CCD-05993AA3-03

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CLINICAL STUDY PROTOCOL

IND No : 133680

A randomized, double-blind, placebo and active-controlled, incomplete block cross-over, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 1531 pMDI (Formoterol Fumarate) in asthmatic subjects

Version No.: 3.0
Date: 31Oct2017

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 Readily available in case of medical questions
MONITORING CRO	[redacted]
CENTRAL LABORATORY OF ANALYSIS:	[redacted]
OTHER CENTRAL TECHNICAL LABORATORIES	Spirometry: [redacted] Central ECG: [redacted]

VERSION HISTORY

Version	Date	Change History
1.0	*16Mar2017*	
2.0	*24Jul2017*	Clarified non-permitted concomitant medications, other changes as specified by Summary of Changes document.
3.0	*31Oct2017*	Increasing FEV_1 range, allowing concomitant treatment with INS and antihistamines for the treatment of allergy symptoms, other changes as specified by Summary of Changes document.

PROTOCOL OUTLINE

Study title	A randomized, double-blind, placebo and active-controlled, incomplete block cross-over, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 1531 pMDI (Formoterol Fumarate) in asthmatic subjects.
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 1531 pMDI (Formoterol Fumarate)
Center(s)	Multi-center, in approximately 15 sites
Indication	Asthma
Study design	Randomized, double-blind, placebo and active-controlled, incomplete block, cross-over, dose ranging study.
Study phase	II
Objectives	***Primary objective:*** To evaluate the efficacy of CHF 1531 pMDI by comparison with placebo in terms of acute bronchodilator effect (change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14). ***Secondary objectives:*** • To evaluate the effect of CHF 1531 pMDI on other lung function parameters and clinical outcome measures. • To assess the safety and the tolerability of the study drug.
Treatment duration	4 treatment periods of 2 weeks, each separate by a 2-week washout period.
Test product dose/route/regimen	**CHF 1531 pMDI: formoterol fumarate administered via pressurized metered dose inhaler (pMDI), available in 3µg per inhalation (FF 3), 6µg per inhalation (FF 6), 12µg per inhalation (FF 12).** Treatment A: FF 6µg Total Daily Dose ➢ FF 3µg per inhalation, 1 inhalation bid* Treatment B: FF 12µg Total Daily Dose ➢ FF 6µg per inhalation, 1 inhalation bid* Treatment C: FF 24µg Total Daily Dose ➢ FF 6µg per inhalation, 2 inhalations bid Treatment D: FF 48µg Total Daily Dose ➢ FF 12µg 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 1531 pMDI** Treatment E: Matched placebo, 2 inhalations bid

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- **PERFOROMIST®: Formoterol Fumarate 20µg / 2mL vial inhalation solution administered by nebulization**

Treatment F: FF 40µg Total Daily Dose
- FF 20µg/2mL, 1 unit-dose vial bid

PERFOROMIST® will be administered as open label.
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<tr><td>Number of subjects</td><td>A total of approximately 60 subjects will be randomized in order to reach a total of 51 completed and evaluable subjects, considering a non-evaluable rate of approximately 15%.</td></tr>
<tr><td>Study population</td><td>Subjects with poorly controlled or uncontrolled moderate asthma on low/medium doses of inhaled corticosteroids.</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td>

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 ≥18 and ≤75 years who have signed an Informed Consent Form prior to initiation of any study-related procedure.
2. A diagnosis of asthma as defined in the GINA Report, 2016, documented for at least 1 year prior to screening.
3. Poorly controlled or uncontrolled asthma evidenced by a score ≥1.5 on the Asthma Control Questionnaire 7 © (ACQ-7) this criterion must be met at screening and at randomization visits).
4. A pre-bronchodilator FEV_1 ≥60% and <85% of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits.
5. Subjects with a positive response to a reversibility test at screening, defined as ΔFEV_1 ≥12% and ≥200mL over baseline within 30 minutes after inhaling 4 puffs of albuterol HFA 90µg/actuation.
   Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomization.
6. Use of ICS (low/medium dose according to GINA Report, 2016) with or without a LABD for 3 months (at a stable dose in the last 4 weeks) before screening visit.

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

**(Table adapted from GINA Report, 2016)*
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ICS/LABA for Asthma	ICS/LABA Daily Dose	QVAR® recommended Daily Dose
ADVAIR® DISKUS® 100/50	100/50µg bid	80µg bid
ADVAIR® DISKUS® 250/50	250/50µg bid	160µg bid
ADVAIR® DISKUS® 500/50	500/50µg bid†	N/A
ADVAIR® HFA 45/21	90/42µg bid	80µg bid
ADVAIR® HFA 115/21	230/42µg bid	160µg bid
ADVAIR® HFA 230/21	460/42µg bid†	N/A
BREO® ELLIPTA® 100/25	100/25µg qd	40-80µg bid
BREO® ELLIPTA® 200/25	200/25µg qd	80-160µg bid
DULERA® 100/5	200/10µg bid	160µg bid
DULERA® 200/5	400/10µg bid†	N/A
SYMBICORT® 80/4.5	160/9µg bid	80µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

† *This ICS/LABA daily dose is **not permitted** as its ICS component exceeds Medium Daily Dose equivalent of QVAR®.*

7. A cooperative attitude and ability to demonstrate correct use of the diary, peak flow meter and pMDI inhaler.

At randomization (V2), inclusion criteria # 3, 4 and 7 should also be re-checked.

Exclusion Criteria:

If a patient 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 a 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 drugs.

   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 Visit 1, Visit 9 and at the early termination visit, urinary pregnancy test will be performed at Visit 1- 8.
   Women of non-childbearing potential defined as physiologically

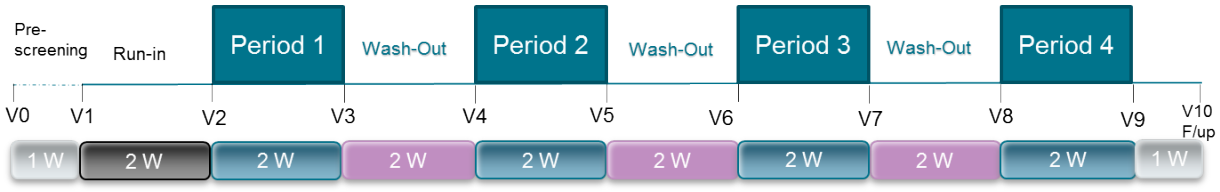
	incapable of becoming pregnant: post-menopausal (defined as no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) are eligible. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to central laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy. 2. Subjects who suffer from COPD as defined by the GOLD Report, 2017, or are suspected of having Asthma COPD Overlap Syndrome (ACOS) as described in the GINA Report, 2016. 3. Inability to carry out pulmonary function testing, to comply with study procedures or with study drug intake. 4. Current smokers or ex-smokers (tobacco, vapor cigarettes, marijuana) with a smoking history of >10 pack-years or having stopped smoking one year or less prior to screening visit. 5. History of life-threatening asthma, clinically significant uncontrolled disease or respiratory infection. 6. An asthma exacerbation requiring oral/intravenous corticosteroids ≤ 30 days, intramuscular depot corticosteroid ≤3 months or hospitalization within 6 months prior to screening. 7. Subjects with unresolved bacterial or viral respiratory tract, sinus, or middle ear infection affecting asthma status within 2 weeks prior to screening. 8. Subjects who received a vaccination within 2 weeks prior to screening or during the run-in. 9. Subjects with oral candidiasis at screening and at randomization. 10. Subjects with any clinically significant, uncontrolled condition 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 conditions which may impact the feasibility or the results of the study according to Investigator's judgment. 11. Subjects with serum potassium levels <3.5 mEq/L (or 3.5 mmol/L) at screening. 12. Subjects who have 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. 13. Subjects who have a clinically significant abnormal 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgment. 14. Subjects whose 12-lead ECG shows Fridericia's corrected QT interval (QTcF) >450ms for males or QTcF >470ms for females at screening or

	randomization visits (criterion not applicable for subjects with a pacemaker or permanent atrial fibrillation). 15. Subjects with known intolerance/hypersensitivity or contra-indication to treatment with inhaled β_2-adrenergic receptor agonists, corticosteroids or propellant gases/excipients. 16. Subjects with concomitant immunosuppressive therapy, use of oral or injected corticosteroids, anti-IgE, anti-IL5 or other monoclonal or polyclonal antibodies within 12 weeks prior to screening. 17. Use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening. 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 screening visit or have a planned surgery during the trial. Exclusion criteria # 1, 3, 8, 9, 13 and 14 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 followed during 4 treatment periods of 2 weeks each separated by 2 weeks washout period. The study will last approximately 18 weeks for each patient and a total of 10 clinic visits will be performed during the study, including a follow-up phone call/visit *(see the flow chart below)*. ▪ A pre-screening visit (V0) will be carried out in order to fully explain the study to potential participants, to obtain their written Informed Consent and to instruct them on screening visit procedures (such as medication restrictions). ▪ A screening visit (V1) not more than 7 days after V0 will help establish the eligibility of subjects for inclusion in the study (including routine weight/height, hematology and blood chemistry, medical history/previous medications, serum and urine pregnancy tests for women of childbearing potential, physical examination, a 12-lead ECG, FEV_1 reversibility testing, ACQ assessment spirometry testing pre and post BD (to determine post-BD reversibility), vital signs, review of concomitant medications, adverse events and training on the use of pMDI inhalers. The subject will be dispensed the paper diary. 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 including current ICS (as monotherapy or as combination ICS/LABA). The subjects will instead be prescribed a daily dose of inhaled beclomethasone dipropionate (QVAR® 40 or 80µg/actuation) equipotent to their ICS and this treatment regimen should remain stable for the entire run-in period. Subjects will receive rescue medication (albuterol) with instructions for "on demand" use for the entire study period.

- Subjects will be randomized at Visit 2 (V2), if all the eligibility criteria are confirmed, to one of the sequences comprising 4 out of 6 possible treatments: CHF 1531 pMDI (6, 12, 24 or 48µg daily) and placebo. The randomized subjects will be followed during 4 consecutive treatment periods of 2 weeks each, separated by 2-week washout intervals.
- During each treatment period, a visit is scheduled on Day 1 and on Day 14. At each study visit the patient will have pre-dose assessments (i.e. vital signs, urine pregnancy test for women of childbearing potential, ACQ questionnaire (at V2 only), concomitant medications, adverse events and paper diary dispensed/returned, 12-lead ECG, lung function testing) and will undergo pre-dose and 12 hours post-dose serial spirometry and serial serum potassium and blood glucose assessments. Post-dose lung function (FEV_1, FVC) will be evaluated and recorded at the following time points: 15, 30, 45 min and 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h and 12h after study drug intake. Post-dose vital signs and 12-lead ECG will be performed at 30 mins, 1h, 4h, 8h and 12h time-points. Post-dose Serum Potassium and Blood Glucose will be measured at 1.5h, 3h, 5h, 7h and 11h time-points.
- At Visit 9, the subject will be discharged from the study after completion of the last assessment of the serial spirometry, Hematology and Blood chemistry, physical examination, 12-lead ECG, review of AEs, concomitant medications, return and accountability of background and study drug, return of subject diary, serum pregnancy test for women of childbearing potential.
- A safety follow-up phone call (V10) will be performed by the investigator or designated staff no later than 1 week after the final visit (V9) or Early Termination Visit to check the status of unresolved AEs and to record any new AEs that may have occurred after V9 as well as related concomitant medications.



Most relevant allowed concomitant treatments	***Permitted concomitant medications*** 1. 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. 2. Cardioselective beta-blocking drugs if taken at stable regimen for at least 2 months before screening. 3. Non-potassium sparing diuretics administered as a fixed-dose combination with a potassium conserving drug. 4. Nasal corticosteroids and oral, nasal, or ocular antihistamines at FDA-approved doses for the treatment of allergy symptoms. 5. Immunotherapy for allergen desensitization at the "maintaining" phase if already taken at stable doses for at least 1 month prior to screening visit (the dose must remain constant for the whole study period). In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluation parameters and does not qualify under the section "Non-Permitted Concomitant Medications".
Most relevant forbidden concomitant treatments	***Non-permitted concomitant medications (from V1)*** 1. Inhaled corticosteroids other than the QVAR® (ICS background treatment). 2. Inhaled short-acting muscarinic antagonists (SAMA), or long-acting muscarinic antagonists (LAMA). 3. Inhaled fixed or free combinations of ICS/LABAs. 4. Nebulized or inhaled long-acting β2-agonist drugs (LABAs) other than study drug. 5. Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers). 6. Any oral/parenteral/intramuscular (depot) corticosteroid therapy for asthma exacerbation or other medical condition. *Note: any subject requiring systemic corticosteroid treatments will be discontinued from the study.* 7. Xanthine derivative (e.g. theophylline). 8. Anti-IgE, anti-IL5 monoclonal antibodies. 9. Tricyclic antidepressants and Monoamine oxidase inhibitors (MAOIs). 10. Systemic anticholinergics and sympathomimetics including immediate and sustained-release oral formulations of phenylephrine and pseudoephedrine. 11. Non-cardioselective ß-blocking drugs (including eye drops), except if taken at stable regimen for at least 2 months before screening. 12. Non-potassium sparing diuretics, except if administered as a fixed-dose combination with a potassium conserving drug. 13. Any drug known to prolong the QT interval (e.g. quinidine, procainamide, amiodarone). 14. Any medication that could interact with the study drug or procedures, according to Investigator's judgment.

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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>
<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>Ketotifen</td><td>7 days</td></tr>
<tr><td>Cromoglycate</td><td>7 days</td></tr>
<tr><td>Oral or parenteral (i.v.) corticosteroid</td><td>3 month</td></tr>
<tr><td>Intramuscular depot corticosteroid</td><td>3 months</td></tr>
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Prior to other visits with spirometry (V2 → V9), 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>
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<tr><td>**Efficacy variables**</td><td>

Primary efficacy variable
Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14.

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 Day 14.
- 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 at Day 14.
- Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Day 14.
- Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Day 14.
- Time to onset of action (change from baseline in post-dose $FEV_1 \geq 12\%$ and ≥ 200mL) at Day 1.

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<tr><td>**Safety variables**</td><td>

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs).
- Vital signs (systolic and diastolic blood pressure).
- 12-lead ECG parameters (HR, QTcF, QRS, PR).
- HR $AUC_{0\text{-}4h}$ normalized by time and HR $peak_{0\text{-}4h.}$
- Serum Potassium and Blood Glucose.

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Sample size calculation	The sample size has been calculated to evaluate the superiority of CHF 1531 pMDI at different doses over placebo in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14. The calculation is based on simulations. A total of 51 evaluable subjects will provide 96% power to detect a mean difference of 200 mL between each dose of CHF 1531 pMDI and placebo at a two-sided significance level of 0.0125, assuming a within-subject standard deviation of 180mL. 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 60 subjects (5 subjects for each of the 12 treatment sequences) will be randomized.
Statistical methods	***Primary efficacy variable*** Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14 will be analyzed using an Analysis of Covariance (ANCOVA) model including treatment, period and patient as fixed effects and baseline (average of the pre-dose FEV_1 measurements on Day 1 of each treatment period) as a covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) at Day 14 will be estimated by the model. The CIs and the p-values of the comparisons between each dose of FF pMDI and placebo 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 1531 pMDI over placebo will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favoring CHF 1531 pMDI. All the other comparisons between treatments will be performed as secondary efficacy analyzes with no multiplicity adjustment. ***Secondary efficacy variables*** No multiplicity adjustment will be performed in the secondary efficacy analyzes. • 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 Day 14 and change from baseline in pre-dose morning FEV_1 at Day 14 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 Day 14 and change from baseline in pre-dose morning FVC at Day 14 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 $FEV_1 \geq$

	12% and ≥ 200mL) at Day 1 will be analyzed using a Cox proportional hazard model stratified by patient and with treatment and period as factor and baseline FEV_1 (average of the pre-dose FEV_1 measurements on Day 1 of each treatment period) as covariate. A Kaplan-Meier plot will be presented. ***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 measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the 95% CI of the mean. **ECG** 12-lead ECG parameters (HR, QTcF, QRS and PR) and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline/pre-dose). The number and the percentage of subjects with a: • QTcF >450ms (males only), >470ms (females only), >480ms (males only) and >500ms; • change from baseline (pre-dose measurement on Day 1 of each treatment period) in QTcF >30ms and >60ms; • for post-dose time-points on Day 14: change from pre-dose on Day 14 in QTcF >30ms and >60ms At each post-dose time-point and at any post-dose time-point will be presented by treatment. At each post-dose time-point, the change from baseline (pre-dose measurement on Day 1 of each treatment period) in 12-lead ECG parameters (HR, QTcF, QRS and PR) will be analyzed using an ANCOVA model including treatment, period and subject as fixed effects and baseline (pre-dose measurement on Day 1 of each treatment period) as a covariate. The adjusted means in each treatment and the adjusted mean differences between treatments will be estimated by the model with 90% CIs.

	HR AUC_{0-4h} normalized by time and HR $peak_{0-4h}$ on Day 1 and Day 14 and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline/pre-dose). **Serum Potassium and Blood Glucose** Serum potassium and blood glucose and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	ANalysis of COVAriance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BDP	Beclomethasone dipropionate
bid	Bis in die (twice a day)
BMD	Bone Mineral Density
BTPS	Body Temperature and ambient Pressure Saturated with water vapor
BUN	Blood urea nitrogen
CFC	Chlorofluorocarbon
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
(e-) CRF	(Electronic) Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	ElectroCardioGram
FA	FORADIL® AEROLIZER®
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
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
HFA	Hydrofluroalkane
HR	Heart Rate
IB	Investigator brochure
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL5	Interleukin 5
IRT	Interactive Response Technology
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 bronchodilators

LAMA	Long Acting Muscarinic Antagonist
LLN	Lower Limit of Normal
LTRA	Leuktriene Receptor Antagonist
µg	Microgram
mab	Monoclonal antibody
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
OCS	Oral Corticosteroid
PEF	Peak Expiratory Flow
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)
qd	Quaque die (once daily)
QRS	Time Interval from the end of the PR interval to the end of the S wave in the ECG
QTc	Time interval from the beginning of the QRS complex to 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
SABA	Short-acting Beta Agonist
SABD	Short acting bronchodilators
SAP	Statistical Analyis Plan
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SBP	Systolic Blood Pressure
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TEADR	Treatment Emergent Adverse Drug Reaction
TDD	Total Daily Dose
VC (SVC / FVC)	Vital Capacity (Slow /Forced)
WOCBP	Women of Childbearing Potential

CONTENTS

APPENDICES

1. BACKGROUNG 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 mixtures of lung abnormalities are characteristic of COPD, including small airway and parenchymal disease (obstructive bronchiolitis; emphysema), with variable contributions in any given patient.[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 COPD modifies the long-term decline in lung function. The mainstays 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.
    - Adverse event of this class of medications are mainly due to their anticholinergic activities, and include dry mouth, constipation, urinary retention and increased intraocular pressure.
  - ***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).[14] 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 combination.

- **Anti-inflammatory agents**
  - **Inhaled Corticosteroids (ICS) alone:** The available evidence does not support a beneficial effect of ICS monotherapy in subjects with COPD.[15]**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.[16][17][18][19][20] 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.[21][22] A meta-analysis suggested that subjects with COPD with lower blood eosinophil counts (<2%) had more pneumonia events than did those with higher counts.[23]RCTs have reported variable outcomes regarding ICS effect on decreased bone mineral density (BMD)[24][25] and risk of fractures,[26] and observational studies suggest an increased risk of diabetes / poorly controlled diabetes,[27] cataracts,[28][29] and mycobacterial infections, including tuberculosis.[30]**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.[31][32][33][34][35][36] 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.

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by variable symptoms of wheezing, shortness of breath, chest tightness and/or cough, and by variable expiratory flow limitation. Variations over time and intensity are often triggered by factors such as exercise, environmental/occupational exposures, or viral respiratory infections.[37] As of 2014, the Center for Disease Control (CDC) estimated that the prevalence of asthma in US adults is 7.4%.[38]
The long-term goals of asthma management are to 1) achieve good symptom control, 2) to minimize future risk of exacerbations, 3) to minimize fixed airflow limitation and 4) to minimize side-effects of treatment.

There are 3 types of asthma medications: *Controller*s, *Relievers*, and *Add-ons*.

- **Controller medications (e.g. ICS, ICS+LABA, LTRA, OCS):** these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce

future risks such as exacerbations and decline in lung function. Controller medication is adjusted up or down in a stepwise approach to achieve these 4 goals.[37]

- **LABAs are drugs that have been associated with serious adverse asthma outcomes such as asthma-related hospitalization, need for intubation, and even death.**[39][40]
- In February of 2010, the US FDA issued a re-labeling requirement for products containing LABAs to include a contraindication of LABA use without concomitant asthma-controller medication (e.g. ICS) and recommendations that LABAs be used only when necessary to achieve and maintain asthma control.[41][42] In April 2011, the FDA issued a requirement for all manufacturers of LABAs marketed in asthma in the US to conduct controlled clinical trials to assess the safety of a regimen of LABA+ICS vs ICS alone in asthma.[43]
- A recently completed trial in 11,679 asthmatics age ≥12 yrs (AUSTRI trial) reported a 21% lower risk of severe asthma exacerbation in the FP+SLM (fluticasone propionate + salmeterol xinafoate fixed-dose 100/50; 250/50 or 500/50µg bid via the DISKUS® dry powder inhaler; GSK) group vs the FP (fluticasone propionate 100, 250 or 500µg bid via the DISKUS® dry powder inhaler; GSK) alone group and no asthma-related deaths.[44] In a second trial in asthmatic children age 4-11yr (VESTRI trial) FP+SLM (100/50 or 250/50µg bid) was non-inferior to FP (100 or 250µg bid) alone in the risk of serious asthma-related event (HR 1.28; [CI] 0.73-2.27).[45] There are similar ongoing trials with other ICS+LABAs which have not reported yet.

- **Reliever (rescue) medications (e.g. SABA):** these are provided to all subjects for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
- **Add-on therapies for subjects with severe asthma (e.g. LAMA, anti-IgE mab, anti-IL-5 mab)**: Some subjects with severe asthma may continue to have exacerbations despite well controlled symptoms, and for subjects with ongoing symptoms, side-effects may be an issue if ICS doses continue to be stepped up. Add-on medications may be considered when subjects have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS+LABA).

According to the GINA Report, 2016, once asthma pharmacotherapy is prescribed, decisions are based on a cycle of assessment, adjustment of treatment (step up / step down), and review of response as shown in this table:[37]

Therapy	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred Controller	Consider low dose ICS	Low dose ICS	Low dose ICS + LABA	Med-High ICS + LABA	Refer to specialist for add-ons (LAMA, anti-IgE mab, anti-IL5 mab)
Other Controller		LTRA Low dose	Med-High dose ICS +	Add tiotropium	Add low-dose OCS

		theophylline	LTRA (or + theo)	High dose ICS + LTRA (or + theo)	
Reliever	SABA prn	SABA prn	SABA prn or low-dose ICS + formoterol		

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 spray-formulated product (pMDI, Modulite®) and as a dry powder for inhalation (DPI) by the NEXThaler® device, releasing extra-fine particles.[46]

Chiesi Limited (Manchester, UK) currently also markets an inhaled formulation of the LABA formoterol fumarate in 20 European countries and over 20 non-European countries and has been marketed since 2004 under the brand name ATIMOS® Modulite pressurized inhalation solution[47] and other trade names. The product is approved in Europe for the long-term symptomatic treatment of persistent, moderate-to-severe asthma in subjects aged ≥12 years requiring regular bronchodilator therapy in combination with long-term anti-inflammatory therapy (inhaled and / or oral glucocorticoids); and for the relief of broncho-obstructive symptoms in subjects with COPD. Each actuation of ATIMOS® delivers 12µg (ex-valve) of formoterol fumarate dihydrate via an HFA-134a pressurized metered dose inhaler (pMDI). The recommended range of dosing is 24-48µg per day. **This product is not FDA-approved and is not available for use in the US.**

Chiesi Farmaceutici is also developing a fixed dose triple combination of a 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.[48]
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.

Since a dose-ranging study with CHF 1531 (HFA FF pMDI) has not been previously conducted, this study aims to characterize the dose-response to HFA FF pMDI using four doses: 3, 6, 12, 24µg (ex-valve) twice daily vs placebo in adult subjects with asthma.

Formoterol Fumarate HFA will not be indicated as monotherapy for asthma, however, the dose selection will be primarily based upon the results from this dose-ranging trial in asthmatics, as an asthma population is the most responsive to β2-agonist bronchodilation and is most likely to demonstrate a dose response. At the request of the FDA, an active comparator arm will be included, for benchmarking purposes. Since FORADIL® AEOLIZER® is no longer marketed in the US, PERFOROMIST® (formoterol fumarate) Inhalation Solution (Mylan Specialty, L.P., Morgantown, WV, USA) will be used as the active comparator.

Formoterol Fumarate:

Description and Mechanism of Action:
Formoterol fumarate is a long-acting β2-adrenergic receptor agonist (LABA). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at β2-receptors than at β1-receptors. Although β2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-receptors are the predominant receptors in the heart, there are also β2-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective β2-agonists may have cardiac effects.

The pharmacologic effects of β2-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.[49]
Clinical Efficacy:[50][51]
A full description of the prescribing information and efficacy data for FORADIL® AEROLIZER® and PERFOROMIST®, can be found in their respective FDA-approved Product Information sheets.

FORADIL® AEROLIZER® (formoterol fumarate inhalation powder) was first approved by US FDA in Feb 2001 for the maintenance treatment of asthma and the prevention of bronchospasm in reversible obstructive airways disease, and for the acute prevention of exercise-induced bronchospasm (EIB), when administered on an occasional, as needed basis. In September 2001, a second FDA approval was obtained for the long term administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema.[52] Manufacturing of this product was discontinued in Oct 2015, and is no longer distributed in the US as of January 2016.[53]

In Adults and Adolescents with Asthma:
Two doses of FA DPI 12 and 24µg bid have been compared to albuterol 180µg QID and to placebo in two (n=541; n=554) 12-week multi-center, randomized, double-blind, parallel-group trials in adults and adolescents ≥12 years of age with mild-moderate asthma. Both doses of FA DPI demonstrated statistically significant improvements vs placebo and albuterol in the primary endpoint (serial FEV_1) and in many secondary efficacy endpoints, including improved combined and nocturnal asthma symptom scores, fewer night-time awakenings, fewer nights in which subjects

used rescue medication, and higher morning and evening peak flow rates. Onset of bronchodilation ($\Delta FEV_1 \geq 15\%$) after the 1st dose was within 5 min for FA DPI 12µg, 24µg, and albuterol.

FA DPI 24µg twice daily did not provide any additional improvements in the primary or secondary endpoints compared to FA DPI 12µg twice daily, but serious asthma exacerbations occurred more commonly in the higher dose group.[54][55]

In COPD:

FA DPI was studied in two phase III, double-blind, placebo-controlled, randomized, multi-center, parallel-group trials in a total of 1634 adult patients with COPD. These studies included approximately equal numbers of patients with and without baseline bronchodilator reversibility, ($\Delta FEV1 \geq 15\%$) after inhalation of 200mcg of albuterol sulfate. A total of 405 patients received FORADIL® AEROLIZER® 12µg bid. Each trial compared FA DPI 12 and 24µg bid with placebo and an active control drug.[49] The active control drug was ipratropium bromide 40µg qid in Trial A[56] (n = 780; 12 weeks) and slow-release theophylline (Theo-Dur 200 or 300mg bid) in Trial B[57] (n = 854; 12 months). The results showed that FA DPI 12µg bid resulted in significantly greater bronchodilation (as measured by post-dose FEV_1 $AUC_{0\text{-}12h}$ - the primary efficacy analysis) compared to placebo after 12 weeks of treatment in both trials, and after 12 months of treatment in the 12-month trial. Compared to FA-DPI 12µg bid, FA DPI 24µg bid did not provide any additional benefit on a variety of endpoints including FEV_1.

PERFOROMIST® (formoterol fumarate) Inhalation Solution (FFIS) received US FDA approval in May 2007[58] for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. PERFOROMIST® Inhalation Solution is not indicated to treat acute deteriorations of COPD and is not indicated to treat asthma. As with all LABAs, PERFORMIST® is contraindicated in patients with asthma without use of a long-term asthma control medication. PERFOROMIST® Inhalation Solution is currently marketed in the US by Mylan Specialty L.P., Morgantown, WV.[59]

PERFOROMIST® was evaluated in one phase III, 12-week, double-blind, placebo- and active-controlled, randomized, parallel-group, multi-center trial conducted in the United States. A total of 351 adults with mod-severe COPD (≤ 30% %predFEV1 < 70%) were enrolled and 237 were randomized to FF IS 20µg or placebo, administered bid via a PARI-LC Plus® nebulizer with a PRONEB® Ultra compressor. Fifty eight percent (58%) of patients had bronchodilator reversibility, defined as a ≥10% increase in FEV_1 after inhalation of 2 actuations (180µg) of albuterol. FF IS 20µg bid resulted in significantly greater post-dose bronchodilation (as measured by serial FEV_1 for 12 hours post-dose, with 78% of subjects achieving a 15% increase from baseline FEV_1 following the first dose. In these subjects, the median time to onset of bronchodilation, defined as 15% increase in FEV_1, was 11.7 minutes. When defined as an increase in FEV_1 of 12% and 200mL, the time to onset of bronchodilation was 13.1 minutes after dosing. The median time to peak bronchodilator effect was 2 hours after dosing.[60]

CHF 1531 (HFA FF pMDI) was especially designed to be equipotent to standard and established doses of FORADIL® AEROLIZER® (formoterol fumarate inhalation powder).[49][61] As part of

the clinical development plan for FOSTER® Pressurized Inhalation Solution, a bridging study (CT04) was conducted to test the equivalent efficacy and safety of a single dose CHF 1531 24µg, (12µg/actuation) to FORADIL® AEROLIZER® 24µg (FA DPI, 12µg/capsule) and to compare the efficacy of 12 and 24µg doses administered via CHF 1531. The study followed a randomized, double-blind, double-dummy, cross-over design with 4 treatments (3 active and placebo) and 4 treatment periods.[62] The equivalence limit was set at ± 0.2L for FEV1, because the upper limit of the normal variability of the FEV1 measurement is known to approximate this value.[63] The primary efficacy variable was the 12-hour average FEV_1 following morning dosing (i.e. FEV_1 $AUC_{0\text{-}12hr} \div 12$).

Fifty one (51) adult subjects with moderate-severe asthma (FEV_1 50-80% of predicted normal) were randomized and 46 were evaluated in the per protocol population. All three active treatments produced a greater mean 12h average FEV_1 when compared to placebo after first dose. Administration of FORADIL® AEROLIZER® 24µg and CHF 1531 24µg improved FEV_1 by similar amounts. Conversely, the improvement was less marked after administration of CHF 1531 12µg. The maximum effect (i.e. peak FEV_1) was achieved at 2 hours after administration, regardless of the formulation used.

Maximum changes from baseline of FEV_1 after the administration of CHF 1531 24µg or FORADIL® AEROLIZER® 24µg were identical, and were higher than after administration of CHF 1531 12µg. Maximum changes from baseline of FEV_1 after the placebo administration were lower than after each of the three active treatments. Onset of bronchodilation was comparable between CHF 1531 24µg and FORADIL® AEROLIZER® 24µg. The numbers of patients with a first FEV_1 improvement ≥ 15% before 20 minutes were 36 with CHF 1531 24µg and 40 with FORADIL® AEROLIZER® 24µg. The duration of action appeared to be comparable between CHF 1531 24µg and FORADIL® AEROLIZER® 24µg. Conversely, the duration of action of CHF 1531 12µg was shorter than that of CHF 1531 24µg or FORADIL® AEROLIZER® 24µg.

Another randomized, double-blind, double-dummy, placebo-controlled cross-over study (CT03) evaluated the bronchoprotective and bronchodilator effects of 12µg formoterol delivered via FF-HFA pMDI (Chiesi Farmaceutici S.p.A, Parma, Italy) compared to FORADIL® AEROLIZER® 12µg Inhalation powder (FA -DPI, 1 inhalation) and CFC FORADIL® inhaler (both by Novartis, Health consumer, Basel, Switzerland) in 38 adult subjects with mild-moderate asthma. The primary endpoint was methacholine challenge provocative dose required for 20% fall in the FEV_1 PD_{20} 90 min post dose. The three formoterol formulations demonstrated significant ($P \leq 0.05$) improvements in bronchoprotection compared to placebo and non-inferiority of the HFA preparation compared to the CFC and DPI preparations. Serum potassium, glucose and formoterol plasma profiles were comparable for the CFC, HFA and DPI devices.[64]

Clinical Safety:[50][51]

A full description of the safety, contraindications, warnings and precautions and drug interactions with FORADIL® AEROLIZER® and PERFOROMIST®, can be found in their respective FDA-approved Product Information sheets.

Long-acting beta2-adrenergic agonists (LABA) increase the risk of asthma-related death. All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication.

Adverse reactions with β2-adrenergic receptor agonists including: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, malaise, insomnia, hypokalemia, hyperglycemia, and metabolic acidosis.

FORADIL® AEROLIZER®:[49]

In Adults and Adolescents with Asthma:

Of the 5,824 patients in multiple-dose controlled clinical trials, 1,985 were treated with FORADIL® AEROLIZER® at the recommended dose of 12µg bid. TEADRs where the frequency was ≥1% in the FORADIL® bid group and where the rates in the FORADIL® group exceeded placebo included: viral infection, bronchitis, chest infection, dyspnea, chest pain, tremor, dizziness, insomnia, tonsillitis, rash, and dysphonia.

A 16-week, randomized, multi-center, double-blind, parallel-group trial enrolled 1568 patients 12 years of age and older with mild-to-moderate asthma (%predFEV1 ≥40%) in three treatment groups: FORADIL® AEROLIZER® 12 and 24µg bid, and placebo. The trial's primary endpoint was the incidence of serious asthma-related adverse events. Serious asthma exacerbations occurred in 3 (0.6%) patients who received FORADIL® AEROLIZER® 12µg bid, 2 (0.4%) patients who received FORADIL® AEROLIZER® 24µg bid, and 1 (0.2%) patient who received placebo. The size of this trial was not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups. All serious asthma exacerbations resulted in hospitalizations. While there were no deaths in the trial, the duration and size of this trial were not adequate to quantify the rate of asthma-related death.

In adults with COPD:

Of the 1634 patients in two pivotal multiple-dose COPD controlled trials, 405 were treated with FORADIL® AEROLIZER® 12µg bid. TEADRs where the frequency was ≥1% in the FORADIL® AEROLIZER® group and where the rates in the FORADIL® AEROLIZER® group exceeded placebo included: upper respiratory tract infection, back pain, pharyngitis, chest pain, sinusitis, fever, leg cramps, muscle cramps, anxiety, pruritis, increased sputum, and dry mouth.

Post-Marketing Experience:

In extensive worldwide marketing experience with FORADIL®, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma, a few have occurred in patients with less severe asthma. It is not possible to determine from these individual case reports whether FORADIL® AEROLIZER® contributed to the events: rare reports of anaphylactic reactions, including severe hypotension and angioedema, hypokalemia, hyperglycemia, cough, rash, angina pectoris, cardiac arrhythmias, e.g. atrial fibrillation, ventricular extrasystoles, tachyarrhythmia, QT prolonged, blood pressure increased (including hypertension).

PERFOROMIST®:[59]

In Adults with COPD:

Adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was ≥ 2% in the PERFOROMIST® Inhalation Solution group (n = 123) and where the rate in the PERFOROMIST® Inhalation Solution group exceeded the rate in the placebo group were: diarrhea, nausea, nasopharyngitis, dry mouth, vomiting, dizziness, and insomnia.

Patients treated with PERFOROMIST® Inhalation Solution 20µg bid in a 52-week open-label trial (n = 463) did not experience an increase in specific clinically significant AEs above the number expected based on the medical condition and age of the patients.

Post-Marketing Experience:

The following adverse reactions have been reported during post-approval use of PERFOROMIST® Inhalation Solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Anaphylactic reactions, urticaria, angioedema (presenting as face, lip, tongue, eye, pharyngeal, or mouth edema), rash, and bronchospasm.

CHF 1531 (HFA FF pMDI):

CT04: No serious adverse events occurred during the study. Overall, 58 treatment-emergent adverse events were reported by 32 patients. Of these, 21 AEs (36.2%) occurred with CHF 1531 24µg, 17 AEs (29.3%) occurred with FORADIL® AEROLIZER® 2µg, 12 AEs (20.7%) occurred with CHF 1531 12µg, and 8 AEs (13.8%) occurred with placebo. The most commonly reported adverse event was hand tremor, which was reported by 9 patients with CHF 1531 24µg (18.8%), by 7 patients with FORADIL® AEROLIZER® 24µg (14.3%), by 5 patients with CHF 1531 12µg (10.4%) and by 2 patients with placebo (4.1%). All adverse events were of mild or moderate intensity. The relationship to the treatment was mostly "likely" with CHF 1531 24µg and mostly "possible" with FORADIL® AEROLIZER® 24µg. All adverse events resolved spontaneously except for one pneumopathy, one asthma exacerbation and one vagal syndrome, which led to patient withdrawal.

The evaluation of the effects of formoterol on the duration of QTc interval showed similar increases with CHF 1531 24µg and FORADIL® AEROLIZER® 24µg formulations, while the QTc interval remained close to baseline with CHF 1531 12µg and with placebo. The maximum changes from baseline were 29.08 msec for CHF 1531 24µg and 23.08 msec for FORADIL® AEROLIZER® 24µg as opposed to 16.06 msec and 15.02 msec for CHF 1531 12µg and placebo respectively. The maximum changes from baseline were mostly seen 2 hours after administration of CHF 1531 24µg or FORADIL® AEROLIZER® 24µg.

A moderate increase in heart rate was recorded 2 hours after administration of each of the three active treatments and this was slightly higher with CHF 1531 24µg and FORADIL® AEROLIZER® 24µg formulations than with CHF 1531 12µg and placebo. The maximum changes from baseline were 11.21 bpm for CHF 1531 24µg and 11.88 bpm for FORADIL® AEROLIZER® 24µg as opposed to 9.52 bpm and 9.23 bpm for CHF 1531 12µg and placebo respectively.

A slight decrease in systolic blood pressure was seen between 2 hours and 4 hours post-dose and a slight decrease in diastolic blood pressure was seen between 1 and 2 hours post-dose regardless of the treatment. The maximum changes from baseline for SBP were 13.38 mmHg for CHF 1531 24µg, 11.65 mmHg for FORADIL® AEROLIZER® 24µg, 12.33 mmHg with CHF 1531 12, and 13.77 mmHg with placebo. The maximum changes from baseline for DBP were -11.8 mmHg for CHF 1531 24µg, -9.69 mmHg for FORADIL® AEROLIZER® 24µg, -10.2 mmHg for CHF 1531 12µg and -11.2 mmHg for placebo. However, these modest variations were regarded as not clinically relevant.

As far as the biological safety is concerned, the three formoterol treatments lowered the serum potassium concentrations and increased glucose concentrations as expected. The maximum change in serum potassium from baseline reached -0.369 mmol/L with CHF 1531 24µg, and was -0.264 mmol/L for FORADIL® AEROLIZER® 24µg, -0.250 mmol/L for CHF 1531 12µg, and -0.239 mmol/L for placebo. Blood glucose showed a similar peak in concentration 2 hours after administration of each of the three active treatments. The maximum change from baseline reached 2.145 mmol/L with CHF 1531 24µg, and was 1.916 mmol/L for FORADIL® AEROLIZER® 24µg, 1.860 mmol/L for CHF 1531 12µg, and 1.253 mmol/L for placebo.

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

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

- To evaluate the efficacy of CHF 1531 pMDI by comparison with placebo in terms of acute bronchodilator effect (change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14).

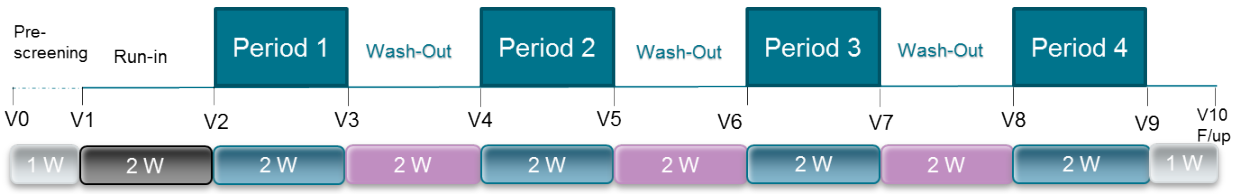
2.2 Secondary Objective(s)

- To evaluate the effect of CHF 1531 pMDI on other lung function parameters and clinical outcome measures.
- To assess the safety and the tolerability of the study drug.

3. STUDY DESIGN

This is a phase II, multi-center, randomized, double-blind, placebo and active-controlled, incomplete block cross-over, dose-ranging study to evaluate the efficacy and safety of 4 doses of CHF 1531 pMDI (Formoterol Fumarate) in adult subjects with asthma.

Following a 2-week run-in period, subjects will be enrolled into 4 consecutive treatment periods of 2 weeks each, separated by 2-week washout period. A follow-up phone contact for adverse events and concomitant medication assessment will be conducted approximately 1 week after the last study visit. The study will last approximately 18 weeks for each patient and a total of 10 clinic visits will be performed during the study, including a follow-up phone call.



The end of the trial is defined as the last follow-up contact with 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 100 subjects will be screened, 60 randomized to yield 51 evaluable subjects. Recruitment will occur across approximately 15 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 ≥18 and ≤75 years who have signed an Informed Consent Form prior to initiation of any study-related procedure.
2. A diagnosis of asthma as defined in the GINA Report, 2016,[37] documented for at least 1 year prior to screening.
3. Poorly controlled or uncontrolled asthma evidenced by a score ≥1.5 on the Asthma Control Questionnaire 7© (ACQ-7) [65] (this criterion must be met at screening and at randomization visits).
4. A pre-bronchodilator FEV_1 ≥60% and <85% of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits.
5. A positive response to a reversibility test at screening, defined as ΔFEV_1 ≥12% and ≥200mL over baseline within 30 minutes after inhaling 4 puffs of albuterol HFA (90µg/actuation).66
   Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomization.
6. Use of ICS (low/medium dose according to GINA Report, 2016) with or without a LABD for 3 months (at a stable dose in the last 4 weeks) before screening visit.

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

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

ICS/LABA for Asthma	ICS/LABA Daily Dose	QVAR® recommended Daily Dose
ADVAIR® DISKUS® 100/50	100/50µg bid	80µg bid
ADVAIR® DISKUS® 250/50	250/50µg bid	160µg bid
ADVAIR® DISKUS® 500/50	500/50µg bid†	N/A
ADVAIR® HFA 45/21	90/42µg bid	80µg bid
ADVAIR® HFA 115/21	230/42µg bid	160µg bid
ADVAIR® HFA 230/21	460/42µg bid†	N/A
BREO® ELLIPTA® 100/25	100/25µg qd	40-80µg bid
BREO® ELLIPTA® 200/25	200/25µg qd	80-160µg bid
DULERA® 100/5	200/10µg bid	160µg bid
DULERA® 200/5	400/10µg bid†	N/A
SYMBICORT® 80/4.5	160/9µg bid	80µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

† *This ICS/LABA daily dose is not permitted as its ICS component exceeds Medium Daily Dose equivalent of QVAR®.*

7. A cooperative attitude and ability to demonstrate correct use of the diary, peak flow meter and pMDI inhaler.

If at Visit 1 the inclusion criterion #5 (reversibility) is not met, the subject may return to repeat the procedure once before randomization. If this occurs, criteria # 3 and 4 must also be repeated on the same day, and before reversibility test is conducted.

At randomization (Visit 2), inclusion criteria # 3, 4 and 7 should also be re-checked.

4.3 Exclusion Criteria

If a patient 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 a 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 drug.

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 V1, V9 and at the Early Termination visit; urinary pregnancy test will be performed at Visits 1-8.

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 central laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy.

2. Subjects who suffer from COPD as defined by the GOLD Report, 2017, or are suspected of having Asthma COPD Overlap Syndrome (ACOS) as described in the GINA Report, 2016.
3. Inability to carry out pulmonary lung function testing, to comply with study procedures or with study drug intake.
4. Current smokers or ex-smokers (tobacco, vapor cigarettes, marijuana) with a smoking history of >10 pack-years or having stopped smoking one year or less prior to screening visit.
5. History of life-threatening asthma, clinically significant uncontrolled disease or respiratory infection.
6. An asthma exacerbation requiring oral/intravenous corticosteroids ≤ 30 days, intramuscular depot corticosteroid ≤ 3 months or hospitalization within 6 months prior to screening.
7. Subjects with unresolved bacterial or viral respiratory tract, sinus, or middle ear infection affecting asthma status within 2 weeks prior to screening.
8. Subjects who received a vaccination within 2 weeks prior to screening or during the run-in.
9. Subjects with oral candidiasis at screening or at randomization.
10. Subjects with any clinically significant, uncontrolled condition 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 conditions which may impact the feasibility or the results of the study according to Investigator's judgment.
11. Subjects with serum potassium levels <3.5 mEq/L (or 3.5 mmol/L) at screening.
12. Subjects who have 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.
13. Subjects who have a clinically significant abnormal 12-lead ECG that results in active medical problem which may impact the safety of the patient according to Investigator's judgment.
14. Subjects whose 12-lead ECG shows Fridericia's corrected QT interval (QTcF) >450ms for males or QTcF >470ms for females at screening or randomization visits (criterion not applicable for subjects with a pacemaker or permanent atrial fibrillation).

15. Subjects with known intolerance/hypersensitivity or contra-indication to treatment with β_2-adrenergic receptor agonists, inhaled corticosteroids or propellant gases/excipients.
16. Subjects with concomitant immunosuppressive therapy, use of oral or injected corticosteroids, anti-IgE, anti-IL5 or other monoclonal or polyclonal antibodies within 12 weeks prior to screening.
17. Use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening.
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 five 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 screening visit or have a planned surgery during the trial.

Exclusion criteria # 1, 3, 8, 9, 13 and 14 should be re-checked at the randomization visit.

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 with the study drug or study procedures. In this case, the appropriate measures will be taken.
    - Subjects who experience a severe asthma 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 asthma exacerbation will be ensured by the study investigator, with the aim to preserve the research subject's well-being at all times.
- The subject receives systemic corticosteroid treatment.
- The subject is lost to follow-up.
- The subject withdraws consent.
- The subject's safety is affected by violation of inclusion or exclusion criteria or use of not-permitted concomitant medication.
- The subject is unwilling or unable to adhere to the study requirements, i.e, non-compliance.
- The sponsor or the regulatory authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular subject.

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. Short-acting β2-adrenergic receptor agonist (albuterol) as rescue medication. A minimum period of 6 hours should elapse between the use of rescue medication and the spirometric measurements.
2. Cardioselective beta-blocking drugs if taken at stable regimen for at least 2 months before screening.
3. Non-potassium sparing diuretics administered as a fixed-dose combination with a potassium conserving drug.
4. Nasal corticosteroids and oral, nasal, or ocular antihistamines at FDA-approved doses for the treatment of allergy symptoms.
5. Immunotherapy for allergen desensitization at the "maintaining" phase if already taken at stable doses for at least 1 month prior to screening visit (the dose must remain constant for the whole study period).

In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluation parameters and does not qualify under the section "Non-Permitted Concomitant Medications".

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-V9) 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 corticosteroids other than the QVAR® (ICS background treatment).
2. Inhaled short-acting muscarinic antagonists (SAMA), or long-acting muscarinic antagonists (LAMA).
3. Inhaled fixed or free combinations of ICS/LABAs.
4. Nebulized or inhaled long-acting β2-agonist drugs (LABAs) other than study drug.
5. Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers).

6. Any oral/parenteral/intramuscular (depot) corticosteroid therapy for asthma exacerbation or other medical condition.
   Note: any subject requiring systemic corticosteroid treatments will be discontinued from the study.
7. Xanthine derivative (e.g. theophylline).
8. Anti-IgE, anti-IL5 monoclonal antibodies.
9. Tricyclic antidepressants and Monoamine oxidase inhibitors (MAOIs).
10. Systemic anticholinergics and sympathomimetics including immediate and sustained-release oral formulations of phenylephrine and pseudoephedrine.
11. Non-cardioselective ß-blocking drugs (including eye drops), except if taken at stable regimen for at least 2 months before screening.
12. Non-potassium sparing diuretics, except if administered as a fixed-dose combination with a potassium conserving drug.
13. Any drug known to prolong the QT interval (e.g. quinidine, procainamide, amiodarone)
14. Any medication that could interact with the study drug or procedures, according to Investigator's judgment.

5.3 Washout Medication Visit 1

Prior to screening spirometry (Visit 1), the following washout periods must be respected:[67]

Caffeinated substances	6 hours
Inhaled and/or nebulized short-acting β_2-agonists	6 hours
Caffeinated substances	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
Ketotifen	7 days
Cromoglycate	7 days
Oral or parenteral (i.v.) corticosteroid	3 month
Intramuscular depot corticosteroid	3 months

5.4 Washout Medication Visits 2-9

Prior to other visits with spirometry (V2 → V9), the following washout periods must be respected:

Inhaled short-acting β2-agonists	6 hours
Caffeinated substances	6 hours

6. TREATMENT(S)

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

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 1531 pMDI 3µg – test product***
  Active ingredient: Formoterol Fumarate 3µg per inhalation
  Excipient: Ethanol, HFA-134a propellant, hydrochloric acid
  Presentation: each canister contains 120 doses

- ***CHF 1531 pMDI 6µg - test product***
  Active ingredient: Formoterol Fumarate 6µg per inhalation
  Excipient: Ethanol, HFA-134a propellant, hydrochloric acid
  Presentation: each canister contains 120 doses

- ***CHF 1531 pMDI 12µg - test product***
  Active ingredient: Formoterol Fumarate 12µg per inhalation
  Excipient: Ethanol, HFA-134a propellant, hydrochloric acid
  Presentation: each canister contains 120 doses

- ***CHF 1531 pMDI matched placebo***
  Active ingredient: None
  Excipient: Ethanol, HFA-134a propellant, hydrochloric acid
  Presentation: each canister contains 120 doses

- ***PERFOROMIST® Inhalation Solution (Mylan Specialty L.P.) – Reference product – Open-label***
  *Active ingredient***:** Formoterol Fumarate 20µg /2mL
  Excipient: water, citric acid, sodium citrate, NaCl
  Presentation: 2mL unit dose vials

- ***QVAR® Inhalation Aerosol (Teva Respiratory, LLC) – Background ICS medication***
  Active ingredient: beclomethasone dipropionate 40µg per inhalation
  Excipient: Propellant HFA-134a (Norflurane), Ethanol
  Presentation: Each canister contains 120 doses

- ***QVAR® Inhalation Aerosol (Teva Respiratory, LLC) - Background ICS medication***
  Active ingredient: beclomethasone dipropionate 80µg per inhalation
  Excipient: Propellant HFA-134a (Norflurane), Ethanol
  Presentation: Each canister contains 120 doses

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

FORADIL® AEROLIZER®: The PK and PD effects of inhaled formoterol fumarate (FF) have been tested in healthy volunteers using single doses ranging from 12 to 120µg. A linear relationship was observed between urinary excretion of formoterol and decreases in serum potassium, increases in plasma glucose, and increases in heart rate. Maximum increase in plasma potassium was observed 1-3h after peak formoterol plasma concentration and a mean max increase in HR at 6h post-dose. Formoterol plasma concentrations were weakly correlated with increased HR and QTc duration. QTc prolongation were transient and returned to baseline within 12-24h post-dosing.

In the asthma clinical development plan, 3 TEADRs showed dose ordering among tested doses of 6, 12 and 24µg bid; tremor, dizziness and dysphonia. In two 12-week controlled trials with combined enrollment of 1095 patients 12 years of age and older, serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL® AEROLIZER® (FA DPI) 24µg bid than with the recommended dose of FORADIL® AEROLIZER® 12µg bid, albuterol, or placebo. In a 16-week, randomized, multi-center, double-blind, parallel-group trial, patients who received either 24µg or 12µg bid doses of FORADIL® AEROLIZER® experienced more serious asthma exacerbations than patients who received placebo.

In the COPD clinical development plan, FA DPI 24µg bid did not provide any additional benefit on a variety of endpoints including FEV_1 compared to FA DPI 12µg bid. Seven TEADRs showed dose ordering among tested doses of 12 and 24mcg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

The US FDA-approved dosage of FORADIL® AEROLIZER® Inhalation Powder is 12µg bid.[49]

PERFOROMIST®: Dose selection for the PERFORMIST® (FF IS) clinical program was based on two single-dose PD (bronchodilation) studies vs. FORADIL® AEROLIZER® (FA DPI) in patients with COPD.[68]

- DL-02: FEV_1 dose-response of FF IS 40 and 80µg and FA DPI 12 & 24µg. Results failed to match either FF IS dose with the approved dose of FA DPI (12µg).
- DL-057: was the primary dose-finding study in 47 subjects with mod-severe COPD (FEV_1/FVC ratio < 0.7 and 30% ≤ FEV_1 <70%). The primary endpoint was FEV_1 $AUC_{0\text{-}12h}$. The doses evaluated were FF IS 2.5, 5, 10, 20 & 40µg vs FA DPI 12µg and PBO. The study Showed comparable BD effect between FF IS 20µg and FA DPI 12µg doses. The FF IS

12µg dose was taken into the Phase III program. The FF IS 10µg dose also matched the FA DPI 12µg dose but was not chosen because the statistical evaluation plan used a descending order approach from highest to lower FF IS dose.[69]

The US FDA-approved dosage of PERFOROMIST® Inhalation Solution is one 20µg/2mL vial every 12 hours.

CHF 1531 (HFA FF pMDI): The clinical equivalence of single dose CHF 1531 (HFA FF pMDI) 6µg (2 X 6µg/actuation) to the once US-marketed formulation of FORADIL® AEROLIZER® 12µg Inhalation Powder (FA DPI) has been previously established in adult subjects with moderate to severe asthma. Therefore, considering the above evidence and the FDA's recommendations, this dose-ranging study will assess 4 doses of CHF 1531: (3, 6, 12, and 24µg bid) vs placebo. PERFOROMIST® Inhalation Solution will be used as the active comparator, at the same dose indicated for COPD.

6.2.2 Dosage

6.2.2.1 Background medication for run-in and treatment periods*:*

Standardized Background ICS therapy – Open label:
QVAR® 40µg (HFA beclomethasone dipropionate, 40µg), Inhalation Aerosol. Each canister contains 120 actuations.
OR:
QVAR® 80µg (HFA beclomethasone dipropionate, 80µg), Inhalation Aerosol. Each canister contains 120 actuations.
Both dose strengths of QVAR® will be provided by the study sponsor to be dispensed as prescribed by the investigator. The subjects will be prescribed a daily dose of (QVAR® 40 or 80µg/actuation; 1-2 puffs bid) between 80 – 320µg, equipotent to their previous ICS (ref. inclusion criterion #6) and this treatment regimen should remain stable for the entire study period. The subject will be asked to not use any other ICS throughout the study.

6.2.2.2 Randomized Treatment period:

An adequate number of inhalations from the Placebo inhalers will be performed to maintain a double blind design. Randomized subjects will receive four of the six following Study Treatments according to the sequence assigned by the randomization list:

- **Treatment A**:
  1 inhalation of CHF 1531 3µg pMDI plus 1 inhalation of CHF1531 matched placebo in the morning and in the evening, giving a total daily dose of 6µg.

- **Treatment B**:
  1 inhalation of CHF 1531 6µg pMDI plus 1 inhalation of CHF1531 matched placebo in the morning and in the evening, giving a total daily dose of 12µg.

- **Treatment C**:
  2 inhalations of CHF1531 6µg in the morning and in the evening, giving a total daily dose of 24µg.

- **Treatment D**:
  2 inhalations of CHF1531 12µg in the morning and in the evening, giving a total daily dose of 48µg.

- **Treatment E:**
  2 inhalations of CHF1531 matched placebo in the morning and in the evening, giving a total daily dose of 0µg.

- **Treatment F:**
  1 inhalation in the morning and in the evening of PERFOROMIST® giving a total daily dose of 40µg. PERFOROMIST® will be administered as open label.

6.2.3 Administration

6.2.3.1 : Background ICS medication kit for run-in period (from Visit 1 to Visit 2)

At screening visit 1 (Visit 1), the Investigator, or designee, will contact the IRT system to dispense to each eligible patient **one background ICS medication kit (QVAR®).** This kit will cover the needs in background ICS maintenance medication until Visit 2.

At Visit 1 (screening visit), all subjects allowed to continue in the study, including those scheduled for V1.1 for a repeat Reversibility test, will receive the following standard ICS medication to cover the 2-week run-in period:

- One commercial pack of **QVAR® 40 or 80µg** containing Beclomethasone dipropionate HFA 40 or 80µg per actuation, respectively, 120 actuations per canister

The investigator will prescribe the subject QVAR® 40µg or QVAR® 80µg 1-2 puffs bid (80 – 320µg/d) at an equipotent dose to replace the subject's prior ICS. The 1st dose of QVAR® will be administered on-site at V1. Subsequently, the subject will be instructed to discontinue the use of any other ICS for the duration of the study.

The recommended time of administration is between 8-10 am for morning dose and between 8-10 pm for evening dose.

All enrolled subjects will be instructed to:

1. take the same dose of QVAR®, daily, as prescribed on V1
2. refrain from taking their morning dose of QVAR® before reporting to the study site at V1.1 and V2
3. return the QVAR® with the rest of their study drug and study material on the next visit.

6.2.3.2 : Randomized Period (from Visit 2 to Visit 8)

Background ICS medication kit (from Visit 2 to Visit 8)

At Visit 2, the Investigator, or designee, will contact the IRT system to dispense to each randomized subject background ICS medication (QVAR®) at the same dose prescribed at V1, according to the following schedule:

- **One commercial pack of QVAR®** will be dispensed at V2, V4, V6 and V8 to each subject prescribed **1 puff bid** of either QVAR® 40 or 80µg dose strength, OR

- **Two commercial packs of QVAR®** will be dispensed at V2, V4, V6 and V8 to each subject prescribed **2 puffs bid** of QVAR® 80µg dose strength.

The recommended time of administration is between 8-10 am for morning dose and between 8-10 pm for evening dose. The morning dose of QVAR® will be administered on-site at V2-V9, immediately after study drug administration. The evening dose of QVAR® will be administered on-site at V2-V8, immediately after all other procedures.

All randomized subjects will be instructed to:
1. take the same dose of QVAR®, daily, as prescribed on V2 until study completion at V9
2. refrain from taking their morning dose of QVAR® before reporting to the study site at each study visit
3. return QVAR® with the rest of their study drug and study material at each visit.

Study Drug Administration (from V2 to V8):
At randomization visit (Visit 2), after the confirmation of the eligibility, the patient will be randomized to one of 12 treatment sequences.

At Visit 2, 4, 6 and 8 the patient will receive 1 box with the randomized study drug. Each box will contain 2 actuators and 2 canisters for subjects randomized to Treatment Arms A to E, or 40 vials of PERFOROMIST® for subjects randomized to Treatment Arm F.

Patient randomized in Treatment F Arm will also receive a standard jet nebulizer equipped with a facemask or mouthpiece.

The first administration of study drug will take place at the clinic on visit 2 **(V2)** after pre-dose procedures have been completed and before the background medication (QVAR®) intake.

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

Morning administration (between 8-10 am):

- Treatment Arms A – E: 1 inhalation from canister numbered 1 and 1 inhalation from canister numbered 2
- Treatment Arm F: One (2mL) vial to be inhaled through standard jet nebulizer

Evening administration (between 8-10 pm):

- Treatment Arms A – E: 1 inhalation from canister numbered 1 and 1 inhalation from canister numbered 2
- Treatment Arm F: One (2mL) vial to be inhaled through standard jet nebulizer

To the extent possible, the time of dosing must remain constant for each patient 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

Asthma 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 through local procurement each subject with 1 canister of albuterol to use as asthma rescue treatment for the treatment of bronchospasm, as 1-2 inhalations q4-6 hours 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 for ≥ 2 consecutive days during the run-in period, or uses ≥ 4 puffs/day above their run-in average for ≥ 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 spirometric measurements. ***Albuterol will not be provided by the study sponsor.***

6.2.4 Subject Training

At screening visit (V1), Investigator or designee will contact IRT system to dispense a pMDI training kit containing one placebo canister plus one actuator for each patient (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 kits 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 pMDI. If needed, training can be repeated at following clinical visits.

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

When the subject is assigned to Treatment Arm F, the Investigator or designee will instruct them on how to use PERFOROMIST® Inhalation Solution in a standard jet nebulizer machine connected to an air compressor, by reading together and showing the PERFOROMIST® patient leaflet to the subjects. At visits requiring the administration of PERFOROMIST®, the subjects will be closely supervised by the Investigator or designee to check that PERFORMIST® administration 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) requirements as required by the current Good Clinical Practices (GCP).

Chiesi will supply the background medication (for run-in and treatment period) 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 1531 pMDI placebo.

- *Primary packaging:* One labeled aluminium canister of CHF 1531 placebo plus labeled standard actuator
- *Secondary packaging*: One carton box labeled with a study label

6.3.2 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.

6.3.3 Treatment kit

Treatment A, B, C, D, E

- *Primary packaging:* Two aluminium canisters labeled with a study label plus standard actuator labeled with a study label. The two inhalers will be numbered 1 and 2.
- *Secondary packaging:* Carton box labeled with a study label.

Treatment F (Open label arm)

- *Primary packaging:* Unit dose vials sealed in an aluminium wrap labeled.
- *Secondary packaging:* Carton box labeled with a study label.

6.3.4 Background medication kit for run in and treatment period

- *Primary packaging:* One canister of QVAR® plus labeled actuator with a dose counter
- *Secondary packaging:* One labeled commercial pack containing 1 canister plus 1 actuator with a dose counter.

6.4 Labeling

All labeling will be in English language and according to local law and regulatory requirements and will be compliant with 21 CFR 312.6 "Labeling of an Investigational New Drug".

6.5 Treatment allocation

An Interactive Response Technology (IRT) system will be used at each visit (from pre-screening to follow-up call) to record patient status. Patient number will be centrally assigned, through the IRT, during the pre-screening visit (Visit 0).

The Investigator, or designee, at the sites will call the IRT system to screen, randomize subjects and assign treatment kits according to the sequence described in the randomization list. The randomization list will be prepared by a specialised external provider and the whole study team, the investigators and the subjects will be blind to sequence assignment. Subjects will be randomized to one of the 12 possible treatment sequences, according to a balanced incomplete block randomization scheme.

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 study treatment code will be done through IRT. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation (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 study 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 Global Pharmacovigilance will have their own passwords to unblind subjects in case of SUSARs to be reported to the competent Regulatory Authorities and IRB.

The subject will be provided with a card with the phone numbers of Hospital 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 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 to 8.

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.

Run-in and Background medication:

- The boxes of QVAR® used as run-in and background medication must be stored **not above 25˚C (77°F)** by Pharmacist/Investigator at the study site and by subjects at home.

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

- ***CHF 1531 pMDI treatment kits and matched*** **placebo** must be stored between 2°C (36˚F) and 8°C (46˚F) by the Investigator/Pharmacist at site. At the time of drug intake at site, the study drug should be removed from the refrigerator and the canister should be taken out of the mouthpiece and warmed with the hands for few minutes before administration to the patient. The canister should never be warmed by artificial means. **The patient should never inhale a cold study drug**.

  Once delivered to subjects, the treatment kits must be stored at ambient temperature (not above 25˚C [77˚F]) **at home**. At this temperature condition, the actual use-by-date of the treatment kits will be three months (**90 days**). Therefore, the Pharmacist/Investigator at the hospital must write the use-by-date on the kit labels once the kits are removed from the refrigerator, before assigning to the subjects.

- ***PERFOROMIST®*** treatment kits must be stored in a refrigerator, between 2°C (36˚F) to 8°C (46˚F). Once delivered to subjects, the treatment kits must be stored **at home**, between 2°C (36˚F) to 25˚C [77˚F]) for up to 3 months.

***Medication for training*:**

- **The pMDI training kits** must be stored between 2°C (36˚F) and 8°C (46˚F) by the Investigator/Pharmacist at the site. At the time of the training, the training medication should be removed from the refrigerator and the canister should be taken out of the mouthpiece and warmed with the hands for few minutes before administration to the patient. The canister

should never be warmed by artificial means. **The patient should never inhale a cold medication.**

After usage, the training kit must be stored at room temperature (not above 25ºC [77˚F]) **at the study sites**. At this temperature condition the actual use-by-date of the training kits will be three months **(90 days)** from the date of removal from refrigerator. The Pharmacist/Investigator at the hospital must write the use-by-date on the kit labels once the kits are removed from the refrigerator, before assigning to the subjects.

The site must check the Min/Max temperatures once daily for adequate storage conditions for the 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 the 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 study drug(s). 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 the Investigator's responsibility to prescribe the appropriate treatment for the subject or to restore their initial therapy or to refer them to their primary care physician.

7. STUDY PLAN

7.1 Study Schedule

Table 1: Study Flow Diagram

	Pre-screening	Screening	Period 1		Period 2		Period 3		Period 4		F/up Call	ET
			D 1	D 14	D 1	D 14	D 1	D 14	D 1	D 14		
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
Time (weeks)		- 2	0	2	4	6	8	10	12	14	15	Early Termination
Time window (days)	-	± 2	-	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	
Informed Consent Form	✓											
Demographic data	✓											
IRT visit confirmation call	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion / exclusion criteria		✓										
Asthma Action Plan Review		✓	✓	✓	✓	✓	✓	✓	✓			
Eligibility recheck[h]			✓									
Medical history/Previous medication		✓										
Weight and Height		✓										
Physical Examination		✓								✓		✓
Assessment for Oral Candidiasis		✓	✓							✓		✓
Hematology and Blood Chemistry		✓								✓		✓
Serum pregnancy test [a]		✓								✓		✓
Urinary pregnancy test [a]		✓	✓	✓	✓	✓	✓	✓	✓			
12-lead ECG [b]		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Vital signs (DBP/SBP) [b]		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Training on the use of pMDI, diary, PEF, PERFOROMIST® [i]		✓	✓		✓		✓		✓			
Randomization			✓									
Spirometry pre and post-BD [c]		✓										
Pre-dose spirometry [d]			✓	✓	✓	✓	✓	✓	✓	✓		✓
Post-dose 12h serial spirometry [e]			✓	✓	✓	✓	✓	✓	✓	✓		
Pre and post-dose Serum Potassium & Glucose [f]			✓	✓	✓	✓	✓	✓	✓	✓		
ACQ questionnaire		✓	✓									
Concomitant medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rescue Medication dispensation[g]		✓										
Dispensation / Return of background ICS: QVAR®		D	D/R		D/R		D/R		D/R	R		R
Study drug dispensation / return and Accountability			D	R	D	R	D	R	D	R		R
Subject diary/PEF dispensation (D) /return (R)		D	D/R	D/R	D/R	D/R	D/R	D/R	D/R	R		R
Schedule next appointment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

[a] In women of childbearing potential only

[b] At V1: before administration of QVAR®; and at V2-V9 : before study drug dosing and at 30min, 1h, 4h, 8h and 12h post-dose.

[c] Spirometry will be carried out before and within 30 minutes after the inhalation of 4 puffs of albuterol.

[d] Pre-dose FEV_1, FVC: T -45'and T -15' before administration of study drug at V2-V9 and ET.

[e] Post-dose serial spirometry (FEV_1, FVC): 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, 12h (V2-V9).

[f] Serum potassium and glucose: Pre-dose before administration of study drug at V2-V9; and Post-dose at 1.5h, 3h, 5h, 7h, and 11h at V2-V9.

[g] One commercial albuterol HFA pMDI (200 actuations) will be prescribed and supplied by the investigator to each subject at V1,and resupplied as needed at V2-8 based on assessment of doses used between visits.

[h] Only Inclusion criteria #3, 4 and Exclusion criteria #1, 3, 8, 9, 13, 14.

i Training on pMDI use will occur on V1 and V2. Training on PERFOROMIST® use will occur when a subject is scheduled to receive Study Treatment F.

7.1.1 Visit 0 (Pre-screening visit)

A pre-screening visit will be carried out in order to identify eligible subjects and to fully explain the study. 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 next screening visit (V1) such as **concomitant medications to be withdrawn** prior to the visit.
- As soon as the Informed Consent is signed, the investigator (or his/her designee) will connect to IRT to allocate a 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 (V1) will be taken in the morning before 9:00 am, **within 1 week**. The appointment day may vary depending on the washout subject shall respect for 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 and caffeinated substances**, **in the 6 hours preceding the next visit**, **and to abstain from taking the non-permitted medications listed in section 5.2,** unless absolutely necessary;

7.1.2 Visit 1 (Screening visit / Week -2)

A screening visit will start 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 morning of the rescheduled visit, the subject will be discontinued and recorded in the IRT and eCRF as screen failure.

The following procedures will take place:

- Confirm that the diagnosis of asthma as defined in the GINA Report, 2016 has been documented for at least 1 year prior to screening.
- The ACQ questionnaire will be completed (see section 7.2.1).
- Weight and height will be recorded.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator and background ICS medication (QVAR®) administration, after 5 minutes of rest, in resting position (see section 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator and run-in medication (QVAR®) administration, after 5 minutes of rest (see section 7.2.4). A subject will not be eligible in case of QTcF >450ms for males or QTcF >470ms 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 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 for oral candidiasis.
- A urine pregnancy test in women with childbearing potential will be performed.
- A blood sample will be collected before albuterol administration, after an overnight fasting (at least 10h), for the assessments of (see section 7.2.8):
  - 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 carried out: to assess FEV_1, FVC (see section 7.2.5). To be eligible, **FEV_1** must be ≥60% and <85% of the subject's predicted normal value.
- Post-bronchodilator spirometry (reversibility) will be carried out within 30 minutes after intake of 4 puffs of albuterol HFA (90µg/actuation). To be eligible, the post-bronchodilator increase in FEV1 must be ≥12% and ≥200mL from subject's pre-bronchodilator baseline.
- *If the reversibility criteria are not met at V1, this test can be performed **once more before Visit 2** after an appropriate washout from bronchodilators. If this occurs, inclusion criteria # 3 and 4 must also be repeated and met on the same day, and before reversibility test is conducted.*
- Any AE occurring since the signature of the Informed Consent will be assessed 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, 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 daily record the medications intake (background ICS and rescue), and adverse events in the paper Diary (see section 7.2.6).
- The investigator will access IRT also in order to obtain the background ICS medication (one commercial box containing 1 canister of QVAR® 40 or 80µg to be dispensed to the subject together with instructions for use. The investigator will prescribe the subject QVAR® 40µg

or QVAR® 80µg 1-2 puffs bid (80 – 320µg/d) at an equipotent dose to replace the subject's prior ICS. Subject will be instructed to take the QVAR® in the morning (between 8-10 am) and in the evening (between 8-10 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 medications (including any other ICS, LABA, or LAMA) in accordance with section 5.2.
- Rescue albuterol, for use as needed, will be dispensed by the Investigator. Subjects will keep this rescue albuterol throughout the study period (will be re-supplied if needed); nevertheless subject will be instructed to return this medication at each visit in order to check the need for replacement.

Before discharge:

- **Rescue albuterol** will be dispensed and the subject will be instructed to take albuterol as rescue if necessary.
- **A paper diary will be dispensed along with a peak flow meter.** Subject must complete the diary on a daily basis through Visit 2. It is important to ensure a good compliance of the subject to the use of the paper Diary during the run-in period and throughout the study.
- **Asthma Action Plan will be communicated to the subject.**
- **An appointment for Visit 2** will be made within 2 week (±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:
  - ➔ **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 and caffeinated substances in the 6 hours preceding the next visit, and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.
  - ➔ **Not to take background ICS medication (QVAR®) in the morning of the next visit.**
  - ➔ To **return the rescue medication** (in their boxes), and the **paper Diary.**

7.1.3 Visit 2 (Randomization / Period 1, Day 1)

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

If caffeine was ingested, or rescue albuterol was inhaled in the previous 6 hours, or the washout for non-permitted medications was not respected, or the background ICS medication (QVAR®) was taken the morning of the visit (before 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 ACQ questionnaire will be completed (see section 7.2.1).

- 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.3).
- 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).
- The investigator (or designee) will check the subject diary whether the subject has recorded rescue medication intake since the screening. The investigator/designee will also check to see if the subject recorded the PEF measurements. **In case of lack of compliance in the diary use, instructions on how to fill the diary will be provided again to the subject.**
- A urine pregnancy test in women with childbearing potential will be performed.
- A pre-dose serum potassium and glucose will be conducted before study drug administration (see section 7.2.7)
- The occurrence of adverse events will be checked and recorded if any.
- The proper use of pressurized metered dose inhaler (pMDI) will be checked and subject will be retrained on the usage of the pMDI using the Training kit previously assigned at V1 (see section 6.2.4).
- Pre-dose spirometry: Pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC prior to subject randomization. This measurement will be taken at T -45' and T -15' before 1st dose of study drug and will constitute the baseline value (see section 7.2.5). Both T -15 min and T -45 min assessments must be performed and the selected best FEV_1 at each timepoint must be ≥60% and <85% of predicted in order to meet Inclusion Criterion #4.
- Assessment for oral candidiasis.
- Eligibility criteria will be rechecked (Inclusion #3, 4, 7; Exclusion #1, 3, 8, 9, 13, 14). 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 rescreened 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 2-week treatment period.
- For subjects randomized to receive open-label PERFOROMIST® Inhalation Solution (Study Treatment F), the Investigator will instruct subjects on how to use PERFOROMIST® 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 (for this treatment period) 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 (e-CRF). The use-by-date must be filled-in on the labels. Drug administration will be done according to section 6.2.3.

- The morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at V1.
- Post-dose spirometry will be performed (FEV1, FVC) at 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, 12h. For each time point, spirometry consists in three acceptable maneuvers (see section 7.2.5).
- Post-dose SBP/DBP assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.2).
- Post-dose 12-lead ECG assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.4).
- Post-dose serum potassium and glucose assessments will be conducted at 1.5h, 3h, 5h, 7h, and 11h (see section 7.2.7)
- The evening dose of study drug will be administered at the clinic under supervision, followed by immediately by the evening dose of the background ICS (**QVAR®**) once the 12h spirometry and all other procedures have been completed.

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.
- **A paper diary will be dispensed along with the same peak flow meter.** Subject must complete the diary on a daily basis and return the completed diary at the next visit.
- **Asthma Action Plan will be reviewed with the subject.**
- **An appointment for Visit 3** will be made at 2 weeks (±2 days) from Visit 2 (at approximately the same time as Visit 2, before 9:00 am). The subject will be instructed:
  - ➔ **To fast overnight** (at least 10 hours) **for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ To **return** the paper Diary, the study medication and rescue medication (in the boxes) at the next visit.
  - ➔ **Not to take albuterol and caffeinated substances in the 6 hours preceding the next visit, and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study drug and background ICS (QVAR®) before coming to the next clinic visit** (they will be administered at the clinic visit).

7.1.4 Visit 3 (Period 1, Day 14)

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

If caffeine was ingested, or rescue albuterol was inhaled in the previous 6 hours, or the washout for non-permitted medications was not respected, or QVAR® or the study drug was taken the morning

of the visit (before 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:

- Study drug from visit 2 will be reviewed for accountability and provided back to the subject.
- Pre-dose vital 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.4).
- 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.
- A pre-dose serum potassium and blood glucose will be conducted.
- The occurrence of other adverse events will be checked and recorded if any.
- The investigator (or designee) will check the subject diary whether the subject has recorded rescue medication intake since the last visit. The investigator/designee will also check to see if the subject recorded the PEF measurements. **In case of lack of compliance in the diary use, instructions on how to fill the diary will be provided again to the subject.**
- The Investigator will access IRT to record the visit.
- Pre-dose spirometry: FVC pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC. This measurement will be taken at T -45' and T -15' prior to study drug intake.
- **The administration of the last dose of study drug (for this treatment period) will take place at the clinic visit (before 10:00 am) under supervision of the Investigator.**
- The morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at V1.
- Post-dose spirometry will be performed 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, and 12h. For each time point, spirometry consists in three acceptable maneuvers (see section 7.2.5).
- Post-dose SBP/DBP assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.2).
- Post-dose 12-lead ECG assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.4).
- Post-dose serum potassium and glucose assessments will be conducted at 1.5h, 3h, 5h, 7h, and 11h (see section 7.2.7).
- The evening dose of the background ICS **QVAR®** will be administered at the clinic under supervision, once the 12h spirometry and all other procedures have been completed.

Before discharge

- **If needed, additional rescue medication** will be dispensed to the subject together with instructions for use.
- **A paper diary will be dispensed along with the same peak flow meter.** Subject must complete the diary on a daily basis and return the completed diary at the next visit.
- **Asthma Action Plan will be reviewed with the subject.**
- **An appointment for Visit 4** will be made at 2 weeks (±2 days) from Visit 3 (at approximately the same time as Visit 3, before 9:00 am). The subject will be instructed:
  - ➔ **To fast overnight** (at least 10 hours) **for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ To **return** the paper Diary, and rescue medication at the next visit.
  - ➔ **Not to take albuterol and caffeinated substances in the 6 hours preceding the next visit, and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.
  - ➔ **Not to take the morning dose of the background ICS (QVAR®) before coming to the next clinic visit** (it will be administered at the clinic visit).

7.1.5 Visit 4 (Period 2, Day 1), Visit 6 (Period 3, Day 1) and Visit 8 (Period 4, Day 1)

The Visit will start in the morning (before 9:00 am), and will begin the applicable period, Day 1.

If caffeine was ingested, or rescue albuterol was inhaled in the previous 6 hours, or the washout for non-permitted medications was not respected, or QVAR® was taken the morning of the visit (before 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:

- Study drug from the previous visit will be collected and reviewed for accountability.
- 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.4).
- 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).
- The investigator (or designee) will check the subject diary whether the subject has recorded rescue medication intake since the last visit. The investigator/designee will also check to see

if the subject recorded the PEF measurements. **In case of lack of compliance in the diary use, instructions on how to fill the diary will be provided again to the subject.**

- A urine pregnancy test in women with childbearing potential will be performed.
- A pre-dose serum potassium and glucose will be conducted.
- The occurrence of adverse events will be checked and recorded if any.
- The Investigator will access IRT to record the visit and to obtain the appropriate kit number for the corresponding 2-week treatment period.
- Pre-dose spirometry: FVC pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC. This measurement will be taken at T -45' and T -15' (see section 7.2.5).
- **The administration of the 1st dose of study drug from the new kit (for this treatment period) 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 (e-CRF). The use-by-date must be filled-in on the labels. Drug administration will be done according to section 6.2.3.
- For subjects randomized to receive open-label PERFOROMIST® Inhalation Solution (Study Treatment F), the Investigator will instruct subjects on how to use PERFOROMIST® by reading together and showing the FDA-approved Patient Information Leaflet to the subjects, in accordance with section 6.2.4.
- The morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at V1.
- Post-dose spirometry will be performed (FEV_1, FVC) at 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, and 12h. For each time point, spirometry consists in three acceptable maneuvers (see section 7.2.5).
- Post-dose SBP/DBP assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.2).
- Post-dose 12-lead ECG assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.4).
- Post-dose serum potassium and glucose assessments will be conducted at 1.5h, 3h, 5h, 7h, and 11h (see section 7.2.7).
- The evening dose of study drug will be administered at the clinic under supervision, followed by immediately by the evening dose of the background ICS (**QVAR®**) once the 12h spirometry and all other procedures have been completed (see section 7.2).

Before discharge

- **Study drug** will be dispensed to the subject together with instructions for use. Drug administration will be done according to section 6.2.2. Subject will be instructed to take albuterol as rescue if necessary. Investigator will also dispense albuterol if needed.
- **A paper diary will be dispensed along with the same peak flow meter.** Subject must complete the diary on a daily basis and return the completed diary at the next visit.
- **Asthma Action Plan will be reviewed with the subject.**

- **An appointment for the next visit** will be made at 2 weeks (±2 days) from current visit (at approximately the same time as current visit, before 9:00 am). The subject will be instructed:
  - ➔ **To fast overnight** (at least 10 hours) **for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ To **return the paper Diary**, the study drug and rescue medication (in the boxes) at the next visit.
  - ➔ **Not to take albuterol and caffeinated substances in the 6 hours preceding the next visit**, **and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study drug and the background ICS (QVAR®) before coming to the next clinic visit** (they will be administered at the clinic visit).

7.1.6 Visit 5 (Period 2, Day 14) and Visit 7 (Period 3, Day 14)

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

If caffeine was ingested, or rescue albuterol was inhaled in the previous 6 hours, or the washout for non-permitted medications was not respected, or QVAR® or the study drug was taken the morning of the visit (before 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 procedures will be performed:

- Study drug from the previous visit will be reviewed for accountability and provided back to the subject.
- Pre-dose vital 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.4).
- 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.
- A pre-dose serum potassium and blood glucose will be conducted.
- The occurrence of adverse events will be checked and recorded if any.
- The investigator (or designee) will check the subject diary whether the subject has recorded rescue medication intake since the last visit. The investigator/designee will also check to see if the subject recorded the PEF measurements. **In case of lack of compliance in the diary use, instructions on how to fill the diary will be provided again to the subject.**

- The Investigator will access IRT to record the visit.
- Pre-dose spirometry: FVC pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC. This measurement will be taken at T -45' and T -15' prior to study drug intake.
- **The administration of the last dose of study drug (for this treatment period) will take place at the clinic visit (before 10:00 am) under supervision of the Investigator.**
- The morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at V1
- Post-dose spirometry will be performed 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, and 12h. For each time point, spirometry consists in three acceptable maneuvers (see section 7.2.5).
- Post-dose SBP/DBP assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.2).
- Post-dose 12-lead ECG assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.4).
- Post-dose serum potassium and glucose assessments will be conducted at 1.5h, 3h, 5h, 7h, and 11h (see section 7.2.7).
- The evening dose of the background ICS **QVAR®** will be administered at the clinic under supervision, once the 12h spirometry and all other procedures have been completed.

Before discharge

- **If needed, additional rescue medication** will be dispensed to the subject together with instructions for use.
- **A paper diary will be dispensed along with the same peak flow meter.** Subject must complete the diary on a daily basis and return the completed diary at the next visit.
- **Asthma Action Plan will be reviewed with the subject.**
- **An appointment for the next visit** will be made at 2 weeks (±2 days) from current visit (at approximately the same time as current visit, before 9:00 am). The subject will be instructed:
  - ➔ **To fast overnight** (at least 10 hours) **for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ To **return** the paper Diary and rescue medication at the next visit.
  - ➔ **Not to take albuterol and caffeinated substances in the 6 hours preceding the next visit, and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.

7.1.7 Visit 9 (Period 4, Day 14)

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

If caffeine was ingested, or rescue albuterol was inhaled in the previous 6 hours, or the washout for non-permitted medications was not respected, or QVAR® or the study drug was taken the morning of the visit (before 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 procedures will be performed:

- Study drug from Visit 8 will be collected and reviewed for accountability.
- Pre-dose vital 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.4).
- The investigator (or designee) will check the subject diary whether the subject has recorded rescue medication intake since the last visit. The investigator/designee will also check to see if the subject recorded the PEF measurements.
- 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 full physical examination will be performed, including an assessment of the presence/absence of oral candidiasis.
- A blood sample will be collected before bronchodilator, background ICS medication (QVAR®) or study drug administration, after an overnight fasting (at least 10h), for the assessments of (see section 7.2.8):
  - standard hematology and blood chemistry;
  - serum β-HCG test in women of childbearing potential.
  - pre-dose serum potassium and glucose.

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

- The occurrence of adverse events will be checked and recorded if any.
- The investigator will collect the paper diary to verify the study drug compliance and rescue medication intake.
- The investigator will access IRT to record the visit.
- Pre-dose spirometry: FVC pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC. This measurement will be taken at T -45’ and T -15’ prior to study drug intake.
- **The administration of the last and final dose of study drug will take place at the clinic visit (before 10:00 am) under supervision of the Investigator.**
- The morning dose of the background ICS **QVAR®** will be administered immediately after the study drug, at the dose prescribed at V1.
- Post-dose spirometry will be performed 15’, 30’, 45’, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, and 12h. For each time point, spirometry consists in three acceptable maneuvers (see section 7.2.5).

- Post-dose SBP/DBP assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.2).
- Post-dose 12-lead ECG assessments will be conducted after 5 minutes of rest at 30min, 1h, 4h, 8h and 12h (see section 7.2.4).
- Post-dose serum potassium and blood glucose assessments will be conducted at 1.5h, 3h, 5h, 7h, and 11h (see section 7.2.7).

Before discharge at Visit 9

- **All study material (study and rescue medications, subject diary including Peak Flow meter) will be collected.**
- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer the subject to their primary care physician.
- An appointment will be made in 1 week time for the follow-up phone call.

7.1.8 Follow-up Phone Call (Visit 10)

A safety follow-up phone call will be performed by the investigator or designated staff no later than 1 week after the final visit (V9) or Early Termination Visit to check the status of unresolved AEs and to record any new AEs that may have occurred after V9, as well as related concomitant medications.

7.1.9 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 including Peak Flow meter) will be collected.
- Site to update IRT .
- Vital 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 7.2.2).
- A 12-lead ECG will be performed before spirometry, bronchodilator, background ICS medication (QVAR®) or study drug administration, after 5 minutes of rest (see section 7.2.4).
- Changes of concomitant medications being taken by the subject will be recorded.
- A full physical examination will be performed, including an assessment of the presence/absence of oral candidiasis.
- A blood sample will be collected before bronchodilator, background ICS medication (QVAR®) or study drug administration, after an overnight fasting (at least 10h, when possible), for the assessments of (see section 7.2.8):
  - standard hematology and blood chemistry;

- 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 adverse events will be checked and recorded if any.
- The investigator will collect the paper diary to verify the study drug compliance and rescue medication intake.
- Spirometry: FVC pre-dose spirometry measurement will then be performed to assess FEV_1 and FVC. This measurement will be taken before the expected time of dosing (T-45 and T-15) (the subject will not be dosed).
- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer the subject to their primary care physician.
- An appointment will be made in 1 week time for the follow-up phone call.

7.2 Investigations

7.2.1 ACQ Questionnaire

The Asthma Control Questionnaire (ACQ) is a validated questionnaire that measures the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ consists of 7 items: six simple, self-administered questions referring to asthma control and rescue treatment usage with one week recall, and a seventh item consisting of the % predicted FEV_1 completed by clinic staff. Scoring uses a 7-point scale, with 0 indicating *"totally controlled"* and 6 indicating *"severely uncontrolled"*. The ACQ score will be calculated as the average of all 7 items. A score of 0.0–0.75 is classified as well-controlled asthma; 0.75–1.5 as a grey zone; and >1.5 as poorly controlled asthma. The MCID is considered to be a change of 0.5 unit.[65][70] The ACQ will be completed on site, at Visit1 and Visit 2. Only subjects with an ACQ-7 score ≥1.5 are eligible for randomization (the criteria must be met at screening and at the end of the run-in period). The 7th item should be populated using the pre-BD FEV_1 at the visit when reversibility is met (V1 or V1.1) and the T-15 minutes FEV_1 assessment at V2.

The ACQ-7 is provided on paper and should be completed by the patient in a quiet place before the pulmonary function testing, only question 7 will be completed after the testing. The investigator (or designated site-personnel) should check that all items have been completed by the patient, but the response to each item should not be questioned. The scores will then be transcribed into the eCRF by the Investigator (or designated site personnel).

7.2.2 Vital Signs

Systolic and diastolic blood pressure will be measured after 5 min rest in resting position. The measurements will be done before morning dose of study drug and background ICS medication (QVAR®) at all visits, and 30 mins, 1h, 4h, 8h and 12h post-dose (V2-V9). SBP and DBP has 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 approximately the same time.

7.2.3 Physical Exam and assessment of oral candidiasis

A full physical examination including an assessment of the presence/absence of oral candidiasis will be performed at V1, V9 and Early Termination. These examinations shall be completed before spirometry testing, administration of study drug, bronchodilator, or background ICS (QVAR®) medication.

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. Generalized immunosuppressive and anti-inflammatory effects of steroids are thought to play a major role in the pathogenesis of candidiasis. Asthmatics who are using β-2 agonists show a decreased salivary flow rate, which in turn can be associated with higher oral Candida counts.

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.

7.2.4 12-lead ECG

A 12-lead ECG will be performed before morning dose of study drug and background ICS medication (QVAR®) at all visits to verify the patient's cardiac safety parameters and his/her eligibility. Subjects will be instructed to refrain from the intake of any caffeinated beverages or foods past midnight before each visit. At Visits 2-9, the ECG will be performed also at 30 min, 1h, 4h, 8h and 12h after the morning dose of study drug. Prior to recording, the patient should be at rest for at least 5 minutes. A 10-second strip will be recorded in triplicate, at 30-sec intervals at each time-point.

Standard electrode placement will be used for these ECG, including placing the limb leads, dual snap electrodes will be used for the precordial leads.

ECG will be evaluated and interpreted at a central laboratory and in case of any abnormality requiring urgent action ECG should be also evaluated on site (before sending to central laboratory).

The specific procedures for ECG recording, reading and transmission of the results will be provided to the investigator by the central laboratory.

QT interval corrections (QTc) will be done using the following formulae:

- QTcF (Fridericia's correction) = $\frac{QT}{\sqrt[3]{RR}}$. This will be done by both the centralized ECG service provider and by the on-site investigator to confirm if the subject meets the Inclusion/Exclusion criteria at V1, and for safety monitoring at subsequent visits.

Digitalized 12-lead ECG will be measured in supine position after at least 5 min rest. ECGs will be digitally recorded and sent to a central laboratory for a high resolution digital manual measurement of the cardiac intervals and morphological changes (HR, PR, QRS, QTcF). ECG measurements will be performed by experienced technicians using digitization software with magnification of the ECG and point to point determination on the digitizing pad and by a centralized cardiologist.

ECGs with computerized protocol interpretation are considered normal if

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

For eligible subjects, QTcF values must be QTcF ≤ 450ms (for males) and ≤ 470ms (for females) (as per Exclusion Criterion 14).

In case of relevant ECG abnormalities, the inclusion of the patient will be judged by the investigator. For any doubts the Investigator may consult the study clinical monitor. The final decision for enrollment 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. A review and interpretation of all ECGs will be performed by the cardiologist of the central laboratory. Any discrepancy observed between the cardiologist and the investigator assessment will be discussed during the study as part of the on-going medical review activities.

7.2.5 Pulmonary Function Test

All pulmonary function tests including FEV_1 and FVC will be performed in accordance with ATS/ERS spirometry criteria,[71] 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.

Pulmonary function measurements will be done with subjects sitting with the nose clipped after at least 10 minutes rest. Calibration of the spirometer must be performed by the same investigator or designee (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 patient.

The following parameters will be recorded at Visit 1-9 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.

Note: some additional standard parameters (for instance PEF, $FEF_{25-75\%}$, or ratio FEV_1/FVC) will be assessed by the spirometer during the visit only for the investigator's informational purpose.

Predicted normal value for FEV_1 will be calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations.[72].

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 (≤ 100mL when FVC is < 1L).[73] If these criteria are not met in 3 maneuvers, additional trials should be attempted, up to, but usually no more than 8.

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 patient 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 patient requires rescue medication within this timeframe, the visit should be rescheduled once within the next two days.

The background ICS 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).

At Visit 1, airway reversibility will be assessed with spirometry in triplicate maneuvers (as described above) before and within 30 minutes after administration of 4 separate doses of albuterol HFA (90µg of albuterol/actuation, total dose 360µg) at 30-sec intervals. An increase in FEV_1 ≥12% of control and ≥200mL constitutes a positive bronchodilator response.[66]

At Visits 2-9, serial spirometry will be conducted at T-45 and T-15 minutes pre-morning dose and 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, pre-dose spirometry measurement will be performed to assess FEV_1 and FVC. Measurements will be taken at 15 and 45 min before the expected time of dosing (T-45 and T-15). The subject will not be dosed.

7.2.6 Subject Diaries

Using paper diary dispensed at visits V1 – V8, subjects will be instructed to:

- Enter a daily record of day-time and night-time **Asthma Symptom Score** (overall symptoms, cough, wheeze, chest tightness and breathlessness), as follows:

  - **Morning (night-time asthma symptom score):**
    0 No symptom
    1 Mild: symptoms not causing awakening
    2 Moderate: discomfort enough to cause awakenings
    3 Severe: causing awakenings for most of the night / do not allow to sleep at all

  - **Evening (daytime asthma symptom score):**
    0 No symptom
    1 Mild: aware of symptoms which can be easily tolerated
    2 Moderate: discomfort enough to cause interference with daily activity
    3 Severe: incapacitating with inability to work/take part in usual activity

- Record the daily use of **Asthma Rescue Medication** as follows: the number of puffs taken during the night will be recorded each morning on awakening, while the number of puffs taken during the day will be recorded each evening, both before taking the study drug
- Perform **Peak Expiratory Flow rate** (PEF, L/min) measurements twice daily, in triplicate, starting at V1 using a portable electronic peak flow meter. (Vitalograph asma-1™). Subjects will be educated on the purpose and technique of PEF home monitoring. Specific instructions for use will be made available to the subjects. During each measurement session (morning or evening before the intake of the background ICS medication QVAR® or the study drug) the patient will perform 3 exhalations and will record the best measurement in the diary. Morning measurements should be done approximately between 7:00 am and 9:00 am and evening measurements should be done approximately between 7:00 pm and 9:00 pm.
- Enter twice daily (am and pm) the number of study drug doses taken.
- Record twice daily all doses of QVAR® background medication.

7.2.7 Serum Potassium and Glucose

β-adrenergic receptor agonist medications may produce significant hypokalemia in some subjects, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects The decrease in serum potassium is usually transient, not requiring supplementation. β-adrenergic receptor agonist medications may also produce transient hyperglycemia in some subjects.[59] At V2-9, blood samples of about 2.5 mL will be collected for measuring serum potassium and glucose pre-dose and at 1.5, 3, 5, 7 and 11h post-dose (total blood volume = 15 mL/Visit).

7.2.8 Hematology, Chemistry, and Pregnancy Tests

Blood samples of about 12 mL will be collected for hematology and serum chemistry at Visit 1, Visit 9 and Early Termination in the morning, after an overnight fasting of at least 10 hours (only water is allowed during the night) and before administration of albuterol, QVAR® or study drug. The blood withdrawal should be performed after vital signs and 12-lead ECG recording. An additional blood sample will be collected for serum pregnancy test in women of childbearing potential at these Visits, and a urine pregnancy test will be performed at visits (V1-8).

The following evaluations will be performed using a central laboratory:

- A hematology test: red blood cells count (RBC), white blood cells count (WBC) and differential, total hemoglobin (Hb), hematocrit (Hct), platelets count (PLT).
- A 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, glucose and electrolytes (sodium, potassium, calcium, and chloride).
- A serum pregnancy test (serum β-hCG) in women of child-bearing potential.
- A urine pregnancy test 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.

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 V1), or as an Adverse Event (if occurred after V1).

7.2.9 Asthma Action Plan and Handling of Asthma Exacerbations

The subject will be instructed to contact the site immediately if they experience a moderate or severe asthma exacerbation based on the following definitions:

Severe Asthma Exacerbation[74]
Severe asthma exacerbations are events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma. The definition of a severe asthma exacerbation for clinical trials should include at least one of the following:

- Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for ≥ consecutive 3 days.
    - For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.
- A hospitalization or ER visit because of asthma, requiring systemic corticosteroids.

Moderate Asthma Exacerbation[75]
A moderate exacerbation is defined as ≥1 of criteria fulfilled ***and*** leading to a change in treatment*:

a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights

b) Increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day)
c) ≥20% decrease in am or pm PEF from respective baseline on ≥ 2 consecutive mornings/evenings or ≥20% decrease in FEV1 from baseline
d) Visit to the emergency room/trial site for asthma treatment not requiring systemic corticosteroids

Subjects who experience a severe asthma exacerbation will be instructed to visit the site as soon as possible for an Early Termination Visit and will be withdrawn permanently from the study. Appropriate medical management of all asthma exacerbations will be ensured by the study investigator with the aim to preserve the research subject's well-being at all times.

**A change in treatment should be reviewed with the subject for any non-permitted concomitant medication that may trigger Early Termination from the study.*

8 EFFICACY ASSESSMENTS

Primary efficacy variable

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14

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 Day 14
- 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 at Day 14
- Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Day 14
- Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Day 14
- Time to onset of action (change from baseline in post-dose FEV_1 ≥ 12% and ≥ 200 mL) at Day 1

9 SAFETY ASSESSMENTS

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure)
- 12-lead ECG parameters (HR, QTcF, QRS, PR)
- HR $AUC_{0\text{-}4h}$ normalized by time and HR $peak_{0\text{-}4h}$
- Serum potassium and blood glucose

10 ADVERSE EVENT REPORTING

10.1 Definitions

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

this treatment". An adverse event can therefore be any 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** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

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

- **Is life-threatening**

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

- **Requires hospitalization or prolongation of existing hospitalization**

Hospitalization refers to a situation whereby an AE is associated with unplanned overnight formal admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as a 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 infectious agent is also considered a serious adverse reaction

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

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (Investigator's Brochure for CHF 1531 pMDI or US-FDA approved Product Information for PERFOROMIST®), 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

- 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 AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the 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.	E-mail
[redacted], MD Medical Safety Officer [redacted]	[redacted]	[redacted]	[redacted]
[redacted] Global Pharmacovigilance, Chiesi Farmaceutici S.p.A.	[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 events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

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.

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 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 medications received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.
- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose either of study drug, the background ICS, or the 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 will sign the Informed Consent will be entered into the database. 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.
Questionnaire (ACQ) patient's answers and daily diary will be databased. Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, 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, 12-Lead ECG, Central Laboratory) will be processed centrally and results will be sent electronically to the designated CRO. 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 patient 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 1531 pMDI at different doses over placebo in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14. The calculation is based on simulations.

A total of 51 evaluable subjects will provide 96% power to detect a mean difference of 200 mL between each dose of CHF 1531 pMDI and placebo at a two-sided significance level of 0.0125, assuming a within-subject standard deviation of 180 mL. Since four dose levels will be tested, the Edwards and Berry method[76]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[76] method is uniformly more powerful than the Bonferroni procedure.

Considering a non-evaluable rate of 15%, a total of approximately 60 subjects (5 subjects for each of the 12 treatment sequences) 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.

The inclusion in each population will be defined on a per-period basis. Since the superiority of CHF 1531 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 analyzes (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 (except for baseline characteristics which will be provided overall) 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

- If one of the spirometry measurements at T-45 min and T-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 for spirometry data, 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 12h post-dose is missing, it will be replaced by the value at 11.5h;
  - 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 12h 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 45min, 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 time-point with change from baseline in $FEV_1 \geq 12\%$ and $\geq$ 200 mL, then Time to onset of action will be equal to the first post-dose time-point with change from baseline in $FEV_1 \geq 12\%$ and $\geq$ 200mL in the time interval considered (12h). In case of no time-point with change from baseline in $FEV_1 \geq 12\%$ and $\geq$ 200mL, and less than four missing values among post-dose spirometry measurements at 15min, 30min, 45min, 1h, 2h, 3h and 4h, then Time to onset of action will be equal to the last available post-dose time-point with non-missing data and the subject will be considered as censored in the analysis.
- HR AUC_{0-4h} will be calculated only if HR data are recorded on each time-point (pre-dose, and 30 minutes, 1h, 4h post-dose).
- HR $peak_{0-4h}$ will be calculated only if HR data are recorded on each post-dose time-point (30 minutes, 1h, 4h post-dose).

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 Patient demographics and baseline characteristics

The following variables will be summarized overall 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_{0-12h} normalized by time at Day 14 will be analyzed using an Analysis of Covariance (ANCOVA) model including treatment, period and subject as fixed effects and baseline (average of the pre-dose FEV_1 measurements on Day 1 of each treatment period) as a covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) at Day 14 will be estimated by the model. The CIs and the p-values of the comparisons between each dose of FF pMDI and placebo will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry.[75] At each dose level, the superiority of CHF 1531 pMDI over placebo will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favoring CHF 1531 pMDI.

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

12.3.5 Secondary efficacy variables

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

- 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 Day 14 and change from baseline in pre-dose morning FEV_1 at Day 14 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 Day 14 and change from baseline in pre-dose morning FVC at Day 14 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 $FEV_1 \geq 12\%$ and ≥ 200 mL) at Day 1 will be analyzed using a Cox proportional hazard model stratified by subject and with treatment and period as factor and baseline FEV_1 (average of the pre-dose FEV_1 measurements on Day 1 of each treatment period) as covariate. A Kaplan-Meier plot will be presented.

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 measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

ECG

12-lead ECG parameters (HR, QTcF, QRS and PR) and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline/pre-dose).

The number and the percentage of subjects with a:

- QTcF >450ms (males only), >470ms (females only), >480ms (males only) and >500ms;
- change from baseline (pre-dose measurement on Day 1 of each treatment period) in QTcF >30 ms and >60ms;
- for post-dose time-points on Day 14: change from pre-dose on Day 14 in QTcF >30ms and >60ms

At each post-dose time-point and at any post-dose time-point will be presented by treatment. At each post-dose time-point, the change from baseline (pre-dose measurement on Day 1 of each treatment period) in 12-lead ECG parameters (HR, QTcF, QRS and PR) will be analyzed using an ANCOVA model including treatment, period and subject as fixed effects and baseline (pre-dose measurement on Day 1 of each treatment period) as a covariate. The adjusted means in each treatment and the adjusted mean differences between treatments will be estimated by the model with 90% CIs.

HR AUC_{0-4h} normalized by time and HR $peak_{0-4h}$ on Day 1 and Day 14 and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline/pre-dose).

Serum potassium and blood glucose

Serum potassium and blood glucose and their changes from baseline (pre-dose measurement on Day 1 of each treatment period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

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 pre-treatment 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 SOURCE DOCUMENTS/DATA

The Investigators or designated 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 regulatory national and/or international regulatory agencies during and after the study has been completed.

18 QUALITY ASSURANCE

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

19 INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies. Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or designee 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 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 to all Institutional Review Boards, to the US Competent Authority and to Investigators.

23 RECORD RETENTION

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

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

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

24 PUBLICATION OF RESULTS

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

25 REFERENCES

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APPENDIX I

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**

APPENDIX II

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A randomized, double-blind, placebo and active-controlled, incomplete block cross-over, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 1531 pMDI (Formoterol Fumarate) in asthmatic subjects

Product: CHF 1531 pMDI (Formoterol Fumarate)

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

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