduled to take place within 2 days. Only one re-scheduling is allowed. If any of these relevant washouts is not respected again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the intake and the number of puffs of rescue medication or of the medication with washout not respected will be recorded in the eCRF.

The following pre-dose procedures will be performed:

- The TDI questionnaire will be completed (see section 7.2.2).
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.4).
- 12-lead ECG will be measured before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.6)
- Changes of concomitant medications being taken by the subject will be recorded. In case of intake of any non-permitted concomitant medication, the subject will be withdrawn from the study and recorded as Early Termination in the IRT (see section 5.2).
- A urine pregnancy test in women with childbearing potential will be performed (see section 7.2.10).
- Pre-dose spirometry: pre-dose spirometry measurements will be then performed to assess FEV_1, FVC and IC at -45 min and to assess FEV_1 and FVC also at -15 min prior to morning dose of study drug (see section 7.2.8).
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check in the e-diary to confirm compliance. **In case of lack of compliance, instructions on how to complete the diary will be given again to the subject** (see section 7.2.11)**.**
- The investigator will collect study drug dispensed at Visit 2 and perform accountability.
- The occurrence of COPD exacerbations will be evaluated (see section 7.2.12) and data recorded in the eCRF. In case a COPD exacerbation occurs post-randomization, the subject will be discontinued from the study and an Early Termination visit performed and recorded in the eCRF and the IRT.
- The occurrence of other adverse events will be checked and recorded if any.

- **The morning dose of study medication will be administered at the clinic (before 10:00 am) under supervision of the Investigator from the kit dispensed at Visit 2.** For those subjects prescribed QVAR® at Visit 1: morning dose will be administered at the clinic visit, immediately after the dose of study drug.
- The Investigator will access IRT to record completion of the study visit.

Before discharge

- **Study drug** (Visit 3 kit) will be dispensed to the subject together with instructions for use. Subject will be instructed to take albuterol as rescue if necessary. For administration of study medications, subject will be given the same instructions as the ones given at Visit 2.
- **The electronic Diary will be returned to the subject.** Subject must continue to complete the e-diary each day until Visit 4.
- **An appointment for the day before Visit 4 (in order to place the 24hr Holter) will be scheduled.**
- **An appointment for Visit 4** will be made within 3 weeks from Visit 3 (at approximately the same time as other visits, before 9:00 am). **The time window should not exceed 6 weeks (±2 days) from Visit 2**.

The subject will be instructed:

- ➔ To **bring back** the **study drug** (in the box), and the e-diary at the next visit.
- ➔ **Not to take albuterol or caffeinated substances in the 6 hours preceding the next visit**, **and to abstain from all non-permitted medications in accordance with section 5.2** unless absolutely necessary.
- ➔ **Not to take the morning dose of the study drug before coming to the clinic visit** (it will be administered at the clinic visit).
- ➔ For those subjects prescribed QVAR® at Visit 1: **Not to take the morning dose of QVAR® before coming to the next clinic visit** (it will be administered at the clinic visit, immediately after the dose of study drug).
- ➔ To fast overnight (at least 10 hours) for the next visit in order to perform blood sampling (only water is allowed).

7.1.5 Visit 4 (Week 6 of Treatment Period)

Reminder: Subject must visit clinic one day prior to Visit 4, in order to have the ambulatory 24-hour digital Holter placed and activated. Monitoring will continue for 24-hours until the following morning (Visit 4 date) when subject will have the Holter removed.

The Visit 4 will start in the morning (before 9:00 am).

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, or the washout for non-permitted medications has not been respected or the study drug has been taken on the morning of the visit (prior to spirometry), the visit needs to be re-scheduled to take place within 2 days. Only one re-scheduling is allowed. If any of these relevant washouts is not respected again on the morning of the re-scheduled visit, the visit will be performed anyway and the time of the

intake and the number of puffs of rescue medication or of the medication with washout not respected will be recorded in the eCRF.

The following pre-dose procedures will be performed:

- The TDI questionnaire will be filled in by the subject and TDI score will be assessed before the study treatment dose intake (see section 7.2.2).
- Pre-dose vital signs (SBP and DBP) will be measured, before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug, after 5 minutes of rest (see section 7.2.4).
- 12-lead ECG will be measured before before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest, in resting position
- Pre-dose spirometry: pre-dose spirometry measurements will then be performed to assess FEV_1, FVC and IC at -45 min and to assess FEV_1 and FVC also at -15 min prior to last dose of study drug (see section 7.2.8).
- Changes of concomitant medications being taken by the subject will be recorded.
- A full physical examination will be performed including assessment of oral candidiasis.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- The investigator will check the e-diary to confirm compliance, and assess adverse events.
- The study drug (in the box) provided at Visit 3 will be collected.
- The occurrence of COPD exacerbations and other adverse events will be evaluated and recorded in the eCRF (if any) (see section 7.2.12).
- A blood sample will be collected prior to study drug administration and **after an overnight fasting** for the assessments of (see section 7.2.9):
  - standard hematology and blood chemistry;
  - a serum β-HCG test will be performed in women of childbearing potential.

  The blood sample must be collected **after the vital signs and 12-lead ECG recording**.
  In case of non-interpretable data, another determination must be performed as soon as possible.
- The 24hr Holter device will be disconnected (but the dual snap leads kept until completion of post-dose ECGs).
- **The morning dose of study medication will be administered at the clinic (before 10:00 am) under supervision of the Investigator from the kit dispensed at Visit 3. This will be the last dose of study drug. Subjects maintained on QVAR® since Visit 1 will also receive their last dose at the clinic visit, immediately after the dose of study drug.**
- Post-dose vital signs (SBP and DBP) will be measured at 30 minutes, 1.5h, 3.5h, 7h, 11h post-dose, after 5 minutes of rest (see section 7.2.4).
- Post-dose 12-lead ECG will be measured at 1.5hr post dosing, after 5 minutes of rest, in resting position (see section 7.2.6)
- Post-dose spirometry (FEV_1, FVC) will be performed T15', T30', T45',T1h, T2h, T3h, T4h, T6h, T8h, T10h, T11.5h, T12h. For each time point, spirometry consists in three acceptable maneuvers (see sections 7.2.7).
- Investigator will access IRT in order to record completion of the study visit.

Before discharge at Visit 4

- **All study material (study drug, background ICS treatment (QVAR®), rescue medications, e-diary) will be collected.**
- The investigator will prescribe each subject an appropriate treatment or restore their initial therapy or refer them to their primary care physician.
- An appointment will be made in 1 week time for the follow-up phone call.

7.1.6 Follow-up Phone Call (Visit 5)

A safety follow up phone call will be performed by the investigator or designated staff no later than 1 week after the final visit (Visit 4) or Early Termination Visit to check the status of unresolved AEs and to record any COPD exacerbation or new AEs that may have occurred after Visit 4, as well as related concomitant medications. Investigator will access IRT in order to record completion of the study visit.

7.1.7 Early Termination Visit

If a subject prematurely discontinues the study after randomization, all efforts will be made to perform an Early Termination visit which will include the following assessments, providing there are no safety issues for the subject and in accordance with the subject's agreement:

- All study material (Study and rescue medications, subject diary) will be collected
- Site to update IRT
- The TDI questionnaire will be completed.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.4).
- A 12-lead ECG will be performed before spirometry, bronchodilator, or study drug administration, after 5 minutes of rest (see section 7.2.6).
- The investigator will check in the electronic diary portal whether subject has been transmitting data daily since previous visit.
- Changes of smoking status will be recorded; pharmacological smoking cessation therapies started during the study will be recorded as concomitant medications.
- Changes of concomitant medications being taken by the subject will be recorded.
- A full physical examination will be performed, including assessment of oral candidiasis.
- A blood sample will be collected, after an overnight fasting (at least 10h, when possible), for the assessments of (see section 7.2.9):
  - standard hematology and blood chemistry;
  - a serum β-HCG test in women of childbearing potential.
  - The blood samples must be collected **after vital signs and 12-lead ECG recording**.
- The occurrence of COPD exacerbation or other adverse events will be checked and recorded if any.
- Pre-dose spirometry: pre-dose spirometry measurements will then be performed to assess FEV_1, FVC and IC at -45 min and to assess FEV1 and FVC also at -15 min prior to the

expected time for the morning dose of study drug (at approximately the same time as done on V2).

- The investigator will prescribe each subject an appropriate treatment or restore their initial therapy or refer them to their primary care physician.
- An appointment will be made in 1 week time for the follow-up phone call.

7.2 Investigations (by order of conduct):

7.2.1 BDI Questionnaire

The Baseline Dyspnea Index (BDI)[61] is a validated, interviewer-administered rating of severity of dyspnea. It provides a multidimensional measurement of dyspnea that evokes dyspnea in activities of daily living, in symptomatic individuals during the last 2 weeks. The BDI consists of 24 items divided into 3 domains: Functional Impairment, Magnitude of Task, and Magnitude of Effort. Each category is rated on a 5-point scale from 0 (very severe) to 4 (no impairment), with a total score ranging from 0-12.

The same investigator or designee will interview the subject for the BDI and TDI during the study period. BDI will be assessed at V1 and the morning of V2.

7.2.2 TDI Questionnaire

The Transitional Dyspnea Index (TDI) is a validated,[62] interviewer-administered questionnaire that measures changes in dyspnea severity from the baseline established by the BDI. TDI consists of the same 24 items and 3 domains as the BDI, with the same 2-week recall period. Each category is rated by 7 grades ranging from -3 (major deterioration) to +3 (major improvement), with a total score ranging from -9 to +9. The MCID is considered a change of ≥1 unit [63].
The same investigator or designee will interview the subject for the BDI and TDI during the study period. TDI will be assessed at V3, V4 and Early Termination.

7.2.3 COPD Assessment Test (CAT™)

The CAT is a subject-completed validated questionnaire [64][65] to measure the global impact of COPD on a subject's life in an objective way and to monitor changes over time. It consists of 8 items scored on a scale of 1 to 5, with a total score range of 0-40. A higher score denotes a more severe impact of COPD on the subject's life. No target score represents the best achievable outcome. Although an MCID has not been determined, mapping to the SGRQ suggests a group-level MCID of 1.6 units. Experts also have suggested that a score < 10 = low impact; 10-20 = medium impact, 21-30 = high impact, and > 30 a very high impact.

The CAT has been used in the GOLD 2011 and GOLD 2017 Reports. A CAT score of ≥ 10 points is considered an indicator of a high symptom burden (GOLD category B & D)[2] and a threshold for initiating regular treatment of COPD symptoms including dyspnea.[66]

The subject will complete the CAT at V1 and V2.

7.2.4 Vital Signs

Systolic and diastolic blood pressure will be measured before spirometry, bronchodilator, QVAR® or study drug administration, after 5 min rest in resting position. At Visit 2 and Visit 4, the measurements will be done pre-dose and at 30 mins, 1.5h, 3.5h, 7h and 11h post-dose. At Visit 1, Visit 3 and Early Termination, the measurements will be done before the expected time of study drug administration. SBP and DBP have to be assessed twice with at least 2 minutes elapsing between the two measurements. The final SBP and DBP values to be considered are the means of the two measurements respectively. These measurements will be repeated at all visits at the same time.

7.2.5 Physical Exam and assessment of oral candidiasis

A full physical examination will be performed at V1, V4 and Early Termination, including an assessment of oral candidiasis.

Oropharyngeal candidiasis is a condition commonly associated with the use of ICS, and is cause by the Candida fungus. This side effect may be attributed to the topical effects of these medications on the oral mucosa.[26] Generalized immunosuppressive and anti-inflammatory effects of steroids are thought to play a major role in the pathogenesis of candidiasis.[67] Asthmatics who are using β-2 agonists show a decreased salivary flow rate, which in turn can be associated with higher oral Candida counts.[68]

The subject's mouth and throat will be visually inspected by the investigator at every study visit to look for the presence of characteristic-looking white lesions / oral thrush. If deemed necessary by the investigator to confirm the diagnosis, the suspected lesion should be swabbed/scraped with a sterile cotton and the tissue sample sent to a laboratory for microscopic and culture identification.

Appropriate treatment of oropharyngeal thrush (e.g. using topical rinses and oral anti-fungal agents) can be prescribed at the discretion of the study investigator as deemed necessary throughout the study.

7.2.6 12-lead ECG

A 12-lead ECG will be performed at visits 1, 2, 3 and 4 to verify the subject's cardiac safety parameters and his/her eligibility. At Visit 2 and Visit 4, the ECG will be done prior to study drug intake and at 1.5h post-dose. At V1, V3 and Early Termination, the ECG will be done before the expected time of study drug administration. Subjects will receive instructions to refrain from intake of caffeinated beverages or foods past midnight before the visit date. Prior to recording, the subject should be at rest for at least 5 minutes.

Safety ECGs (10-sec strip) will be taken using the site's own instrument. Standard electrode placement will be used for these ECGs, including placing the limb leads; dual snap electrodes will be used for the precordial leads. The ECG will be evaluated by the investigator/sub-investigator on-site for any abnormality.

The QTc interval value will be calculated using the Fridericia formula (Fridericia-corrected QTc= $\frac{QT}{\sqrt[3]{RR}}$). It will be calculated automatically by the ECG recorder. Heart rate (HR), PR and QRS interval values will be also evaluated from ECG at all visits.

ECGs with computerized protocol interpretation are considered normal if:

- 40 ≤ Heart rate ≤ 110 bpm,
- 120 ms ≤ PR interval ≤ 210 ms
- QRS interval ≤ 120 ms

For eligible subjects, QTcF values must be QTcF ≤ 450 (for males) and 470 ms (for females) (as per Exclusion Criterion #11).

In case of relevant ECG abnormalities, the inclusion of the subject will be judged by the investigator. If there are any doubts the Investigator may consult the study's medical monitor. The final decision for enrolment would be documented in the Medical File of the subject. Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at the following visits, in the medical opinion of the investigator, will be reported as adverse events in the eCRF.

7.2.7 24-hour digital ECG Holter Recorder

Subjects will have an ambulatory 24-hour digital Holter recording for 24 hours before and 24 hours after the 1st dose of study drug (Visit 2) and for 24 hours before the last dose of study drug (Visit 4). Two sets of analysis will be conducted for this trial: arrhythmia and electrocardiographic analysis.
For the arrhythmia analysis, the 12-lead Holter recording will be scanned for the presence or absence of arrhythmia including, but not limited to:

- Atrial fibrillation,
- Sinus Pauses,
- PACs,
- SVT,
- PVCs,
- Ventricular tachycardia,
- AV Blocks.

Details of arrhythmia analysis and how the Holter variables are calculated will be provided in the Holter Analysis Plan.

The ECGs database will be made from discrete 12-lead ECGs (10-sec recording duration each) that will be extracted from the Holter recording. To facilitate data quality, the subject will be asked to assume a supine posture and remain quiet, but awake, beginning at 10 minutes before the nominal extraction time and then for five minutes afterward. For each subject, there will be:

- 3 nominal extraction times in the day before Visit 2 (time-matched with the post-study drug extraction times on Visit 2);
- 3 extraction times at +5min, +55min, and +2.5h after 1st dose of study drug on Visit 2; and
- 3 extraction times at +5min, +55min, and +2.5h after the morning dose of study drug on the day before Visit 4.

ECGs taken from the Holter recording will have the limb leads placed on the torso. At each nominal timepoint, ECGs will be extracted in triplicate, separated by 30-second intervals.

In addition, HR will be extracted and the average calculated on hourly basis during each 24 hour monitoring period.

A detailed description and training on the 24hr Holter procedure will be provided by [redacted] ([redacted]).

7.2.8 Pulmonary Function Test

All pulmonary function tests including FEV_1 and FVC will be performed in accordance with ATS/ERS spirometry criteria,[69] using standardized equipment provided by a Contract Research Organization. The specific procedures for centralized spirometry will be provided to the investigator by the centralized spirometry company ([redacted]). The investigator and/or qualified delegate will be trained by [redacted] on the calibration and testing procedures for the spirometer prior to the scheduled first subject's visit.

Pulmonary function measurements will be done with subjects in sitting position with the nose clipped after at least 10 minutes rest. Calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to any spirometry maneuvers and the reports must be kept with the source study documents.

Throughout the study (after randomization), the clinic visits and the lung function measurements will start in the morning between 7:00 and 9:00 a.m. preferably, approximately at the same time of the day for each subject.

The following parameters will be recorded at Visits 1, 2, 3 and 4 or Early Termination Visit:

- Forced Expiratory Volume in the 1st second (FEV_1, L)
  - The volume exhaled during the first second of a forced expiratory maneuver starting from the level of total lung capacity. FEV_1 is decreased in obstructive lung diseases.
- Forced Vital Capacity (FVC, L)
  - The maximal volume of gas that can be exhaled from full inhalation by exhaling as forcefully and rapidly as possible.

The following parameter will be recorded at Visits 2, 3 and 4 or Early Termination Visit:

- Inspiratory Capacity (IC, L)
  - The volume of air that can be inspired without hesitation, after a normal, relaxed expiration. It is the sum of the tidal volume and the inspiratory reserve volume. It equates to the difference between the Total Lung Capacity (TLC) and Functional Residual Capacity (FRC, or the amount of gas remaining at the end of normal quiet respiration). IC is decreased in obstructive lung diseases.

The following parameter will be recorded at Visit 1:

- FEV_1/FVC also called Tiffeneau-Pinelli index, is a calculated ratio used in the diagnosis of obstructive and restrictive lung disease. It represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration.[70]

Note: some additional standard parameters (for instance PEF, $FEF_{25-75\%}$) will be assessed by the spirometer during the visit only for the investigator's information purpose.

Predicted normal value for FEV_1 will be calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations.[71]
Subjects should be relaxed (shoulders down and relaxed) and asked to breathe regularly for several breaths until the end expiratory lung volume is stable (this usually requires at least three tidal maneuvers). They are then urged to take a deep breath to TLC (Total Lung Capacity) with no hesitation. FEV_1 and FVC will be recorded at each clinic visit from a forced vital capacity maneuver. The highest FVC and the highest FEV_1 (values corrected for BTPS) will be selected after examining the data from all of the usable spirograms, even if they do not come from the same maneuver. An adequate test requires a minimum of 3 acceptable FVC maneuvers.

Acceptable repeatability is achieved when the difference between the largest and the next largest FEV_1 and FVC is ≤ 150mL (≤ 100 mL when FVC is < 1L).[72] If these criteria are not met in 3 maneuvers, additional trials should be attempted, up to, but usually no more than 8.

IC will be assessed at -45 min pre-dose at V2, V3, V4 and Early Termination using the Slow Vital Capacity (SVC) maneuver. The average of at least 3 acceptable slow vital capacity (SVC) maneuvers will be recorded. Acceptable IC repeatability is considered when the coefficient of variation for all IC values is ≤ 6%. **The SVC maneuvers must be performed before the FVC maneuvers used to assess FEV_1.**

In the rare event where a subject shows a progressive decline in FEV_1 or FVC with a cumulative drop exceeding 20% of start value, the test procedure should be terminated in the interest of subject safety.

The rescue medication (albuterol) must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit. If the subject requires rescue medication within this timeframe, the visit should be rescheduled once within the three next days.

During the serial 12-hour spirometry, rescue medication (albuterol) use should be avoided as much as possible, and administered only under investigator's oversight. The serial measurements may continue after rescue treatment intake, if there is no safety risk to the subject. Details including exact time of the intake of rescue medication during the study visits must be recorded in the eCRF.

The run-in medication (QVAR®) or the study drug should not be taken on the morning of the visit. If taken, the measurements should be deferred (i.e. the visit needs to be re-scheduled to take place within 2 days). Repeated failure (more than once) to meet the washout window at Visit 1 and Visit 2 will result in a screening failure and the subject's permanent discontinuation from the study. All efforts need to be taken to respect the washout periods for Visit 3 and Visit 4.

To optimize the treatment response in this study, subjects will be required to demonstrate a bronchodilator response (airway reversibility) to ipratropium at Visit 1. Baseline (pre-bronchodilator) spirometry will be assessed before administration of the bronchodilator, and reversibility (post-bronchodilator) will be assessed with triplicate FVC maneuvers (as described above) at 30-45 minutes after administration of 4 separate doses of ATROVENT® HFA (ipratropium bromide HFA) Inhalation Aerosol (21µg/ actuation, total dose = 84µg) at 30-sec intervals.[73][74][75] The following inclusion criteria must be met at Visit 1:

- A post-bronchodilator FEV1/FVC ratio of < 0.7, and
- a post-bronchodilator FEV1 ≥40% and <80% of the predicted normal value.
- An increase in FEV_1 of ≥5% from pre-bronchodilator value constitutes a positive reversibility test.[59][76] In case the reversibility threshold is not met at screening, the test can be performed once before randomization.

At Visit 2, Visit 3, and Visit 4, spirometry will be conducted at 45 and 15 minutes pre-morning dose. At Visit 2 and Visit 4, spirometry will be conducted also at 15, 30, 45 minutes, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h and 12h post-morning dose. Time excursions for serial spirometry assessments should be avoided and kept to a minimum as follows: ±5 min for assessments done pre-dose and during the first hour post-dose; ±10 min during hours 2-6 and 11.5 – 12 post-dose; and ±15 min during hours 8-10 post-dose.

At the Early Termination Visit, spirometry will be conducted at 45 and 15 minutes before the expected time of dosing (the subject will not be dosed) only.

7.2.9 Blood Hematology and Chemistry

Blood samples of approximately 12 mL will be collected for hematology and serum chemistry at Visit 1 (screening), Visit 4 and Early Termination in the morning, after an overnight fasting of at least 10 hours (only water is allowed during the night). The blood withdrawal should be performed after vital signs and 12-lead ECG recording and before administration of ipratropium, QVAR® or study drug. An additional blood sample will be collected for serum pregnancy test in women of childbearing potential at these Visits.

The following evaluations will be performed using a central laboratory:

- Hematology test: red blood cells count (RBC), white blood cells count (WBC) and differential, total hemoglobin (Hb), hematocrit (Hct), and platelets count (PLT).
- Serum chemistry test: blood urea nitrogen (BUN), cholesterol, triglycerides, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatases, albumin, total proteins, and electrolytes (sodium, potassium, calcium, and chloride).
- Fasting blood glucose
- Serum pregnancy test (serum β-hCG) in women of child-bearing potential.

Blood collection and sample preparation will be performed according to procedures provided by the laboratory which will be in charge to transmit the results to the Investigator. In case of clinically significant abnormality, findings will be reported in the medical history (if occurred at Visit 1), or as an Adverse Event (if occurred after Visit 1).

7.2.10 Urine Pregnancy Test

A urine pregnancy test will be administered using a commercial urine hCG pregnancy test strip. This test kit is used to obtain a quick (within a few minutes), visual, qualitative result for the early detection of pregnancy at Visit 1, Visit 2 and Visit 3.

7.2.11 Daily Subject Diary

Daily symptom assessments offers several potential advantages over periodic assessments, including 1) reduced recall bias, providing a prospective, daily account of symptom severity, 2) information on day-to-day symptom variability, 3) analytical flexibility, allowing the evaluation of symptoms over various time intervals.

To date, however, there is no standardized method for evaluating respiratory symptoms of stable COPD.[77][78] Formerly known as the EXACT-Respiratory Symptoms Scale, the Evaluating Respiratory Symptom in COPD (E-RS™: COPD) instrument uses 11 respiratory symptom items from the 14-item questionnaire, and has been shown to be a reliable, valid and responsive measure of respiratory symptom severity in stable COPD, suitable for use in clinical trials. The E-RS total score quantifies respiratory symptom severity and 3 domains: breathlessness, cough and sputum, and chest symptoms. [redacted] Higher E-RS scores indicate more severe symptoms and a declining total score indicates health improvement.

Using the electronic diary dispensed at V1, subjects will be instructed to enter once daily a record of their COPD symptom scores and for each 24h period as follows:

- Subjects are instructed to complete the E-RS diary each evening just prior to bedtime, reflecting back on their experiences "today".[79]
- Enter daily number of study drug doses taken.
- Enter daily number of albuterol rescue doses taken.
- Record daily all doses of QVAR® (only for subjects on background ICS).

7.2.12 Handling of COPD Exacerbations:

Subjects who experience a moderate or severe COPD exacerbation any time after screening (V1) as defined below will be instructed to visit the site as soon as possible for an Early Termination Visit and will be withdrawn permanently from the study. The Adverse Event form will be completed and appropriate medical management of the COPD exacerbation according to standard medical practice will be ensured by the study investigator, with the aim to preserve the research subject's wellbeing at all times.

A COPD exacerbation is defined as "a sustained worsening of the subject's condition (increased dyspnoea, cough, wheeze, sputum purulence/volume), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication including prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalization."
The exacerbations will be classified as:

- *Moderate exacerbations* will be defined as worsening symptoms of COPD necessitating treatment with SABD plus oral corticosteroids and/or antibiotics;
- *Severe exacerbations* will be similar events that necessitate visits to the emergency room, require hospital admission or result in death. Severe exacerbations may also be associated with acute respiratory failure.[2][80]

8. EFFICACY ASSESSMENTS

Primary efficacy variable

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 6

Secondary efficacy variables

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1
- Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time and in FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Week 6
- Change from baseline in FVC $AUC_{0\text{-}12h}$ normalized by time, in FVC $AUC_{0\text{-}4h}$ normalized by time and in FVC $peak_{0\text{-}4h}$ at Day 1 and Week 6
- Time to onset of action (change from baseline in post-dose $FEV_1 \geq 100$ mL[15][81]) at Day 1
- Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 3 and Week 6
- Change from baseline in pre-dose morning IC at Week 3 and Week 6
- TDI focal score at Week 3 and Week 6
- TDI response (TDI focal score ≥ 1) at Week 3 and Week 6
- Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period
- Change from baseline in average use of rescue medication (number of puffs/day) during inter-visit periods and entire treatment period
- Change from baseline in average E-RS total score and domain scores during inter-visit periods and entire treatment period

9. SAFETY ASSESSMENTS

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure)
- 24-hour digital Holter ECG parameters (HR, QTcF, QRS, PR)
- 24-hour HR average, minimum and maximum and hourly average HR
- 24-hour Holter ECG abnormal findings
- Standard blood chemistry and hematology

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 responses to an investigational medicinal product related to any dose administered".

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

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

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)** 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 anemia, 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 hospitalization or prolongation of existing hospitalization**

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 hospitalization are AEs. If a complication prolongs hospitalization, 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 hospitalization 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 hospitalization; 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 infection agent in also considered a serious adverse reaction.

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

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (Investigator's Brochure for CHF 5259 pMDI or US-FDA approved Product Information for SPIRIVA® HANDIHALER®), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labeled 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 drug(s);
- Mechanism of action of the study drug;
- Class effects;
- Other treatments-concomitant or previous;
- Withdrawal of study drug(s);
- Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study drug (or concomitant);
- Protocol related process.

10.5 Action taken with the study drug due to the AE

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

10.6 Other actions taken

- Specific therapy/medication
- Concomitant procedure
- Not applicable

10.7 Outcome

Each Adverse Event must be rated by choosing among:

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

10.8 Recording Adverse Events

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

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

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

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on the 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 [redacted] 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 [redacted] 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.	Safety E-mail
[redacted]	[redacted] (office) [redacted] (mobile)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be reported if the investigator becomes aware of them.
- Up to the closure of the site, SAE reports should be reported to the [redacted] Safety Contact. New serious adverse event occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

The Sponsor or designated CRO will report adverse events to the regulatory authorities in compliance with the timelines and standards of reporting according to local regulations (Guidance for industry and Investigators-Safety Reporting Requirements for INDs and BA/BE studies, December 2012). All suspected unexpected serious adverse reactions (SUSARs), which occur with the investigational medicinal product or marketed active comparator, within or outside the concerned clinical trial, will be reported by the Sponsor or designated CRO to regulatory authorities, as required, as well as to the Investigators and Central IRB, if applicable, by MedWatch/CIOMS form. The Investigator (or Sponsor/CRO where required) must inform the IRB per Sponsor instruction upon receipt of the SUSAR notification. An IND and/or NDA Safety Report will be submitted to regulatory authorities unblinded. Participating Investigators and IRB will receive a blinded IND Safety Report, unless otherwise specified.

With regard to regulations in force for Pharmacovigilance, the Investigator must fulfil 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 [redacted]/Chiesi 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 [redacted]/Chiesi Safety Contact as soon as available, retaining a copy on site.
- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be followed with due diligence until the outcome of the pregnancy is known. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail/via Monitor to the [redacted]/Chiesi Safety Contact using the paper Pregnancy Report Form. The [redacted] 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 [redacted]/Chiesi 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 medication received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.

- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in /rescue medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee. All subjects who sign the informed consent will be databased. For subjects who are screened but not randomized, a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, prior medications, adverse events and concomitant medications if any. Subject's questionnaire (BDI, TDI, CAT) answers will be databased.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, Concomitant Procedures and Adverse Events will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC).

External data (IRT, Spirometry, Holter ECG, electronic Diary, Central Laboratory) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities.
After cleaning of data, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened and the planned statistical analysis will be performed. Only authorised and well-documented updates to the study data are possible after database lock.
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

The sample size has been calculated to evaluate the superiority of CHF 5259 pMDI at different doses over placebo in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 6.

A total of 594 evaluable subjects (99 per group) will provide 80% power to detect a mean difference of 120 mL between each dose of CHF 5259 pMDI and placebo [51][52] at a two-sided significance level of 0.0125 (since 4 dose levels will be tested, the Bonferroni adjustment has been taken into account: 0.0125 = 0.05/4), assuming a standard deviation of 250 mL.

Since four dose levels will be tested, the Edwards and Berry method will be used to control the family-wise Type I error rate at the 0.05 (two-sided) level. In the sample size calculation, the Bonferroni adjustment of the significance level has been taken into account (0.0125 = 0.05/4). This will ensure the required power for each test, since the Edwards and Berry method is uniformly more powerful than the Bonferroni procedure.

Considering a non-evaluable rate of 15%, a total of approximately 702 subjects (117 per group) will be randomized.

12.2 Populations for Analysis

- **Safety population:** all randomized subjects who receive at least one dose of study drug.
- **Intention-to-Treat population (ITT):** all randomized subjects who receive at least one dose of the study drug and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after the baseline.
- **Per-protocol population (PP):** all subjects from the ITT population without any major protocol deviation (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.

Since the superiority of CHF 5259 pMDI at different doses over placebo will be tested, the primary efficacy analysis will be based on the ITT population. The primary efficacy analysis will be also performed on the PP population for sensitivity purposes.

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

The safety variables will be analyzed in the Safety population.

In case of deviation between randomized treatment and treatment actually received, the treatment actually received will be used in the safety analyses (i.e. an as-treated analysis will be performed).

12.3 Statistical Analysis

A detailed statistical analysis plan will be described in a separate document. The plan might be reviewed and updated as a result of the blind review of the data and will be finalized before breaking the blind.

12.3.1 Descriptive Statistics

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

Descriptive statistics for quantitative variables will include n (the number of non-missing values), mean, SD, median, minimum and maximum values.

Categorical variables will be summarized by using frequency count and percent distribution.

12.3.2 Missing data

- For the primary efficacy analysis, a linear mixed model for repeated measures will be used to handle missing data. Under the Missing At Random (MAR) assumption, this model provides an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment for the full study duration. This approach addresses efficacy (or de jure) hypotheses, estimating the causal effects of the initially randomized drug if taken as directed (in contrast with effectiveness, or de facto, hypotheses, evaluating the effect of the drug as actually taken) [82]. The efficacy estimand is considered appropriate in the context of a phase II study aiming at characterising dose-response.[83][84][85]
- If one of the spirometry measurements at 45 min and 15 min pre-dose is not available, then the non-missing measurement will be taken as the pre-dose value (corresponding to time 0 for the calculation of AUC). If no measurement is available, then the pre-dose value will be considered as missing.
- In the calculation of AUC normalized by time, missing values will be replaced as follows:
  - If the pre-dose value is not available, the entire curve will be considered as missing;
  - Single, isolated missing values (not pre-dose or last value) will be replaced by linear interpolation using the adjacent values;
  - If the value at 12 h post-dose is missing, it will be replaced by the value at 11.5 h;
  - In case of two or more consecutive missing values or more than three missing values, the entire curve will be missing.
- In case of rescue medication intake during the serial spirometry (from pre-dose to 12 h post-dose), all spirometry data recorded from the time of rescue medication intake onwards for 6 hours will be excluded from the analysis of primary efficacy endpoint on PP population.
- In case of less than three missing values among post-dose spirometry measurements at 45 min, 1h, 2h, 3h, 4h, the peak value will be calculated as the maximum of the available post-dose values over the time interval considered (4h). In case of three or more missing values, the peak value will be considered as missing.
- In case of at least one post-dose timepoint with change from baseline in $FEV_1 \geq 100$ mL, then Time to onset of action will be equal to the first post-dose timepoint with change from baseline in $FEV_1 \geq 100$ mL in the time interval considered (12 h). In case of no timepoint with change from baseline in $FEV_1 \geq 100$ mL, and less than four missing values among post-dose spirometry measurements at 15 min, 30 min, 45 min, 1h, 2h, 3h and 4h, then Time to onset of action will be equal to the last available post-dose timepoint with non-missing data and the subject will be considered as censored in the analysis.
- A minimum of 7 days with available measurements will be required for each inter-visit period (including run-in period) to consider the following variables as non-missing: percentage of rescue medication-free days, average use of rescue medication, average E-RS total score and domain scores.
- The BDI and the TDI focal scores will be considered as missing if at least one response will be included among the following: “W”, “X”, “Y”, “Z”.
- In the responder analysis, subjects with missing data at the relevant visit will be considered as non-responders.

Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed during the review of the data. Decisions will be fully documented in the Data Review Report.

12.3.3 Subject demographics and baseline characteristics

The following variables will be summarized by treatment group on the ITT population (and on the Safety or PP populations, if relevant): demographic characteristics, medical history and concomitant diseases, previous and concomitant medications, efficacy and safety parameters at screening and/or at baseline.

12.3.4 Primary efficacy variables

Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time will be analyzed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, US regions and smoking status at screening as fixed effects, and the baseline value (average of the pre-dose FEV_1 measurements on Day 1) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed.

The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 5259 pMDI and placebo at Week 6 will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry.[86] At each dose level, the superiority of CHF 5259 pMDI will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favouring CHF 5259 pMDI.

All the other comparisons between treatments will be performed as secondary efficacy analyses with no multiplicity adjustment.

12.3.5 Secondary efficacy variables

No multiplicity adjustment will be performed in the secondary efficacy analyses.

- For change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1, the adjusted means in each treatment group and the adjusted mean differences between treatments at Day 1 will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis.
- Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time and in FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Week 6 and change from baseline in pre-dose morning FEV_1 at Week 3 and Week 6 will be analyzed using the same model as for the primary efficacy variable.
- Change from baseline in FVC $AUC_{0\text{-}12h}$ normalized by time, in FVC $AUC_{0\text{-}4h}$ normalized by time and in FVC $peak_{0\text{-}4h}$ at Day 1 and Week 6 will be analyzed using a similar model as the one used for the primary efficacy analysis.
- Time to onset of action (i.e., change from baseline in post-dose $FEV_1 \geq 100$ mL[15][81]) at Day 1 will be analyzed using a Cox proportional hazard model including treatment, US regions and smoking status at screening as fixed effects, and baseline (average of the pre-dose FEV_1 measurements on Day 1) as covariate. A Kaplan-Meier plot will be presented.
- Change from baseline in pre-dose morning IC at Week 3 and Week 6 will be analyzed using a similar model as the one used for the primary efficacy analysis.
- TDI focal score at Week 3 and Week 6 will be analyzed using a similar model as the one used for the primary efficacy analysis.

- TDI response at Week 3 and Week 6 will be analyzed using a logistic regression model including treatment, US regions and smoking status at screening as fixed effects and baseline (BDI [Baseline Dyspnea Index] focal score assessed on Day 1) as a covariate.
- Change from baseline to each inter-visit period in percentage of rescue medication-free days, in average use of rescue medication and in average E-RS total score and domain scores will be analyzed using a similar model as the one used for the primary efficacy analysis. The inter-visit period will be considered instead of visit in the model. Comparison between treatments over the entire treatment period will also be derived from this model.

12.3.6 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 Events (TEAEs). Any adverse event started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. Pre-treatment adverse events will be listed only.

The number of TEAEs and the number and percentage of subjects who experienced at least one TEAE will be presented by treatment for all AEs, ADRs, serious AEs, serious ADRs, severe AEs, AEs leading to study discontinuation and AEs leading to death. Summaries will be presented overall and by system organ class and preferred term based on the MedDRA dictionary.

Vital signs

Vital signs (systolic and diastolic blood pressure) and their changes from baseline (pre-dose on Day 1) and from pre-dose on Week 6 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

Holter

ECG parameters extracted from Holter (HR, QTcF, QRS and PR) and their changes from baseline (time-matched on day before V2) will be summarized for all timepoints on Day 1 and Week 6 by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline).

Change from baseline (time-matched on day before V2) in ECG parameters extracted from Holter (HR, QTcF, QRS and PR) will be analyzed using a linear mixed model for repeated measurements including treatment, timepoint, treatment by timepoint interaction, US regions and smoking status at screening as fixed effects, and the baseline value (time-matched on day before V2), baseline by timepoint interaction and time-averaged baseline as covariates. An unstructured covariance matrix will be assumed.

The number and the percentage of subjects with a

- QTcF >450 ms (males only), >470 ms (females only) or >480 ms (males only) and >500 ms (males and females)
- change from baseline (time-matched on day before V2) in QTcF >30 ms and >60 ms

at each post-dose timepoint and at any post-dose timepoint will be presented by treatment group.

24-hour HR average, minimum and maximum extracted from the Holter and their changes from baseline (day before V2) will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

Change from baseline (day before V2) in 24-hour HR average, minimum and maximum extracted from Holter will be analyzed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, US regions and smoking status at screening as fixed effects, and the baseline value (day before V2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed.

Hourly average HR will be summarized by treatment using descriptive statistics and the 95% CI of the mean.
The number and the percentage of subjects with abnormal findings (including supraventricular arrhythmias, ventricular arrhythmias and non-sustained ventricular tachycardia) in the 24-hour Holter will be summarized by treatment group.

Laboratory parameters

Shift tables from screening to the end of treatment, based on normal ranges, will be presented by treatment group for the laboratory parameters.

12.3.7 Interim analysis

Interim analysis not planned.

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States FDA regulations, the ICH E6 GCP guidelines, the Declaration of Helsinki, and other local regulations as applicable.

14. INFORMED CONSENT

Written informed consent will be obtained from all subjects as per IRB guidelines before any study-related procedures (including any pretreatment procedures) are performed. The investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or IEC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8, and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or IEC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigator (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB- or IEC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

15. INSTUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE

This protocol, the written informed consent form, and any materials presented to the subject shall be submitted to the IRB or IEC identified with this responsibility. Notification in writing of approval must come from the IRB or IEC chairman or secretary to the investigator, either as a letter or as a copy of the appropriate section of the IRB or IEC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or IEC member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB or IEC as required by the governing body. The IRB or IEC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or IEC all changes in research (protocol amendments), and will not make such changes without IRB or IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or IEC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or IEC and must agree to share all such documents and reports with the Sponsor.

16. DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

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

17. STUDY MONITORING

Monitoring will be performed by [redacted] who has been designated by Chiesi. It is understood that the monitor(s) will contact and visit the Investigator/center before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data (source data is any data that is recorded elsewhere to the case report forms), provided that subject confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study;
- to review the compliance with the study protocol;
- to discuss any emergent problem;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the eCRFs 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 national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

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

19. INSURANCE AND INDEMNITY

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

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

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi. The Investigator must assure the 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/Institutional Review Board providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

At the end of the trial a summary of the clinical study report will be provided, as required, to all Ethics Committees/Institutional Review Boards, to the Competent Authority of the EU Member State or US concerned and to Investigators.

23. RECORD RETENTION

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

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

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

24. PUBLICATION OF RESULTS

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

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APPENDIX I

A 6-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 5259 pMDI (glycopyrronium bromide) in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Product: CHF 5259 pMDI (glycopyrronium bromide)

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

Approval of Clinical Study Protocol by the Principal Investigator:

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

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

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

The undersigned agrees that the trial will be carried out in conformity with the Code of Federal Regulations (21 CFR 50) and the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), Good Clinical Practices 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

Center No.: _____

_____ _____
Signature Date

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

APPENDIX II

MINIMUM LIST OF SOURCE DATA REQUIRED

The following list should be considered as an example (not exhaustive list):

- *Subjects demography file*
- *Subjects medical file*
- *Study number*
- *Subject identity/number*
- *Randomization number*
- *Medical and surgery history*
- *Previous and concomitant medications*
- *Weight, height*
- *Date of informed consent signature*
- *Date of specific study visits*
- *Labels of study drugs*
- *Examination or assessments carried out during the study*
- *Laboratory reports*
- *Adverse events / serious adverse events*
- *If subject is withdrawn, reason for withdrawal*