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CLINICAL STUDY PROTOCOL

IND No. : 133679

An 8-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (beclomethasone dipropionate) in asthmatic subjects

Version No.: 4.0
Date: 05Jun2018

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]
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CENTRAL LABORATORY OF ANALYSIS:	[redacted]
OTHER CENTRAL TECHNICAL LABORATORIES	Spirometry: [redacted]

VERSION HISTORY

Version	Date	Change History
1.0	*24Feb2017*	
2.0	*19May2017*	Removal of morning serum total cortisol from V4, clarification of non-permitted conmeds, other changes as specified by Summary of Changes document.
3.0	*18Oct2017*	Increasing BMI range, increasing FEV_1 range, other changes as specified by Summary of Changes document.
4.0	*05Jun2018*	Increasing basal morning serum cortisol level range, clarification on additional screening attempts, clarification on dosing at Visit 4 (none), other changes are specified by the Summary of Changes document.

PROTOCOL OUTLINE

Study Title	An 8-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (beclomethasone dipropionate) in asthmatic subjects
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 718 pMDI (beclomethasone dipropionate)
Center(s)	Multi-center, in approximately 105 sites
Indication	Asthma
Study design	Randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study
Study phase	II
Objectives	***Primary objective:*** ▪ To evaluate the efficacy of CHF 718 pMDI by comparison with placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8. ***Secondary objectives:*** ▪ To evaluate the effect of CHF 718 pMDI on other lung function parameters and clinical outcome measures. ▪ To assess the safety and the tolerability of the study drug.
Treatment duration	A 2-week run-in period on ICS monotherapy followed by an 8-week randomized treatment period.
Test product dose/route/regimen	▪ **CHF 718 pMDI: beclomethasone dipropionate pressurized metered dose inhaler (pMDI), available in 50µg per inhalation (BDP 50) and 100µg per inhalation (BDP 100).** Treatment A: BDP 100µg Total Daily Dose (TDD) ➢ BDP 50µg per inhalation, 1 inhalation bid* Treatment B: BDP 400µg TDD ➢ BDP 100µg per inhalation, 2 inhalations bid* Treatment C: BDP 800µg TDD ➢ BDP 100µg per inhalation, 4 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 718 pMDI** Treatment D:

	➢ Matched placebo, 4 inhalations bid ▪ **QVAR® 80µg (beclomethasone dipropionate HFA, 80µg) Inhalation Aerosol: Each canister contains 120 actuations.** Treatment E: BDP 320µg TDD ➢ BDP 80µg per inhalation, 2 inhalations bid **QVAR®** will be administered as open label.
Number of subjects	A total of approximately 585 subjects will be randomized in order to reach a total of 495 completed and evaluable subjects, considering a non-evaluable rate of 15%.
Study population	Subjects with poorly controlled or uncontrolled moderate asthma on low/medium doses of inhaled corticosteroids
Inclusion/exclusion criteria	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Male or female subjects aged ≥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 ≥50% and <85% of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits. 5. A documented positive response to a reversibility test (pre – post BD) within 1 year prior to or 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 (stable dose in the last 4 weeks) before screening visit.

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

**(Table adapted from GINA 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	› 160µg 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	› 160µg 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	› 160µg bid - N/A†
SYMBICORT® 80/4.5	160/9µg bid	80µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

† *This ICS/LABA 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 electronic diary, peak flow meter, and pMDI inhalers.
8. A basal morning (7-10 am) serum cortisol level between 5-28µg/dL at screening (V1).
9. A Body Mass Index: 18.5≤ BMI <35 kg/m^2.

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 and met on the same day, and before reversibility test is conducted.
At randomization (V2), inclusion criteria # 3, 4 and 7 should also be re-checked.

Exclusion Criteria:

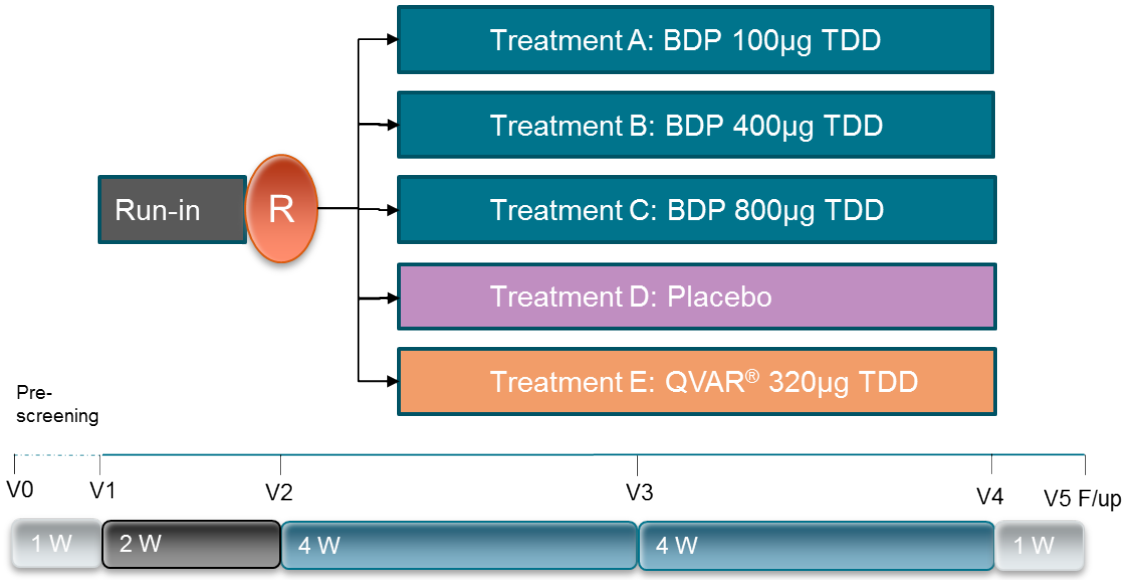
If a subject meets any of the following criteria, he/she will NOT be enrolled into the study:

1. Pregnant (as evident by a positive urine hCG or serum β-hCG test) or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are willing to use a highly effective birth control method such as:
   a. Placement of an intrauterine device (IUD) or intrauterine releasing system (IUS).
   b. Oral, intravaginal, transdermal combined estrogen and progesterone containing hormonal contraception or oral, injectable, implantable progesterone only hormonal contraception.
   c. Bilateral tubal ligation.
   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 screening, at Visit 4 and at the early termination visit; urinary pregnancy test will be performed at screening, Visit 2 and 3. Women of non-childbearing potential defined as physiologically incapable of becoming pregnant: post-menopausal (defined as no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) are eligible. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy. 2. Subjects who suffer from COPD as defined by the GOLD Report, 2017, or are suspected of having Asthma COPD Overlap Syndrome (ACOS) as defined 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 corticosteroids within 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 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.

	12. Subjects who have a clinically significant abnormal 12-lead ECG that results an active medical problem which may impact the safety of the subject according to Investigator's judgment. 13. Subjects whose 12-lead ECG shows Fridericia corrected QT interval (QTcF) >450ms for males or QTcF >470ms for females at screening or randomization visits. 14. Subjects with known intolerance/hypersensitivity or contra-indication to treatment with inhaled $ß_2$-adrenergic receptor agonists, corticosteroids or propellant gases/excipients. 15. 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. 16. Use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening. 17. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening. 18. 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. 19. Subjects who are mentally or legally incapacitated or subjects accommodated in an establishment as a result of an official or judicial order. 20. 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, 12 and 13 should be re-checked at the randomization visit (V2).
Study plan	The details of the assessments that will be performed during the study are summarized in the study flow diagram in table 1. After a 2-week run-in period, subjects will be randomized to one of the 5 treatment arms and will enter a period of 8 weeks of study treatment. The study will last approximately 12 weeks for each subject and a total of 5 clinic visits will be performed during the study *(see the flow chart below*) A one week follow-up will be conducted. ▪ A pre-screening visit (Visit 0) 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 (Visit 1) not more than 7 days after V0 will help establish the eligibility of subjects for inclusion in the study (including routine hematology and blood chemistry, morning serum cortisol, medical history, physical examination, weight/height/BMI, serum and urine pregnancy tests for female subjects of childbearing potential, a 12-lead ECG, ACQ assessment, spirometry testing pre and post BD (to determine post-BD reversibility if not documented within the past 1

	year, vital signs and training for the use of inhalers). Concomitant Medications and Adverse Events will be assessed. Dispensing of subject diary will be done. Eligible subjects will be provided with a container for the 24-h urine collection, to be returned to the site the day after completing the collection, 1-2 days before or on the date of their next visit (V2). This visit will be followed by a 14±2 day 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 be instead prescribed an equivalent daily dose of ICS as beclomethasone dipropionate (QVAR® 40 or 80µg/actuation) 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. ▪ At randomization visit (Visit 2), inclusion/exclusion criteria, adverse events and concomitant medications will be reviewed. Eligibility recheck will be completed. Pre-dose vital signs and spirometry testing [FEV_1, FVC] will be performed. A 12-lead ECG, physical examination, urine pregnancy test will be performed, and training on the use of inhalers will be conducted. The ACQ will be assessed. The 24-h urine collection container will be collected from the subject if not already done, and shipped to a central laboratory for 24-h urine free cortisol and creatinine measurement. Eligible subjects will then be randomized to one of the treatment groups and will receive the 1st dose of study drug under medical supervision. The subjects will then leave the clinical center and will be instructed to return in 4 weeks. ▪ At Week 4 (Visit 3) subjects will undergo a physical examination, urine pregnancy test, concomitant medications review, adverse events, study drug dispensation and vital signs assessment. Study drug will be returned and accountability will be performed. Pre-dose spirometry testing (FEV_1, FVC) will be performed and ACQ will be assessed. Subjects will be provided with a container for the 24-h urine collection, to be returned to the site the day after completing the collection, 1-2 days before or on the date of their next visit (V4). The subject will be instructed to return to the clinical center in 4 weeks. ▪ At Week 8 (Visit 4) subjects will come to the clinical center and will undergo a physical examination, hematology and blood chemistry, serum/urine pregnancy test and vital signs assessment. A 12-lead ECG will be performed. Concomitant medications and adverse events will be assessed. Pre-dose spirometry testing [FEV_1, FVC] will be performed. **No administration of the study drug will take place at V4.** The ACQ will be assessed. The 24-h urine collection container will be collected from the subject if not already done, and shipped to a central laboratory for 24-h urine free cortisol and creatinine measurement. Study drug will be returned and accountability will be done. Subject diary will be returned by the subject. After the last assessment a follow-up phone call will be scheduled with the subject. ▪ At Week 9 (Visit 5): A safety follow up phone call will be performed by the investigator or designated staff no later than 1 week after the final visit (V4) or Early Termination Visit to check the status of unresolved AEs and to record any new AEs that may have occurred

	after V4, 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. Nasal corticosteroids if already taken at stable doses for at least 2 months prior to screening visit (the dose must remain constant for the whole study period) or taken in short courses (10 days) during the study period. 4. Treatment for desensitization at the "maintenance" 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). 5. Antihistamines (intranasal, ocular or oral ± decongestant) at no greater than FDA-approved doses for the treatment of allergy symptoms. 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 "most relevant forbidden concomitant treatment".
Most relevant forbidden concomitant treatments	***Non-permitted concomitant medications (from V1)*** 1. Inhaled corticosteroids other than the run-in medication and study drug. 2. Inhaled short-acting muscarinic antagonists (SAMA), or long-acting muscarinic antagonists (LAMA). 3. Inhaled fixed or free combinations of ICS/LABAs. 4. Inhaled long-acting β2-agonist drugs (LABAs). 5. Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers).

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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.
11. Non-cardioselective ß-blocking drugs (including eye drops), except if taken at stable regimen for at least 2 months before screening.
12. Any drug known to prolong the QT interval (e.g. quinidine, procainamide, amiodarone) except if taken at a stable regimen for at least 2 months before screening.
13. Any medication that could interact with the study drug, according to Investigator’s judgment.

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>1 month</td></tr>
<tr><td>Intramuscular depot corticosteroid</td><td>3 months</td></tr>
</table>

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

<table>
<tr><td>Inhaled short-acting β_2-agonists</td><td>6 hours</td></tr>
<tr><td>Caffeinated substances</td><td>6 hours</td></tr>
</table>
</td>
</tr>
<tr>
<td>Efficacy variables
(and/or pharmacokinetics variables)</td>
<td>
Primary efficacy variable
▪ Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 8
</td>
</tr>
</table>

	Secondary efficacy variables ▪ Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 4 ▪ Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Week 4 and Week 8 ▪ Change from baseline in ACQ-7 score at Week 4 and Week 8 ▪ Change from baseline in average use of rescue medication during inter-visit periods and entire treatment period ▪ Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period ▪ Change from baseline in daily asthma symptoms score during inter-visit periods and entire treatment period ▪ Change from baseline in percentage of asthma symptoms-free days during inter-visit periods and entire treatment period ▪ Change from baseline in percentage of asthma control days during inter-visit periods and entire treatment period Change from baseline in morning and evening pre-dose PEF during inter-visit periods and entire treatment period
Safety variables	▪ Adverse Events (AEs) and Adverse Drug Reactions (ADRs) ▪ Vital signs (systolic and diastolic blood pressure) ▪ 12-lead ECG parameters (HR, QTcF, QRS, PR) ▪ Standard blood chemistry and hematology ▪ 24-h Urinary Free Cortisol and Creatinine
Sample size calculation	The sample size has been calculated to evaluate the superiority of CHF 718 pMDI at different doses over placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8. A total of 495 evaluable subjects (99 per group) will provide 80% power to detect a mean difference of 200mL between each dose of CHF 718 pMDI and placebo at a two-sided significance level of 0.0167 (since 3 dose levels will be tested, the Bonferroni adjustment has been taken into account: 0.0167 = 0.05/3), assuming a standard deviation of 430mL. Considering a non-evaluable rate of 15%, a total of approximately 585 subjects (117 per group) will be randomized.
Statistical methods	***Primary efficacy variable*** Change from baseline in pre-dose morning FEV_1 will be analysed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, ICS dose before study (low/medium daily dose) and US regions as fixed effects, and the baseline value (average of the pre-dose FEV_1 measurements at Visit 2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% two-sided Confidence Intervals (CIs) at Week 8 will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 718 pMDI and placebo at Week 8 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 718 pMDI over placebo will be demonstrated by a

	statistically significant difference (adjusted p-value < 0.05) favoring CHF 718 pMDI. All the other comparisons between treatments will be performed as secondary efficacy analyses with no multiplicity adjustment. ***Secondary efficacy variables*** No multiplicity adjustment will be performed in the secondary efficacy analyses. • For change from baseline in pre-dose morning FEV_1 at Week 4, the adjusted means in each treatment group and the adjusted mean differences between treatments at Week 4 will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis. • Change from baseline in pre-dose morning FVC at Week 4 and Week 8 will be analyzed using a similar model as the one used for the primary efficacy analysis. • Change from baseline in ACQ-7 score at Week 4 and Week 8 will be analyzed using a similar model as the one used for the primary efficacy analysis. • Change from baseline to each inter-visit period in average use of rescue medication, in percentage of rescue medication-free days, in daily asthma symptoms scores, in percentage of asthma symptoms-free days, in percentage of asthma control days and in morning and evening pre-dose PEF will be analyzed using a similar model as the one used for the primary efficacy analysis. The inter-visit period will be considered instead of visit in the model. Comparison between treatments over the entire treatment period will also be derived from this model. ***Safety variables*** **Adverse Events** All adverse events starting on or after the time of first study drug intake will be classified as Treatment Emergent Adverse Events (TEAEs). Any adverse event started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. Pre-treatment adverse events will be listed only. The number of TEAEs and the number and percentage of subjects who experienced at least one TEAE will be presented by treatment for all AEs, ADRs, serious AEs, serious ADRs, severe AEs, AEs leading to study discontinuation and AEs leading to death. Summaries will be presented overall and by system organ class and preferred term based on the MedDRA dictionary. **Vital signs** Vital signs (systolic and diastolic blood pressure) and their changes from baseline (Visit 2) 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 (Visit 2) 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). The number and the percentage of subjects with a: • QTcF >450ms (males only), >470ms (females only), >480ms (males only) and >500ms • change from baseline (Visit 2) in QTcF >30ms and >60ms at post-baseline visit will be presented by treatment group. **Laboratory parameters** Shift tables from screening to the end of treatment, based on normal ranges, will be presented by treatment group for the laboratory parameters. Mean change from baseline (Visit 2) to the end of treatment in 24-h urinary cortisol and creatinine will be calculated with its 95% CI by treatment group.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACI	Andersen Cascade Impactor
ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BD	Bronchodilator
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
CRA	Clinical Research Associate
(e-) CRF	(Electronic) Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	ElectroCardioGram
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
FPFV	First Patient First Visit
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GCP	Good Clinical Practices
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSD	Geometric Standard Deviation
h	hour
hCG	human Chorionic Gonadotropin hormone
HFA	Hydrofluoroalkane
HR	Heart Rate
IB	Investigator Brochure
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL5	Interleukin 5
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intention to Treat

IU (D or S)	Intra Uterine (Device or System)
L	Liter
LABA	Long Acting β_2-adrenergic receptor Agonist
LDH	Lactate dehydrogenase
LABD	Long-acting bronchodilators
LAMA	Long Acting Muscarinic Antagonist
LLN	Lower Limit of Normal
LPLV	Last Patient Last Visit
LS	Least Square
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
MMAD	Mass Median Aerodynamic Diameter
mMRC	modified Medical Research Council
NYHA	New York Heart Association
OCS	Oral Corticosteroid
PEF	Peak Expiratory Flow
PIL	Patient Information Leaflet
pMDI	Pressurized Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval from the beginning of the upslope of the P wave to the beginning of the QRS wave in the ECG
PRO	Patient Reported Outcome
prn	Pro re nata (as-needed)
qd	Every Day
Q	Quaque (every so-,any hours)
QRS	Time Interval from the end of the PR interval to the end of the S wave in the ECG
QTc	Time interval between the start of the Q wave and the end of the T wave in the ECG (corrected for HR)
QTcF	QT interval corrected for HR using Fridericia's formula
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SABA	Short-acting Beta Agonist
SABD	Short acting bronchodilators
SADR	Serious Adverse Drug Reaction
SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events

TDD	Total Daily Dose
UFC	Urinary free cortisol
ULN	Upper Limit of Normal
VC (SVC / FVC)	Vital Capacity (Slow /Forced)
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

CONTENTS

APPENDICES

1. INTRODUCTION

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 subject.[2]

The NHANES III national survey estimated the U.S. prevalence of COPD to be 10.2% to 20.9% based on whether pre- or post-bronchodilator values were used and which diagnostic criterion (fixed ratio or lower limit of normal {LLN}) was applied.[3][4] 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.[5]

Smoking cessation can have the greatest influence on stopping the progression of COPD, as well as increasing survival and reducing morbidity.[6] However, long-term cessation success rates rarely exceed 25%.[2][7]

Existing pharmacologic therapy is used to improve airflow, symptoms, exercise capacity, health status, and reduce the frequency and severity of exacerbations in stable COPD. To date, there is no conclusive evidence that any available pharmacotherapy for COPD modifies the long-term decline in lung function. The 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.[8][9][10]
  - ***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,[11] effectiveness of pulmonary rehabilitation,[12][13] and to reduce exacerbations and related hospitalizations[14] compared to placebo.

- Adverse events of this class of medications are mainly due to their anticholinergic activities, and include dry mouth, constipation, urinary retention and increased intraocular pressure.

- ***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 $FEV_1 \geq 25\%$ 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).[15] Combining a SABA and a SAMA or a LABA and LAMA can be done using separate inhalers or using a single inhaler containing a fixed dose combination.

- **Anti-inflammatory agents**
  - **Inhaled Corticosteroids (ICS) alone:** The available evidence does not support a beneficial effect of ICS monotherapy in subjects with COPD.[16]
  - **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.

    - Post-hoc analyses suggest that sputum and blood eosinophil count may be a predictor of ICS efficacy, particularly in preventing exacerbations.[17]
    - High quality evidence has confirmed an increased rate of pneumonia, oral candidiasis, hoarseness and skin bruising with ICS treatment.[18][19][20][21][22] Factors associated with a higher risk for pneumonia on ICS include: current smokers, age $\geq$ 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.[23][24] A meta-analysis suggested that subjects with COPD with lower blood eosinophil counts (<2%) had more pneumonia events than did those with higher counts.[25]
    - RCTs have reported variable outcomes regarding ICS effect on decreased bone mineral density (BMD)[26][27] and risk of fractures,[28] and observational studies suggest an increased risk of diabetes / poorly controlled diabetes,[29] cataracts,[30][31] and mycobacterial infections, including tuberculosis.[32]

- **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.[33][34][35][36][37][38] 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 characterized by variable symptoms of wheezing, shortness of breath, chest tightness and/or cough, and by variable expiratory flow limitations. Variations over time and intensity are often triggered by factors such as exercise, environmental/occupational exposures, or viral respiratory infections.[39] As of 2014, the Center for Disease Control (CDC) estimated that the prevalence of asthma in US adults is 7.4%.[40]
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, *Reliever*s, 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. The controller medication is adjusted up or down in a stepwise approach to achieve these 4 goals.
- **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:

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 theophylline	Med-High dose ICS + LTRA (or + theo)	Add tiotropium High dose ICS + LTRA (or + theo)	Add low-dose OCS
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 Pressurized Inhalation Solution (pMDI, Modulite®) and as a dry powder for inhalation (DPI) by the NEXThaler® device, releasing extra-fine particles.[41] FOSTER® pMDI has been developed with a high "extrafine" (< 1.1µm) BDP particle size fraction, similarly to another HFA BDP marketed formulation (QVAR® Inhalation Aerosol, Teva Respiratory, LLC).

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

The submission of the EMEA dossier is based on the results of a large and comprehensive development program performed by Chiesi since 2009, which included 12 clinical studies involving more than 8,000 subjects.[42]

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. A dose-ranging study with Chiesi's formulation of HFA BDP pMDI has not been previously done.

The aim of this study is to characterize the dose-response of Chiesi's BDP Pressurized Inhalation Solution delivered via a non-CFC-propelled metered-dose inhaler (CHF 718 pMDI) and containing the same excipients as in FOSTER®. Three doses of CHF 718 pMDI: 50, 200, 400µg (ex-valve) twice daily will be assessed vs placebo, with QVAR® Inhalation Aerosol 320µg (400µg ex-valve) twice daily as an active comparator.

Dose selection of ICS in COPD is challenging given the lack of efficacy for ICS monotherapy that has been observed to date. Therefore, the study will be conducted in adult subjects with asthma, since asthmatics are thought to be more steroid-sensitive than subjects with COPD, using trough FEV_1 as the primary endpoint. While exacerbations may be a more meaningful assessment of the added benefit of an ICS in an ICS/LABA combination in subjects with COPD, the design and conduct of an exacerbation trial for the purposes of dose selection are challenging.[43][44]

Beclomethasone dipropionate (BDP):

Description and Mechanism of Action:
BDP is a pro-drug with weak glucocorticosteroid receptor binding affinity that is rapidly activated by hydrolysis via esterase enzymes to an active metabolite beclomethasone 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6

times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical significance of these findings is unknown.[45]

The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids may not affect symptoms immediately. Individual subjects will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.[46]

Beclomethasone dipropionate was first patented in 1962 and used medically in 1972. It was approved for medical use in the United States in 1976. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[47]

An HFA BDP inhalation aerosol was originally approved by the US FDA in Sep 2000 under the brand name QVAR®, as the first CFC-free metered dose inhaler containing a corticosteroid (a solution of beclomethasone dipropionate in propellant HFA-134a). It was the first inhaler designed to deliver smaller particle sized medication to the large, intermediate and small airways. This allowed QVAR® to control asthma at a lower dose than conventional CFC-containing BDP inhalers.[48]

Today, in the US, QVAR® is indicated for 1) Maintenance treatment of asthma as prophylactic therapy in subjects 5 years of age and older; and 2) Treatment of asthma in subjects who require oral corticosteroid therapy, where QVAR® may reduce or eliminate the need for the systemic corticosteroids. In May 2014, the FDA additionally approved the use of QVAR® with a dose counter for the ongoing treatment of asthma as a preventative therapy in subjects five years of age and older. QVAR® is supplied in two strengths: 40 and 80µg/actuation and contains 120 actuations/canister.[45]

***Clinical Efficacy of HFA BDP*:**
Previously, a bridging study established the clinical equipotency with CHF 718 (HFA BDP) pMDI 100µg 2 puffs bid (TDD = 400µg) to CFC BDP 250µg 2 puffs bid (1,000µg) in adult subjects with mild-moderate symptomatic asthma, previously not well-controlled on low dose ICS.[49]

QVAR® 40, 160, and 320µg (ex-actuator) twice daily doses were evaluated vs. 42, 168 or 336µg CFC BDP twice-daily for 6 weeks in asthmatics who exhibited a deterioration in asthma control during an ICS washout period. Treatment with increasing doses of both QVAR® and CFC BDP resulted in increased improvement in FEV_1, $FEF_{25-75\%}$ and asthma symptoms. Thus, in subjects 12 years and older on ICS, the recommended starting dose of QVAR® was set as 40 – 160µg twice daily, and the maximum dose as 320µg twice daily.[50]

Clinical Safety of HFA BDP:
In clinical trials, Adverse Events reported by at least 3% of the subjects on QVAR® included headache, pharyngitis, upper respiratory tract infection, rhinitis, increased asthma symptoms, oral symptoms inhalation route, sinusitis, pain, back pain, and dysphonia. Other adverse events that occurred in these clinical trials using QVAR® with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were nausea, dysmenorrhea, and coughing. Oropharyngeal candidiasis occurred in <1% of subjects in both QVAR® and placebo treatment groups.

Warning and precautions in the QVAR® USPI include:

- Localized infections with *Candida albicans*
- Not indicated for relief of acute episodes of bronchospasm (i.e. not a reliever therapy)
- Glaucoma, increased intraocular pressure, and cataracts
- Particular care is needed in transfering subjects from systemic corticosteroid therapy due to the potential for fatal adrenal insufficieny
- Immunosuppression
- Paradoxical bronchospasm
- Immediate hypersensitivity reactions
- Hypercorticism and adrenal suppression
- Reduction in growth velocity in pediatric subjects
- Reduction in bone mineral density

In addition to adverse reactions experienced in the clinical trials, the following adverse events have been reported during post-approval use of QVAR®: Localized infections with *Candida albicans*, aggression, depression, sleep disorders, psychomotor hyperactivity, and suicidal ideation (primarily in children)[45]

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 E6 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 718 pMDI by comparison with placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8.

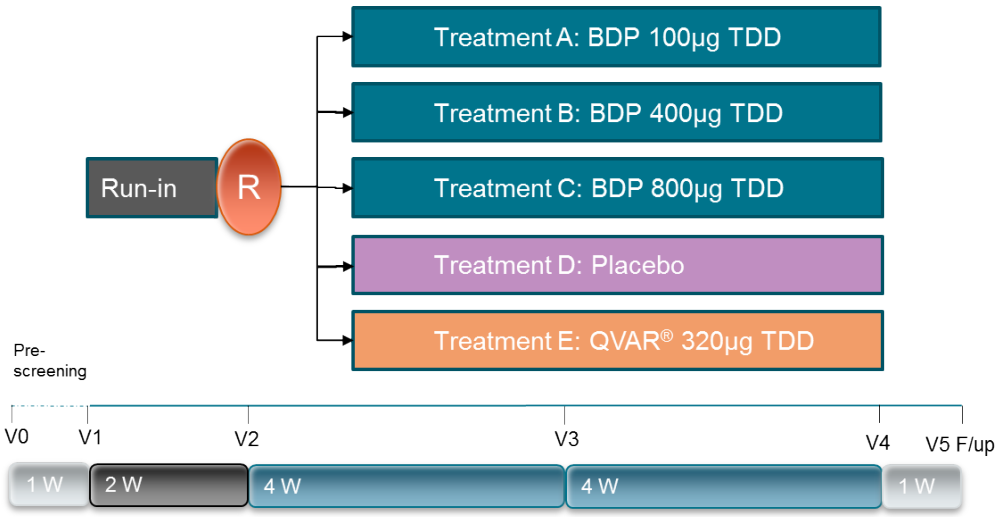
2.2 Secondary Objective(s)

- To evaluate the effect of CHF 718 pMDI on other lung function parameters and clinical outcome measures.
- To assess the safety and the tolerability of the study drugs.

3. STUDY DESIGN

This is a phase II, multi-center, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (HFA beclomethasone dipropionate) in adult subjects with asthma. Following a 2-week run-in period on

ICS monotherapy, eligible subjects will be randomized to one of five study drugs (1:1:1:1:1) delivered twice-daily for 8 weeks. After the last assessment a follow-up phone call will be scheduled with the subject. The study will last approximately 12 weeks for each subject and a total of 5 clinic visits will be performed during the study.



The end of the trial is defined as the last follow-up contact with 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 975 subjects will be screened and 585 randomized (117 per group) to yield 495 evaluable subjects. Recruitment will occur at approximately 105 participating outpatient study center(s) 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, documented for at least 1 year prior to screening.[39]
3. Poorly controlled or uncontrolled asthma evidenced by a score ≥1.5 on the Asthma Control Questionnaire 7 © (ACQ-7)[51] (this criterion must be met at screening and at randomization visits).
4. A pre-bronchodilator FEV_1 ≥50% and <85% of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits.
5. A documented positive response to a reversibility test (pre – post BD) within 1 year prior to or at screening, defined as ΔFEV_1 ≥12% and ≥200mL[52] over baseline within 30 minutes after inhaling 4 puffs of albuterol HFA 90µg/inhalation.

Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomization.[53]

6. Use of ICS (low/medium dose according to GINA Report, 2016) with or without a LABD for 3 months (stable dose in the last 4 weeks) before screening visit.

ICS*	Low daily dose	Medium daily dose
BDP extrafine (HFA pMDI) - QVAR®	80-160µg	>160-320µg
Budesonide (DPI)	200-400µg	>400-800µg
Ciclesonide (HFA pMDI)	80-160µg	>160-320µg
Flunisolide (HFA pMDI)	160 – 320µg	>320-640µg
Fluticasone furoate (DPI)	100µg	200µg
Fluticasone propionate (HFA pMDI/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	› 160µg 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	› 160µg 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	› 160µg bid - N/A†
SYMBICORT® 80/4.5	160/9µg bid	80µg bid
SYMBICORT® 160/4.5	320/9µg bid	160µg bid

† *This ICS/LABA 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 electronic diary, peak flow meter, and the pMDI inhalers.
8. A basal morning (7-10 am) serum cortisol level between 5-28µg/dL at screening (V1).[54]
9. A Body Mass Index: 18.5≤ BMI <35kg/m^2.[55][56][57]

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 and met on the same day, and before reversibility test is conducted.
At randomization (V2), inclusion criteria # 3, 4 and 7 should also be re-checked.

4.3 Exclusion Criteria

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

1. Pregnant (as evident by a positive urine hCG or serum β-hCG test) or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are willing to use a highly effective birth control method such as:
    a. Placement of an intrauterine device (IUD) or intrauterine releasing system (IUS).
    b. Oral, intravaginal, transdermal combined estrogen and progesterone containing hormonal contraception or oral, injectable, implantable progesterone only hormonal contraception.
    c. Bilateral tubal occlusion ligation.
    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 screening, at Visit 4 and at the early termination visit; urinary pregnancy test will be performed at screening, Visit 2 and 3.
    Women of non-childbearing potential defined as physiologically incapable of becoming pregnant: post-menopausal (defined as no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy) are eligible.
    If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges) in women not using hormonal contraception or hormonal replacement therapy.
2. Subjects who suffer from COPD as defined by the GOLD Report, 2017,[2] or are suspected of having Asthma COPD Overlap Syndrome (ACOS) as described in GINA Report, 2016.[39]
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 corticosteroids within 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 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.

12. Subjects who have a clinically significant abnormal 12-lead ECG that results in active medical problem which may impact the safety of the subject according to Investigator's judgment.
13. Subjects whose 12-lead ECG shows Fridericia corrected QT interval (QTcF) >450ms for males or QTcF >470ms for females at screening or randomization visits.
14. Subjects with known intolerance/hypersensitivity or contra-indication to treatment with inhaled ß2-adrenergic receptor agonists, corticosteroids or propellant gases/excipients.
15. 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.
16. Use of potent cytochrome P450 3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole) and inducers within 4 weeks prior to screening.
17. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening.
18. 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.
19. Subjects who are mentally or legally incapacitated, or subjects accommodated in an establishment as a result of an official or judicial order.
20. 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, 12 and 13 should be re-checked at the randomization visit (Visit 2).

4.4 Subject Withdrawals

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

- An adverse event occurs that, in the opinion of the investigator, makes it unsafe for the subject to continue 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 non-permitted concomitant medications.
- 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-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. Nasal corticosteroids if already taken at stable doses for at least 2 months prior to screening visit (the dose must remain constant for the whole study period) or taken in short courses (10 days) during the study period.
4. Treatment for desensitization at the "maintenance" 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).
5. Antihistamines (intranasal, ocular or oral ± decongestant) at no greater than FDA-approved doses for the treatment of allergy symptoms.

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 "most relevant forbidden concomitant treatment".

5.2 Non-Permitted Concomitant Medications

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

1. Inhaled corticosteroids other than the run-in medication and study drug
2. Inhaled short-acting muscarinic antagonists (SAMA), or long-acting muscarinic antagonists (LAMA)

3. Inhaled fixed or free combinations of ICS/LABAs
4. Inhaled long-acting β2-agonist drugs (LABAs)
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 treatment will be discontinued from the study.
7. Xanthine derivative (e.g. theophylline)
8. Anti-IgE and anti-IL5 monoclonal antibodies
9. Tricyclic antidepressants and Monoamine oxidase inhibitors (MAOIs)
10. Systemic anticholinergics
11. Non-cardioselective ß-blocking drugs (including eye drops), except if taken at stable regimen for at least 2 months before screening
12. Any drug known to prolong the QT interval (e.g. quinidine, procainamide, amiodarone), except if taken at a stable regimen for at least 2 months before screening
13. Any medication that could interact with the study drug, according to Investigator's judgment

Prior to screening spirometry (Visit 1), the following washout periods must be respected:[58]

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

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

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

6. TREATMENT(S)

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

6.1 Appearance and Content

Study drug

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

- ***CHF 718 pMDI 100µg - Test product***
  Active ingredient: beclomethasone dipropionate 100µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 doses

- ***CHF 718 pMDI 50µg - Test product***
  Active ingredient: beclomethasone dipropionate 50µg per inhalation
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 doses

- ***CHF 718 pMDI matched Placebo***
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 puffs

- ***QVAR® Inhalation Aerosol (Teva Respiratory, LLC) - Reference product***
  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

An in-vitro assessment of HFA BDP (the ICS component in CHF 1535 or FOSTER®) has been undertaken in comparison with QVAR® Inhalation Aerosol (3M Healthcare) using the Andersen Cascade Impactor (ACI). A very similar deposition profile between extrafine HFA BDP and QVAR® was obtained in the therapeutically useful range 1.1-4.7µm, being 22.0µg for HFA BDP and 23.2µg for QVAR®. The Fine Particle Dose = 36.1µg for HFA BDP and 43.3µg for QVAR®. MMAD and its associated geometric standard deviation (GSD) evidenced comparable particle size distribution, being 1.34µm ± 2.11 for BDP component in CHF 1535 and 1.14µm ± 1.87 for QVAR®, respectively, smaller compared to the 3.5-4.0µm found with CFC BDP).[59]

Additionally, and as part of the clinical development plan for FOSTER® Pressurized Inhalation Solution, a bridging study was conducted to confirm the bioequivalence of HFA BDP pMDI 100µg 2 puffs bid (TDD = 400µg) vs. BECLOFORTE® Inhaler (CFC BDP) 250µg 2 puffs bid (1,000µg)

in adult subjects with mild-moderate symptomatic asthma, previously not well-controlled on low dose ICS. The equivalence limit was set at ± 25L/min for the change from baseline in morning pre-dose Peak Expiratory Flow rate (AM PEF, primary endpoint),[49] similar to development studies with QVAR®,[60][61][62] and at ± 0.2L for FEV_1, because the upper limit of the normal variability of the FEV_1 measurement is known to approximate this value.[63]The results showed a LS mean difference in AM PEF and AM FEV_1 of 10.06 L/min (95% CI 0.88 to 19.24) and 0.05 L (95% CI (-0.04 to 0.14) respectively at the end of 8-week treatment between HFA BDP (n=115) and CFC BDP (n=118) in the ITT population, this confirming a clinical equipotency ratio of 1:2.5.

With QVAR®, clinical evidence confirms that adult and elderly subjects required approximately ½ the dose of extrafine HFA BDP to achieve the same degree of asthma control as with CFC BDP.[59]

Considering that the doses assessed in the QVAR® dose-ranging studies were 40, 160, and 320µg (ex-actuator) twice daily[50] (corresponding to 50, 200, and 400 ex-valve, respectively), The same ex-valve doses of CHF 718 pMDI will be used in this dose-ranging trial, namely 50µg, 200µg, and 400µg twice daily.

6.2.2 Dosage

6.2.2.1 Run-in period:

Standardized Run-in 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

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:

- **Treatment A**:

CHF 718 pMDI 50µg (Total daily dose: 100µg BDP)
An adequate number of inhalations from Placebo inhalers will be performed to maintain a double blind design.

  - One inhalation of CHF 718 pMDI 50µg plus three inhalations of CHF 718 pMDI matched placebo in the morning
  - One inhalation of CHF 718 pMDI 50µg plus three inhalations of CHF 718 pMDI matched placebo in the evening

- **Treatment B**

CHF 718 pMDI 100µg (Total daily dose: 400µg BDP)
An adequate number of inhalations from Placebo inhalers will be performed to maintain a double blind design.

  - Two inhalations of CHF 718 pMDI 100µg plus two inhalations of CHF 718 pMDI matched placebo in the morning
  - Two inhalations of CHF 718 pMDI 100µg plus two inhalations of CHF 718 pMDI matched placebo in the evening

- **Treatment C**

CHF 718 pMDI 100µg (Total daily dose: 800µg BDP)

  - Four inhalations of CHF 718 pMDI 100µg and in the morning
  - Four inhalations of CHF 718 pMDI 100µg and in the evening

- **Treatment D**

CHF 718 pMDI Matched Placebo

  - Four inhalations of CHF 718 pMDI matched placebo in the morning
  - Four inhalations of CHF 718 pMDI matched placebo in the evening

- **Treatment E (Open label arm):**

QVAR® 80µg (HFA beclomethasone dipropionate, 80µg), (Total daily dose: 320µg) Inhalation Aerosol.

  - Two inhalations from Qvar® in the morning
  - Two inhalations from Qvar® in the evening

Note: For the administration of treatment A, B, C, D, 4 separates inhalers will be dispensed in one box. Subject will take 1 inhalation from each inhaler in the morning and 1 inhalation from each inhaler in the evening. The same kit will be used for morning and evening administration.

6.2.3 Administration

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

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

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

The recommended time of administration is between 8-10 am for the morning dose and between 8-10 pm for the evening dose, at the same time every day. At Visit 1 (screening visit), all subjects allowed to continue in the study, including those scheduled for Visit 1.1 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 background QVAR® medication should not be taken in the morning before coming to the clinic (at V1.1 and V2) and will be discontinued at V2.

6.2.3.2 Randomized period (from Visit 2 to 4):

At randomization visit (V2) after the confirmation of eligibility, the subject will be randomized to one of the 5 treatment arms (A, B, C, D, E). The investigator or designee will use the IRT system to allocate the treatment kit which will cover the period until V3. At Visit 3 the investigator or designee will use again the IRT system to allocate the subsequent treatment kit to cover the period until V4 (4 weeks).

For Treatment Arms A, B, C, D (*CHF-718 pMDI treatments and placebo*), each subject will receive one box at Visit 2 and one box at Visit 3 containing four pMDI inhalers of double-blinded study drug. Each canister will be labeled with a small label numbered 1, 2, 3 or 4 identifying the sequence to be followed during the administration.

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

- **Morning administration (between 8-10 am):**
  - ➔ One inhalation from the canister labeled 1
  - ➔ One inhalation from the canister labeled 2
  - ➔ One inhalation from the canister labeled 3
  - ➔ One inhalation from the canister labeled 4

- **Evening administration (between 8-10 pm):**
  - ➔ One inhalation from the canister labeled 1
  - ➔ One inhalation from the canister labeled 2
  - ➔ One inhalation from the canister labeled 3
  - ➔ One inhalation from the canister labeled 4

For Treatment Arm E (*Open Label arm*), each subject will receive two QVAR® 80µg commercial pack carton at V2 and two QVAR® 80µg commercial pack at V3.

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

- **Morning administration (between 8-10 am):**
  Two inhalations from QVAR® 80µg
- **Evening administration (between 8-10 pm):**
  Two inhalations from QVAR® 80µg

The first administration of study drug will take place at the clinic on visit 2 (V2), after pre-dose procedures have been completed.

To the extent possible, the time of dosing must remain constant for each subject for the 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 Q4-6h as needed (prn). Albuterol may be re-supplied by the investigator to the subject at subsequent visits during the study as needed, based on assessment of used and remaining doses. The maximum dose allowed is 8 puffs per day. If the subject's needs exceed 4 puffs/day 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 the spirometric measurements. ***Albuterol will not be provided by the study sponsor.***

6.2.4 Subject Training

During the V1 (screening), each subject will receive one training kit containing pMDI placebo.
With these kits, the subject will be instructed on how to use the pMDI according to the instructions for use. These training kits will be kept at the site by the Investigator (will not be dispensed to the subjects) and they will be used again at V2 (randomization) in order to check again the proper use of the inhalers.

6.2.5 Subject Training on QVAR®

Investigator will instruct subjects on how to use the inhaler by reading together and showing the QVAR® leaflets 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

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 study drugs for the run-in period and the randomized treatment period.

6.3.1 Training kits

The training kit is one box. The box will contain one CHF 718 pMDI placebo.

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

6.3.2 Run-in period

At visit 1, the investigator will deliver to each eligible subject one commercial box containing 1 canister of QVAR® metered dose inhaler:

- *Primary packaging***:** 1 canister plus 1 actuator with a dose counter
- *Secondary packaging*:1 labeled commercial box containing 1 canister of QVAR® metered dose inhaler

6.3.3 Treatment period

At randomization visit (V2) and at Visit 3, each subject will be provided with 1 box according to the randomization list.

Treatment A, B, C, D:

- *Primary packaging*: 1 labeled canister of CHF 718 50µg, 100µg or placebo plus standard actuator
- *Secondary packaging*: 1 box containing 4 canisters plus 4 standard actuators

Treatment E (open label arm):

- *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

6.3.4 Rescue medication

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

6.4 Labeling

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

6.5 Treatment allocation

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

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

6.6 Treatment Code

Study drug will be packaged and uniquely numbered. Each primary packaging in the study drug 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 a username and password for randomization purposes and a separate username and password to unblind the study drug in case of emergency situations, where he/she considers it 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 Corporate 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 study site and Investigator to be called in case of emergency.

6.7 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the subject on the digital diary as well as the information recorded in the eCRF during the treatment visits.
The evaluation of compliance will be done using the following formula:

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

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each subject. A range 65-135 % will be taken into account for a satisfactory level of compliance. Subjects with compliance level less than 75% will receive additional coaching during study visits 2 and 3.

6.8 Drug Storage

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

Run-in medication:
The boxes of QVAR® used as study drug for the run-in period and for treatment E 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 718 pMDI and matched placebo pMDI kits must be stored at ambient temperature, not above 25°C (77°F) either by Pharmacist/Investigator at the study site and by subjects at home.

***Medication for training*:**
The training inhaler (pMDI) must be kept at site and **not** dispensed to the subjects. pMDI training kit must be stored at ambient temperature, not above 25°C (77°F), by Pharmacist/Investigator at the study center.

The site must check the Min/Max temperatures once daily for adequate storage of ambient kits.
The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation to the requirement for storage will be promptly reported and 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 the study drugs to be used for the study. Study drugs that should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study drugs.
An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study drug(s) received, dispensed and returned by each subject during the trial.

At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies. The study drugs supplied, used or unused, will be returned to the designated distribution center under Sponsor's responsibility. Return and destruction will not occur until authorized by Chiesi.

6.10 Provision of additional care

At completion of subject's study participation, it is 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	Treatment period			Follow-Up	ET
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	
Time (Weeks)		-2	0	4	8	9	Early Termination
Window (days)			±2	±2	±2	±2	
Informed consent form	✓						
Demographic data	✓						
IRT visit confirmation call	✓	✓	✓	✓	✓	✓	✓
Inclusion / exclusion criteria		✓					
Asthma Action Plan Review		✓	✓	✓			
Eligibility recheck			✓				
Medical history/Previous medication		✓					
Weight, Height and BMI		✓					
Physical examination		✓	✓	✓	✓		✓
Hematology and Blood Chemistry		✓			✓		✓
Morning serum cortisol assessment		✓					
Dispensing Container for 24-h Urine Collection[d]		✓		✓			
Collecting container for 24-h UFC & creatinine analysis[d]			✓		✓		
Serum pregnancy test[a]		✓			✓		✓
Urinary pregnancy test[a]		✓	✓	✓			
12-lead ECG[f]		✓	✓		✓		✓
Vital signs (SBP/DBP)[e]		✓	✓	✓	✓		✓
Spirometry pre and post-bronchodilator[b]		✓					
Pre-dose spirometry[c]			✓	✓	✓		✓
ACQ questionnaire		✓	✓	✓	✓		✓
Concomitant medications		✓	✓	✓	✓	✓	✓
Adverse Events assessment		✓	✓	✓	✓	✓	✓
Training on use of pMDI, e-diary and PEF meter		✓	✓				
e-diary, PEF meter completion		✓ **(daily)**					
Dispensation (D) / Return (R) of run-in QVAR®		D	R				R
Dispensation of rescue albuterol[g]		✓	✓	✓			
Study Drug dispensation(D)/ return & Accountability (R)			D	D/R	R		R
Subject diary dispensation (D) /return (R)		D	D/R	D/R	R		R

[a] In female subjects of childbearing potential only

[b] Spirometry will be carried out before and within 30 minutes after the inhalation of 4 puffs of albuterol to establish airway reversibility, if no documentation is available within 1 yr prior to V1.

[c] Pre-dose FEV_1, FVC: T -45' and T -15' before study drug administration at V2, V3, and at V4 and Early Termination at approximately the same time as done on V2 (no study drug administration at V4 and Early Termination).

[d] At V1, eligible subjects will be provided with a container for the 24-h urine collection, to be returned to the site the day after completing the collection, 1-2 days before or on the date of V2. At V3, subjects will be provided with a container for the 24-h urine collection, to be returned to the site after completing the collection, 1-2 days before or on the date of V4.

[e] Vital signs (SBP/DBP) will be measured at each visit, before the spirometry, bronchodilator, run-in ICS medication (QVAR®) or study drug intake

[f] A 12-lead ECG will be measured at V1, V2 and V4 or Early Termination before the spirometry, bronchodilator, run-in ICS medication (QVAR®) or study drug intake.

[g] One commercial albuterol HFA MDI (200 actuations) will be prescribed and supplied by the investigator to each subject at V1, and resupplied as needed At V2-3 based on assessment of doses used between visits.

7.1.1 Visit 0 (Pre-screening visit)

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

- The written informed consent signed by the subject will be collected after the study has been fully explained by the investigator. The investigator or his/her designee should provide them ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
- Demographic data will be collected.
- Instructions will be given to the 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 scheduled for the morning before 9:00 am, within 1 week. The appointment day may vary depending on the washout period necessary for the subject prior to the screening visit.
- Subjects will be instructed:
  - ➔ **To fast overnight (at least 10 hours) for the next visit** in order to perform blood sampling (only water is allowed);
  - ➔ **Not to take albuterol 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 be carried out in the morning (before 9:00 am) in order to identify eligible consenting subjects for the study.

If any of the washouts for non-permitted medications have not been respected, the visit needs to be re-scheduled within 2 days. Only one re-scheduling is allowed. If any of the relevant washouts is not respected again on the 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.
- Weight, height and BMI will be recorded.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator and run-in ICS medication (QVAR®) administration, after 5 minutes of rest, in resting position (see section 7.2.3).
- A 12-lead ECG will be performed before spirometry, bronchodilator and run-in ICS medication (QVAR®) administration, after 5 minutes of rest (see section 7.2.5). 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.
- 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 7.2.10):
  - standard hematology and blood chemistry;
  - serum total cortisol test
  - a serum β-HCG test (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 and FVC (see section 7.2.6). To be eligible, **FEV_1** must be ≥50% and <85% of the subject's predicted normal value.
- If documented airway reversibility within 1 year prior to V1 is not available, post-bronchodilator spirometry (reversibility) will be carried out within 30 minutes after intake of 4 puffs of albuterol HFA (90 µg/actuation). To be eligible, post-bronchodilator increase in FEV_1 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 and none of the exclusion criteria (screening failure) at V1 under protocol version 4.0 may be re-screened again, up to one additional time, after 2 weeks from the date of the initial screening failure. A re-screened subject will be treated as a new subject. Subjects who have failed (once or twice) to meet all inclusion and none of the exclusion criteria under a previous protocol version may be eligible for re-screening once more under this version of the study protocol (i.e. up to a total of 3 attempts for this study).
- 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.

- The subject will be instructed on how to daily record the medications intake (run-in and rescue), and asthma symptoms in the electronic diary/portable electronic peak flow meter (see section 7.2.12).
- The investigator will access IRT also in order to obtain the run-in ICS medication (one commercial box containing 1 canister of QVAR® 40 or 80 µg 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 run-in ICS medication 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 bring 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 it as rescue medication if necessary.
- **An electronic diary will be dispensed.** Subject must complete and transmit daily their electronic diary entries until Visit 2. It is important to ensure good compliance of the subject with the use of the electronic diary during the run-in period.
- **Asthma Action Plan will be communicated to the subject.**
- A container for the 24-h urine collection will be dispensed with instructions. The container will be returned to the site at V2.
- **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:
  - ➔ **Not to take albuterol or 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 run-in ICS medication (QVAR®) on the morning of the next visit.**
  - ➔ **To return the rescue medication** (in their boxes), and the **electronic Diary.**

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

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

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, or the washout for non-permitted medications has not been respected, or the run-in ICS medication (QVAR®) has been taken in 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 a screen failure in the IRT and eCRF.

The following pre-dose procedures will be performed:

- The ACQ questionnaire will be completed.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, and study drug administration, after 5 minutes of rest, in resting position (see section 7.2.3).
- A 12-lead ECG will be performed before spirometry, bronchodilator, and study drug administration, after 5 minutes of rest (see section 7.2.5).
- The investigator will check in the electronic diary portal whether subject has been transmitting data daily since screening. **In case of lack of compliance, instructions on how to use it will be provided again to the subject** (see section 7.2.12).
- 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 a screen failure in the IRT. (see section 5.2).
- A full physical examination will be performed including assessment for oral candidiasis.
- A urine pregnancy test in women with childbearing potential will be performed.
- 24-hour urine sample will be processed for 24-hour urine cortisol and creatinine (see section 7.2.8).
- The occurrence of other adverse events will be checked and recorded if any.
- The proper use of pressurized metered dose inhaler will be checked and subject will be retrained to the usage of the pMDI using the Training kit previously assigned at V1 (see section 6.2.4).
- Run-in ICS medication (QVAR®) will be collected and disposed of per the study sponsor's instructions.
- 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 min and T -15 min before 1st dose of study drug, and will constitute the baseline value (see section 7.2.6). Both T -15 and T -45 min assessments must be performed and FEV_1 must be ≥50% and <85% of predicted in order to meet Inclusion Criterion #4.
- Eligibility criteria will be rechecked (Inclusion #3, 4 and 7 and Exclusion #1, 3, 8, 9, 12 and 13). At the discretion of the investigator, a subject who fails to meet all inclusion and none of the exclusion criteria (screening failure) at V2 under protocol version 4.0 may be re-screened again, up to one additional time, after 2 weeks from the date of the initial screening failure. A re-screened subject will be treated as a new subject. Subjects who have failed (once or twice) to meet all inclusion and none of the exclusion criteria under a previous protocol version may be eligible for re-screening once more under this version of the study protocol (i.e. up to a total of 3 attempts for this study).

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 4-week treatment period.
- **The first administration of the study drug will take place at the clinic visit (before 10 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.

Before discharge

- **Study drug** will be dispensed to the subject together with instructions for use. Study drug administration will be done according to section 6.2.3. Subject will be instructed to take albuterol as rescue medication if necessary. Investigator will also dispense albuterol if needed.
- **The electronic diary (the same given at V1) will be given back to the subject.** Subject must continue to complete and transmit the data on a daily basis in the digital platform until Visit 3.
- **Asthma Action Plan will be reviewed with the subject.**
- **An appointment for Visit 3** will be made at 4 weeks (±2 days) from Visit 2 (at approximately the same time as Visit 2, before 9:00 am). The subject will be instructed:
  - ➔ To **return** the **study drug** (in the box) and the e-diary at the next visit.
  - ➔ **Not to take albuterol or caffeinated substances in the 6 hours preceding the next visit, and to abstain from taking the non-permitted medications listed in section 5.2** unless absolutely necessary.
  - ➔ **Not to take the morning dose of the study drug before coming to the next clinic visit** (it will be administered at the clinic visit).

7.1.4 Visit 3 (Week 4 of Treatment Period)

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

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, or the study drug has been taken on the morning of the visit (prior to spirometry), or the washout for non-permitted medications has not been respected, 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 Early Termination Visit performed and recorded in the IRT and eCRF.

The following pre-dose procedures will be performed:

- The ACQ questionnaire will be completed.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, and study drug administration, after 5 minutes of rest, in resting position (see section 7.2.3).

- The investigator will check in the electronic diary portal whether subject has been transmitting data daily since screening. **In case of lack of compliance, instructions on how to use it will be given again to the subject.** (see section 7.2.12)
- 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 assessment of oral candidiasis.
- A urine pregnancy test in women with childbearing potential will be performed.
- The occurrence of other adverse events will be checked and recorded if any.
- 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 min and T -15 min before the expected time for the morning dose of study drug, at approximately the same time as done on V2.
- **The administration of the study drug will take place at the clinic visit (before 10 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.

Before discharge

- **Study drug** will be dispensed to the subject together with instructions for use. Drug administration will be done according to section 6.2.3. Subject will be instructed to take albuterol as rescue if necessary. Investigator will also dispense albuterol if needed.
- **The electronic diary (the same given at V1) will be given back to the subject.** Subject must continue to complete and transmit the data on a daily basis in the digital platform until Visit 4.
- **Asthma Action Plan will be reviewed with the subject.**
- A container for the 24-h urine collection will be dispensed. The container will be returned to the site at 1-2 days before or on the date of V4.
- **An appointment for Visit 4** will be made at 4 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 **bring back** the **study drug** (in the box) and the e-diary 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 before coming to the next clinic visit**.

7.1.5 Visit 4 (Week 8 of Treatment Period)

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

If caffeine has been ingested, or rescue albuterol has been inhaled in the previous 6 hours, or the study drug has been taken on the morning of the visit (before spirometry), or the washout for non-permitted medications has not been respected, 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 Early Termination Visit performed and recorded in the IRT and eCRF.

The following pre-dose procedures will be performed:

- The ACQ questionnaire will be completed.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.3).
- A 12-lead ECG will be performed before spirometry, bronchodilator, or study drug administration, after 5 minutes of rest (see section 7.2.5).
- The investigator will check in the electronic diary portal whether subject has been transmitting data daily since Visit 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 Early Termination in the IRT. (see section 5.2).
- A full physical examination will be performed, including assessment of oral candidiasis.
- 24-hour urine sample will be processed for 24-hour urine cortisol and creatinine
- A blood sample will be collected, after an overnight fasting (at least 10h), for the assessments of (see section 7.2.10):
  - standard hematology and blood chemistry;
  - a serum β-HCG test in women of childbearing potential.

  The blood samples must be collected **after vital signs and 12-lead ECG recording**.
  In case of non-interpretable data, another determination must be performed as soon as possible and prior to the follow up safety phone call (V5).
- The occurrence of other adverse events will be checked and recorded if any.
- Pre-dose spirometry: FVC pre-dose spirometry measurement will be then performed to assess FEV_1 and FVC. This measurement will be taken at T -45 min and T -15 min before the expected time for the morning dose of study drug at approximately the same time as done on V2.
- **No administration of study drug will take place at Visit 4.**

Before discharge at Visit 4

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

7.1.6 (Visit 5) Follow-up Phone Call (Week 9)

A safety follow up phone call will be performed by the investigator or designated staff no later than 1 week after the final visit (V4) or Early Termination Visit to check the status of unresolved AEs and to record any new AEs that may have occurred after V4, as well as related concomitant medications.

7.1.7 Early Termination Visit

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

- All study material (Study and rescue medications, subject diary) will be collected.
- **No administration of study drug will take place at the Early Termination Visit.**
- Site to update IRT.
- The ACQ questionnaire will be completed.
- Vitals signs [systolic (SBP) and diastolic (DBP) blood pressure] will be measured before spirometry, bronchodilator, or study drug administration, after 5 minutes of rest, in resting position (see section 7.2.3).
- A 12-lead ECG will be performed before spirometry and/or bronchodilator, after 5 minutes of rest (see section 7.2.5).
- The investigator will check in the electronic diary portal whether subject has been transmitting data daily since previous visit.
- Changes of concomitant medications being taken by the subject will be recorded.
- A full physical examination will be performed, including assessment of oral candidiasis.
- A blood sample will be collected, after an overnight fasting (at least 10h, when possible), for the assessments of (see section 7.2.10):
  - standard hematology and blood chemistry;
  - a serum β-HCG test in women of childbearing potential.
  - The blood samples must be collected **after vital signs and 12-lead ECG recording**.
- The occurrence of other adverse events will be checked and recorded if any.
- Spirometry: FVC spirometry measurement will be then performed to assess FEV_1 and FVC. This measurement will be taken at T -45 min and T -15 min before the expected time for the morning dose of study drug at approximately the same time as done on V2.
- The investigator will prescribe each subject an appropriate treatment or restore their initial therapy or refer them to their primary care physician.
- An appointment will be made in 1 week time for the follow-up phone call.

7.2 Investigations

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.[51][64]
The ACQ will be completed on site, at every Study Visit. 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 considering the pre-BD FEV_1 assessment at V1 and V1.1 and the T-15 min* pre-dose FEV_1 assessment at V2, 3, 4 and ET.
The ACQ-7 is provided on paper and **should be completed by the subject 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 subject, 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).

** If the FEV_1 from the T -15 min assessment is not available at V3, V4, or ET, the FEV_1 from the T -45 min assessment will be used.*

7.2.2 Body Mass Index

Body Mass index (kg/m^2) will be calculated at Visit 1 using the following equation:
Body weight (in kilograms) ÷ by height (in meters)^2. Only subjects with a BMI 18.5 ≤ BMI <35 kg/m^2 will be enrolled, to limit the potential impact of obesity on the ICS-treatment response, [55][56], and also to accommodate for the rising rate of obesity in the US, especially in the non-Hispanic Blacks and Hispanic populations.[57]

7.2.3 Vital Signs

Systolic and diastolic blood pressure will be measured before spirometry, bronchodilator, QVAR® or study drug administration, after 5 min rest in resting position. The measurements will be done before administration of run-in ICS (V1) and study drug (V2, V3, V4). 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 the same time.

7.2.4 Physical Exam and assessment of oral candidiasis

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

Oropharyngeal candidiasis is a condition commonly associated with the use of ICS, and is cause by the Candida fungus. This side effect may be attributed to the topical effects of these medications on the oral mucosa.[21] Generalized immunosuppressive and anti-inflammatory effects of steroids are thought to play a major role in the pathogenesis of candidiasis.[65] Asthmatics who are using β-2

agonists show a decreased salivary flow rate, which in turn can be associated with higher oral Candida counts.[66]

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.

7.2.5 12-lead ECG

A local ECG instrument will be used. A single ten-second 12-lead ECG will be performed before spirometry, bronchodilator, administration of run-in ICS (V1) and study drug (V2, V4) to verify the subject's cardiac safety parameters and his/her eligibility. Prior to recording, the subject should be at rest for at least 5 minutes.

Safety ECGs will be taken using the site's own instrument. 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 by the investigator/sub-investigator on-site for any abnormality and clinical significance.

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

ECGs with computerized protocol interpretation are considered normal if

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

For eligible subjects, QTcF values must be QTcF ≤ 450ms (for males) and 470ms (for females) (as per Exclusion Criterion 13).

In case of relevant ECG abnormalities, the inclusion of the subject will be judged by the investigator. For any doubts the Investigator may consult the study's 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.

7.2.6 Pulmonary Function Test

All pulmonary function tests including FEV_1 and FVC will be performed in accordance with ATS/ERS spirometry criteria,[67] 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 maneuver and the reports must be kept with the source study documents.

Throughout the study (after randomization), the clinic visits will start before 9 a.m. and the pulmonary function measurements will be conducted between 7 – 10 a.m., approximately at the same time of the day for each subject.

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

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

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.[68]

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 forced vital capacity maneuvers. 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).[69] 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 FEV1 or FVC with a cumulative drop exceeding 20% of start value, the test procedure should be terminated in the interest of subject safety.

The rescue medication (albuterol) must be withheld as much as possible for at least 6 hours prior to

starting the pre-dose assessment at each visit. If the subject requires rescue medication within this timeframe, the visit should be rescheduled once within the next two days.

The run-in 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, if documentation of airway reversibility within 1 year prior to V1 is not available, 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/actuation, total dose 360µg) at 30-sec intervals. An increase in FEV_1 ≥12% of control and ≥200mL constitutes a positive bronchodilator response.[52]

At Visits 2, 3, 4 and Early Termination, spirometry will be conducted at T -45 and T -15 minutes before the expected time of study drug administration.

7.2.7 Morning Serum Cortisol

On the morning of Visit 1, a blood sample (5mL) will be collected between 7-10 AM to measure basal serum total cortisol level. Serum samples will be analyzed in duplicate in a blinded manner for serum cortisol using solid-phase extraction in combination with liquid chromatography tandem mass spectrometry.[70]
The specific procedures for serum processing and shipping will be provided to the investigator by the laboratory.

7.2.8 24-h Urine Free Cortisol and Creatinine

Cortisol is a steroid hormone synthesized from cholesterol by a multi-enzyme cascade in the adrenal glands. It is the main glucocorticoid in humans. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the kidney's glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). Subjects with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed UFC.[71]
A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome.[72] LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

24-hour urine samples will be collected for the measurement of UFC concentration and creatinine excretion. At V1, eligible subjects will be provided with a container for the 24-h urine collection, to be returned to the site the day after completing the collection, 1-2 days before or on the date of V2. At V3, subjects will be provided with a container for the 24-h urine collection, to be returned to the site after completing the collection, 1-2 days before or on the date of V4. For the purpose of this

study, a normal range for UFC in subjects ≥18 years of age is considered between 4.0 – 50 µg/24 hs, and the normal range in adults for 24-h Urine creatinine = 0.63-2.50 g/24hs.[73]
The specific procedures for 24-h urine collection, processing and shipping will be provided to the investigator by the laboratory.

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 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 subject 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 1 of the following:

- Initiation of systemic corticosteroids (tablets, suspension, or injection), or an increase (e.g. doubling) from a stable maintenance dose, **for ≥ 3 consecutive 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.

**Any change in treatment should be reviewed with the subject, and all concomitant medications should be recorded in the CRF.*

7.2.10 Blood Hematology and Chemistry

Blood samples of approximately 12 mL will be collected for hematology and serum chemistry at Visit 1 (screening), Visit 4 and Early Termination in the morning, after an overnight fasting of at least 10 hours (only water is allowed during the night). At V1, the blood draw should be performed after vital signs and 12-lead ECG recording, but before administration of albuterol and background

QVAR®. An additional blood sample will be collected for serum pregnancy test in women of childbearing potential at visits 1 and 4 (including an early termination visit).

The following evaluations will be performed using a laboratory:

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

Blood collection and sample preparation will be performed according to procedures provided by the laboratory which will be in charge to transmit the results to the Investigator. In case of clinically significant abnormality, findings will be reported in the medical history (if occurred at V1), or as an Adverse Event (if occurred after V1).

7.2.11 Urine Pregnancy Test

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 at V1, V2 and V3.

7.2.12 Subject Diaries

Using the ePRO diary (system details to be provided by selected vendor) dispensed at V1, and with time and date stamped, subjects will be instructed to:

- Enter a daily record of daytime 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

- The derived variable of **Asthma Control Days**[76] will be calculated according to the following definition:
  - Days (night-time plus daytime) with a total asthma score = 0
  - No rescue medication use.

- Perform **Peak Expiratory Flow rate** (PEF, L/min) measurements twice daily, in triplicate, starting at V1 using using a portable electronic peak flow meter. (Instrument description TBD). The device will be customised with a specific program, according to the parameters required by the study protocol. 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 run-in ICS medication or study drug) the subject will perform 3 exhalations. Data will be recorded in the device. 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. An alarm will remind the subjects to perform measurements. Data from the electronic peak flow meter will be automatically transmitted from home to the Vendor's database on a daily basis. A regular check of the recorded data will be done by the Investigator (or designee) through a dedicated portal to verify the correct use of the device, to detect any clinical abnormality and to check subject's compliance. In case of bad compliance and/or worsening of asthma control during the study, phone call(s) to the subject will be done by the site and instructions will be given again to the subject if appropriate.

- Enter their daily intake of run-in ICS medication and Study Drug, twice daily.

8. EFFICACY ASSESSMENTS

Primary efficacy variable

- Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 8

Secondary efficacy variables

- Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 4
- Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Week 4 and Week 8
- Change from baseline in ACQ-7 score at Week 4 and Week 8
- Change from baseline in average use of rescue medication during inter-visit periods and entire treatment period
- Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period
- Change from baseline in daily asthma symptoms scores during inter-visit periods and entire treatment period
- Change from baseline in percentage of asthma symptoms-free days during inter-visit periods and entire treatment period

- Change from baseline in percentage of asthma control days during inter-visit periods and entire treatment period
- Change from baseline in morning and evening pre-dose PEF during inter-visit periods and entire treatment period

9. SAFETY ASSESSMENTS

- Adverse Events (AEs), Adverse Drug Reactions (ADRs)
- Vital signs (systolic and diastolic blood pressure)
- 12-lead ECG parameters (HR, QTcF, QRS, PR)
- Standard blood chemistry and hematology
- 24-h Urinary Free Cortisol and Creatinine

10. ADVERSE EVENT REPORTING

10.1 Definitions

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

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

An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".
All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.

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

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** 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 an AE. Complications that occur during the hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

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

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

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

- **Is a medically significant adverse event**

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

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant. Any suspected transmission via a medicinal product of an 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 product information (Investigator's Brochure for an CHF 718 pMDI or US-FDA approved Product Information for QVAR®), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis. In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

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

- **Mild:** The event causes a minor discomfort, or does not interfere with daily activity of the subject, or does not lead to either modification of test treatment dosage or establishment of a correcting treatment.
- **Moderate:** The event perturbs the usual activity of the subject and is of a sufficient severity to make the subject uncomfortable. The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** The event prevents any usual routine activity of the subject and causes severe discomfort. It may be of such severity to cause the definitive interruption of test treatment.

10.4 Causality Assessment

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

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

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

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

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

10.5 Action taken with the study drug due to the AE

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

10.6 Other actions taken

- Specific therapy/medication
- Concomitant procedure
- Not applicable

10.7 Outcome

Each Adverse Event must be rated by choosing among:

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

10.8 Recording Adverse Events

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

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings.

The recording period for Adverse Events is the period starting from the Informed Consent signature until the subject's study participation ends.

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

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

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or until the subject is lost to follow-up. Follow-up may therefore continue after the subject has left the study. In this case, the follow-up will continue with no timelines for related SAEs, while for unrelated SAEs the type and extent of follow-up undertaken will be determined for each individual case and will depend upon the nature (e.g. events with poor prognosis or which do not resolve), severity and medical significance of the event.

10.9 Reporting Serious Adverse Events to Chiesi

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

Name and Title	Telephone no.	Fax no.	E-mail
[redacted], MD Medical Safety Officer	[redacted]	[redacted]	[redacted]
[redacted] Global Pharmacovigilance Operation Specialist 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 event occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

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

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 the 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 or of the run-in ICS /rescue medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.
All subjects who sign the informed consent will be 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.
Subject's questionnaire (ACQ) answers will be databased.
Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

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

External data (IRT, Spirometry, e-diary, Laboratory) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities. After cleaning of data, a review

meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened and the planned statistical analysis will be performed. Only authorised and well-documented updates to the study data are possible after database lock.

At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The investigators will receive copies of the 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 718 pMDI at different doses over placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8.

A total of 495 evaluable subjects (99 per group) will provide 80% power to detect a mean difference of 200mL between each dose of CHF 718 pMDI and placebo at a two-sided significance level of 0.0167, assuming a standard deviation of 430mL.

Since three 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 (0.0167 = 0.05/3). 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 585 subjects (117 per group) will be randomized.

12.2 Populations for analysis

- **Safety population:** all randomized subjects who receive at least one dose of study drug.
- **Intention-to-Treat population (ITT):** all randomized subjects who receive at least one dose of the study drug and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after the baseline.
- **Per-protocol population (PP):** all subjects from the ITT population without any major protocol deviation (i.e., wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

Since the superiority of CHF 718 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 analysed in the ITT population.

The safety variables will be analysed in the Safety population.

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

12.3 Statistical analysis

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

12.3.1 Descriptive Statistics

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

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

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

12.3.2 Missing data

- For the primary efficacy analysis, a linear mixed model for repeated measures will be used to handle missing data. Under the Missing At Random (MAR) assumption, this model provides an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment for the full study duration. This approach addresses efficacy (or de jure) hypotheses, estimating the causal effects of the initially randomized drug if taken as directed (in contrast with effectiveness, or de facto, hypotheses, evaluating the effect of the drug as actually taken).[77] The efficacy estimand is considered appropriate in the context of a phase II study aiming at characterising dose-response.[78][79][80]
- If one of the spirometry measurements at 45 min and 15 min pre-dose is not available, then the non-missing measurement will be taken as the pre-dose value. If no measurement is available, then the pre-dose value will be considered as missing.
- A minimum of 7 days with available measurements will be required for each inter-visit period (including run-in period) to consider the following variables as non-missing: average use of rescue medication, percentage of rescue medication-free days, daily asthma symptoms, and percentage of asthma symptom-free days, percentage of asthma control days, morning and evening PEF.
- For ACQ-7 questionnaire, the total score will be calculated only if all the scores derived from all the seven items are recorded.

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

12.3.3 Subject demographics and baseline characteristics

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

12.3.4 Primary efficacy variables

Change from baseline in pre-dose morning FEV_1 will be analysed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, ICS dose before study (low/medium daily dose) and US regions as fixed effects, and the baseline value (average of the pre-dose FEV_1 measurements at Visit 2) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed.

The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% two-sided Confidence Intervals (CIs) at Week 8 will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 718 pMDI and placebo at Week 8 will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry.[81] At each dose level, the superiority of CHF 718 pMDI over placebo will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favoring CHF 718 pMDI.

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

12.3.5 Secondary efficacy variables

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

- For change from baseline in pre-dose morning FEV_1 at Week 4, the adjusted means in each treatment group and the adjusted mean differences between treatments at Week 4 will be estimated with their 95% CIs and p-values by the same model used for the primary efficacy analysis.
- Change from baseline in pre-dose morning FVC at Week 4 and Week 8 will be analysed using a similar model as the one used for the primary efficacy analysis.
- Change from baseline in ACQ-7 score at Week 4 and Week 8 will be analysed using a similar model as the one used for the primary efficacy analysis.
- Change from baseline to each inter-visit period in average use of rescue medication, in percentage of rescue medication-free days, in daily asthma symptoms scores, in percentage of asthma symptoms-free days, in percentage of asthma control days and in morning and evening pre-dose PEF will be analysed using a similar model as the one used for the primary efficacy analysis. The inter-visit period will be considered instead of visit in the model. Comparison between treatments over the entire treatment period will also be derived from this model.

12.3.6 Safety variables

Adverse Events

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

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

Vital signs

Vital signs (systolic and diastolic blood pressure) and their changes from baseline (Visit 2) 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 (Visit 2) 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).

The number and the percentage of subjects with a:

- QTcF >450ms (males only), >470ms (females only), >480ms (males only) and >500ms
- change from baseline (Visit 2) in QTcF >30ms and >60ms
- at post-baseline visit will be presented by treatment group.

Laboratory parameters

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

Mean change from baseline (Visit 2) to the end of treatment in 24-h urinary free cortisol and creatinine will be calculated with its 95% CI by treatment group.

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/site 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 deputy's supervision and in strict accordance with accepted medical practice and with the study protocol. The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.
The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, and addresses and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21. PREMATURE TERMINATION OF THE STUDY

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

22. CLINICAL STUDY REPORT

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

23. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.
Regulations require that essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study.

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

24. PUBLICATION OF RESULTS

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

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APPENDIX I

An 8-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (beclomethasone dipropionate) in asthmatic subjects

Product: CHF 718 pMDI (beclomethasone dipropionate)

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), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Principal Investigator's Name: _____ , MD

Center No.: _____

_____ _____
Signature Date

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

APPENDIX II

MINIMUM LIST OF SOURCE DATA REQUIRED

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

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