

CLINICAL STUDY PROTOCOL**EUDRACT No.: 2015-000716-18**

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 100/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN PATIENTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING B2-AGONISTS

Version No.: 2.0
Date: 12 May 2016

The information contained in this document is confidential and will not be disclosed to others without written authorization from Chiesi Farmaceutici S.p.A., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered or for discussions with local regulatory authorities, Ethics Committee/Investigational Review Boards, or people participating in the conduct of the study.

**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
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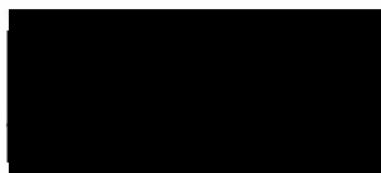
A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 100/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN PATIENTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING B2-AGONISTS

Product: CHF 5993 100/6/12.5 µg (fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose)

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

Approval of the Clinical Study Protocol by the Sponsor's Representative:

Clinical Program Leader



Date: 20/5/2016

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

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRA FINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 100/6 µg pMDI (FIXED COMBINATION OF EXTRA FINE BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN PATIENTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING β 2-AGONISTS

Product: CHF 5993 100/6/12.5 µg (fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose)

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

Approval of Clinical Study Protocol by the Investigator:

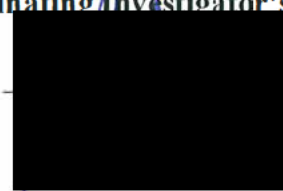
I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

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

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

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

International Coordinating Investigator's Name: Prof J. Christian Virchow, MD



25.V.2016

Date

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

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 100/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN PATIENTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING β 2-AGONISTS

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Investigator's Name: _____,MD

Centre No. : _____

Signature

Date

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

PROTOCOL OUTLINE

Study title	A 52 week, randomized, double blind, multinational, multicentre, active controlled, 2-arm parallel group trial comparing CHF 5993 100/6/12.5 µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 100/6 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) in patients with asthma uncontrolled on medium doses of inhaled corticosteroids in combination with long-acting β ₂ -agonists
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 100/6/12,5µg pMDI (beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide [GB])
Centre(s)	About 200 sites
Indication	Asthma
Study design	Double-blind, randomized, multinational, multicentre, 2-arm parallel group study with active control group
Study phase	III
Objectives	Primary objectives ▪ To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI in terms of change from baseline in pre-dose FEV₁ at Week 26. ▪ To demonstrate the reduction of moderate and severe asthma exacerbations rate with CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI during the entire 52-week treatment period. Key secondary objectives ▪ To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI in terms of change from baseline in peak FEV₁ within 3 hours post-dose at Week 26. ▪ To demonstrate the superiority of CHF 5993 100/6/12.5 compared to CHF 1535 100/6 in terms of change from baseline in morning PEF averaged over 26-week treatment period. ▪ To demonstrate the reduction of severe asthma exacerbations rate with CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI during the entire 52-week treatment period in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 trials. Other secondary objectives ▪ To compare the study treatments for other lung function assessments, patient's health status and clinical outcome measures. ▪ To collect data in order to assess the impact of study treatments on health economic outcomes. ▪ To assess the safety and the tolerability of the study treatments.

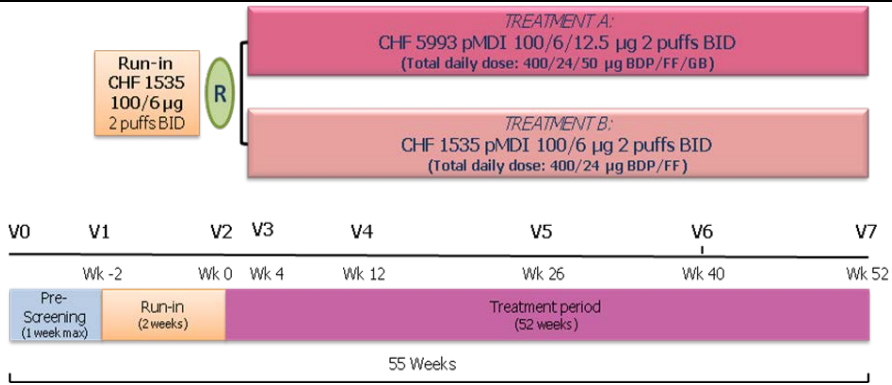
	To perform a population PK analysis in a subset of patients treated with CHF 5993 investigating the inter-subject variability in the drug exposure and the effect of selected covariates on PK beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide.
Treatment duration	A 2-week run-in period on CHF 1535 100/6 µg 2 puffs BID followed by a 52-week treatment period on randomized treatment.
Test product dose/route/regimen	<u>Treatment A: CHF 5993 100/6/12.5 µg</u> Fixed combination of extrafine beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose (BDP/FF/GB) <u>Dose regimen:</u> BDP/FF/GB 100/6/12.5 µg per inhalation, 2 inhalations BID, daily dose 400/24/50 µg <u>Administration:</u> pressurised metered dose inhaler (pMDI) Note: Patients used to inhale their asthma pMDI medications with a spacer should continue using a spacer (AeroChamber Plus Flow Vu Antistatic™) to take the pMDI study drugs.
Reference product dose/route/regimen	<u>Treatment B: CHF 1535 100/6 µg</u> Fixed combination of beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg / metered dose (BDP/FF) <u>Dose regimen:</u> BDP/FF 100/6 µg per inhalation, 2 inhalations BID, daily dose 400/24 µg <u>Administration:</u> pressurised metered dose inhaler (pMDI) Note: Patients used to inhale their asthma pMDI medications with a spacer should continue using a spacer (AeroChamber Plus Flow Vu Antistatic™) to take the pMDI study drugs.
Number of subjects	Approximately 1148 patients will be randomised (574 per group). A subset of patients (about 450) will be selected in order to reach about 200 evaluable patients for the PK analysis (CHF 5993 pMDI group).
Study population	Patients with uncontrolled asthma on medium doses of inhaled corticosteroids in combination with β ₂ long-acting bronchodilator
Inclusion/exclusion criteria	Inclusion Criteria Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study: 1. Patient's written informed consent obtained prior to any study-related procedures. 2. Male or female patients aged ≥18 and ≤75 years. 3. Patients must have a documented history of asthma for at least 1

	year and asthma must have been diagnosed before the patient's age of 40. 4. Patients with uncontrolled asthma with double therapy only on medium doses of ICS (>500-1000 µg daily dose BDP non-extrafine or estimated clinical comparable dose) in combination with a β₂ long-acting bronchodilator (LABA) at a stable dose for at least 4 weeks prior to screening. LABA daily dose: patients under formoterol 24 µg or salmeterol 100 µg or vilanterol 25 µg or other approved dose of LABA as clinically comparable to the others in the list can be included. <table border="1" data-bbox="547 667 1406 1025"> <thead> <tr> <th>Drug*</th><th>Medium daily dose</th></tr> </thead> <tbody> <tr> <td>BDP non-extrafine</td><td>>500-1000 µg</td></tr> <tr> <td>BDP extrafine</td><td>>200-400 µg</td></tr> <tr> <td>Budesonide (DPI)</td><td>>400-800 µg</td></tr> <tr> <td>Ciclesonide (HFA)</td><td>>160-320 µg</td></tr> <tr> <td>Fluticasone (HFA/DPI)</td><td>>250-500 µg</td></tr> <tr> <td>Mometasone furoate</td><td>>220-440 µg</td></tr> <tr> <td>Triamcinolone acetonide</td><td>>1000-2000 µg</td></tr> </tbody> </table> <i>*(Table adapted from GINA 2015)</i> 5. Patients with a pre-bronchodilator FEV₁ <80% of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits. 6. Patients with a positive response to a reversibility test at screening, defined as ΔFEV₁>12% and >200mL over baseline 10-15 minutes after inhaling 400 µg of salbutamol pMDI. <i>Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomisation.</i> 7. Patients with uncontrolled asthma evidenced by a score at the Asthma Control Questionnaire 7[®] (ACQ-7) ≥1.5 (this criterion must be met at screening and at the end of the run-in period). 8. A documented history of one or more asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalization in previous 12 months. 9. A co-operative attitude and ability: ▪ to be trained to correctly use the pMDI inhalers; ▪ to perform all trial related procedures including technically acceptable pulmonary function tests; ▪ to correctly use the electronic diary/peak flow meter. Exclusion Criteria Any of the following will exclude a patient from enrolment: 1. Inability to carry out pulmonary lung function testing, to comply with study procedures or with study treatment intake. 2. Run-in compliance < 50% at randomisation. 3. History of near fatal asthma or of a past hospitalisation for asthma	Drug*	Medium daily dose	BDP non-extrafine	>500-1000 µg	BDP extrafine	>200-400 µg	Budesonide (DPI)	>400-800 µg	Ciclesonide (HFA)	>160-320 µg	Fluticasone (HFA/DPI)	>250-500 µg	Mometasone furoate	>220-440 µg	Triamcinolone acetonide	>1000-2000 µg
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	in intensive care unit which, in the judgement of the investigator, may place the patient at undue risk. 4. Hospitalisation, emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period. 5. Patients with any asthma exacerbation or respiratory tract infection in the 4 weeks prior to the screening visit or during run-in period. 6. Any change in dose, schedule or formulation of the combination ICS plus LABA in the 4 weeks prior to screening visit. 7. Patients using systemic corticosteroid medication in the 4 weeks or slow release corticosteroids in the 12 weeks, prior to screening. 8. Patients who suffer from COPD as defined by the current GOLD guidelines. 9. History of a diagnosis of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease which may interfere with study evaluations. 10. Current smokers or ex-smokers with total cumulative exposure equal or more than 10 pack-years or having stopped smoking one year or less prior to screening visit. 11. Patients who have clinically significant cardiovascular condition according to investigator's judgement, such as but not limited to: congestive heart failure (NYHA class > 3), acute ischemic heart disease in the last year prior to study screening, history of sustained cardiac arrhythmias or sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months (sustained means lasting more than 30 seconds or ending only with external action, or leads to hemodynamic collapse; non-sustained means > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), high degree impulse conduction blocks ($\geq 2^{\text{nd}}$ degree AV block type 2). Similarly, patients affected by persistent, long standing or paroxysmal atrial fibrillation will not be considered for enrolment. <i>Note: Patients with Permanent Atrial Fibrillation (for at least 6 months) with a resting ventricular rate < 100/min, controlled with a rate control strategy (i.e., selective β-blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) can be considered for the enrolment.</i> 12. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement. 13. Patients whose electrocardiogram (12-lead ECG) shows QTcF >450 ms for males or QTcF >470 ms for females at screening or at randomisation visits (criterion not applicable for patient with pacemaker or permanent atrial fibrillation). 14. Patients with a medical history or current diagnosis of narrow-angle glaucoma, symptomatic prostatic hypertrophy, urinary retention bladder neck obstruction that, in the opinion of the investigator, would prevent use of anticholinergic agents. <i>Note: Benign Prostatic Hyperplasia (BPH) patients who are stable</i>
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	<i>under treatment can be considered for inclusion.</i> 15. Other severe acute or chronic medical or malignancy or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. 16. Patients having received a vaccination within 2 weeks prior to screening or during the run-in. 17. Patients mentally or legally incapacitated, or patients accommodated in an establishment as a result of an official or judicial order. 18. Patients with a history of alcohol or drug abuse within two years prior to the start of the study. 19. Patients with known intolerance/hypersensitivity or contraindication to treatment with β_2-agonists, inhaled corticosteroids, anticholinergics or propellant gases/excipients. 20. Patients with major surgery in the 3 months prior to screening visit or planned surgery during the trial. 21. Patients treated with non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening), non-selective beta-blocking drugs, quinidine, quinidine-like anti arrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation. 22. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. 23. Patients being treated with monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs. 24. Patients who are receiving any therapy that could interfere with the study drugs according to investigator's opinion. 25. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are using one <u>or more</u> of the following highly effective contraceptive measures: ▪ Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) ▪ Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal) ▪ Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) ▪ Bilateral tubal occlusion ▪ Vasectomised partner. Reliable contraception should be maintained throughout the study. Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative
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	medical cause”) or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study. Pregnancy tests will be performed at study entry (a serum test at the screening visit and a urine test at screening and randomisation visits) in all women of childbearing potential. 26. Patients who have received an investigational drug within 2 months or six 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. <u>Only for patients included in the subset for PK assessment</u> 27. Patients with unsuitable veins for repeated venipuncture. 28. Blood donation (equal or more than 450 mL) or blood loss in the 4 weeks before randomization.
Study plan	A total of 8 clinic visits (V0 to V7) will be performed during the study, as follows: ▪ A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients and to obtain the written informed consent from the patient and instruct the patient on screening visit procedures (such as medication restrictions). ▪ A screening visit (V1) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead ECG, ACQ-7, spirometry including FEV₁ reversibility after salbutamol intake, and training for the use of inhalers and diary/peakflow meter). ▪ This visit will be followed by a 2-week $\pm$ 2 days open-label run-in period, where patients will receive CHF 1535 100/6 μg 2 inhalations BID (daily dose 400/24 μg). ▪ After the randomisation visit (V2), patients will be assessed after 4, 12, 26, 40 and 52 weeks of treatment (from V3 to V7) at clinic/hospital. At each visit from V2 to V7, spirometry pre-dose and 3-hour post dose (serial test during 3 hours), as well as ACQ-7 and EQ-5D-3L, will be performed in addition to other safety tests. ▪ AEs and SAEs will be monitored throughout the study. Total study duration (V0 to V7) = 55 weeks

	 Time points for serial spirometry (over 3-hour post-dose): -45min, -15 min, 15 min, 30 min, 60 min, 120 min and 180 min.
Most relevant allowed concomitant treatments	Permitted concomitant medications 1. Inhaled salbutamol administered as rescue medication. A minimum wash-out period of 6 hours between the use of rescue salbutamol and the start of the spirometric study assessments is required. If a patient needs rescue medication within this time window, the visit must be postponed. 2. Short courses (≤ 14 days each) of systemic corticosteroid and/or brief uses of nebuliser containing β_2-agonists and/or corticosteroids, and/or antibiotics therapy for severe asthma exacerbation are permitted. 3. Antihistamines and nasal corticosteroids 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). 4. Treatment for desensitisation 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). Sublingual immunotherapy started before the study can be continued at a stable dose. 5. In case of concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluations and it is not listed below under the section "non-permitted medications".
Most relevant forbidden concomitant treatments	Non-permitted concomitant medications (from V1) 1. Inhaled corticosteroids other than the study drugs. 2. Inhaled LABA other than the study drugs. 3. Inhaled fixed combinations ICS/LABAs (e.g. Seretide[®], Symbicort[®]) other than the study drugs. 4. Inhaled Short-Acting Muscarinic Antagonists (SAMAs) and Inhaled Long-acting Muscarinic Antagonists (LAMAs). 5. Inhaled free combinations of ICS/LABAs and/or LAMA other than the study drugs. 6. Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers). 7. Theophylline. 8. Systemic anticholinergics.

	9. Systemic corticosteroids (except short courses for severe asthma exacerbations) 10. Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs). 11. Non-selective β-blocking drugs (including eye drops). 12. Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening). 13. Quinidine and Quinidine-like anti arrhythmics. 14. Any medication with a QTc prolongation potential. 15. Monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs. 16. Any medication that could interact with the study drug, according to Investigator's judgement. Prior to screening (V1), the following wash-out periods apply: ▪ Inhaled/nebulized SABA: 6 hours, ▪ Inhaled/nebulized SAMA: 8 hours, ▪ Inhaled/nebulized combination of SABA/SAMA fixed combination: 8 hours, ▪ Inhaled LABA for BID administration: 12 hours, ▪ Inhaled LABA for once daily administration (e.g. indacaterol): 72 hours, ▪ Inhaled fixed combination of LABA/ ICS for BID administration: 12 hours, ▪ Inhaled fixed combination of LABA/ ICS for once daily administration: 72 hours, ▪ ICS: 12 hours, ▪ Theophylline and leukotriene modifiers: 72 hours.
Efficacy variables	Primary variables ▪ Change from baseline in pre-dose FEV₁ at Week 26. ▪ Moderate and severe exacerbations rate over 52 weeks of treatment Key secondary variables ▪ Change from baseline in peak FEV₁ (within 3 hours post dosing) at Week 26. ▪ Change from baseline in morning PEF measured by patients at home over the 26-week treatment period. ▪ Severe exacerbations rate over 52 weeks of treatment in a pre-specified pooled analysis of the two pivotal studies CCD-05993-AB1-03 and CCD-05993-AB2-02 Secondary efficacy variables ▪ Change from baseline in Peak FEV₁ (within 3 hours post dosing) at all clinical visits ▪ Change from baseline in pre-dose FEV₁ at all clinical visits ▪ FEV₁ AUC normalised by time at all clinical visits

	▪ Change from baseline in ACQ-7 at all clinical visits ▪ Change from baseline in morning and evening PEF over the 52-week treatment period ▪ Change from baseline in the average use of rescue medication (number of puffs/day) over the 52-week treatment period ▪ Time to first moderate or severe exacerbation. ▪ Time to first severe exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 ▪ Moderate exacerbations rate over 52 weeks of treatment in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02. ▪ Time to first moderate exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 ▪ Moderate exacerbations rate over 52 weeks of treatment. ▪ Time to first moderate exacerbation. ▪ Daily asthma symptoms over the 52-week treatment period ▪ Percentage of asthma control days over the 52-week treatment period Exploratory variables ▪ Pre-dose morning FVC, IC and VC at all clinical visits Health economic variables (from Visit 2 to Visit 7) ▪ EQ-5D-3L VAS score and EQ-5D-3L index at all clinic visits ▪ Number of hospital admissions due to asthma ▪ Number of days in hospital due to asthma ▪ Number of emergency room visits due to asthma ▪ Number of unscheduled contacts with health care providers due to asthma: ○ Family practitioner ○ Specialist outpatient setting ○ Specialist hospital outpatient setting ▪ Unplanned diagnostic tests or instrumental tests due to asthma ▪ Concomitant medications ▪ Lost productivity (sick leave days from work, anticipated retirement) due to asthma
Pharmacokinetics variables	Clearances and volumes of distribution will be estimated by population PK analysis starting from B17MP, FF and GB plasma levels measured in a subset of patients in the CHF 5993 100/6/12.5 pMDI group at steady state at Visit 3 (Week 4) and at Visit 6 (Week 40). Other pharmacokinetic parameters of interest could also be reported like for example AUCtau (AUC during a dosing interval at steady state).

Safety variables	- Adverse events (AEs) and adverse drug reactions (ADRs). - Vital signs (systolic and diastolic blood pressure). 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS. - Standard haematology and blood chemistry.
Sample size calculation	The sample size has been calculated to demonstrate the superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in terms of both co-primary and key secondary endpoints. Approximately 1148 patients will be randomised (574 per group). A log-normal distribution is assumed for drop-out time, estimating approximately 13% drop-out rate at Week 12, 16.5% at Week 26 and 20% at Week 52. Approximately 958 completed patients (479 per group) will be available for the analysis at that time point. This sample size will ensure: - approximately 99% power to detect a mean difference of 90 ml in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in change from baseline in pre-dose FEV₁ at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 311 ml; - approximately 93% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI at a two-sided significance level of 0.05 using a negative binomial model and assuming a rate of 2.70 moderate and severe exacerbation per patient per year in the CHF 1535 100/6 pMDI group and an overdispersion parameter of the negative binomial distribution of 0.56. The same number of patients will provide: - approximately 99% power to detect a mean difference of 100 ml in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in Peak FEV₁ change from baseline at Week 26 at a two-sided significance level of 0.05, assuming a SD of 338 ml. - at least 99% power to detect a mean difference of 20 L/min in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in morning PEF change from baseline at Week 26 at a two-sided significance level of 0.05, assuming a SD of 45 L/min. - approximately 86% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI at a two-sided significance level of 0.05, in the pooled analysis using a negative binomial model and assuming a rate of 0.60 exacerbation per patient per year in the CHF 1535 100/6 pMDI group and an overdispersion parameter of the negative binomial distribution of 0.56.
Statistical methods	Primary efficacy variables Change from baseline (Visit 2 pre-dose) in pre-dose FEV₁ at week 26 will be analysed using a linear mixed model for repeated

	measures including treatment, visit, treatment by visit interaction, Country as fixed effects, and baseline value and baseline by visit interaction as covariates. ▪ The number of moderate and severe exacerbations during the 52-week treatment period will be analysed using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset. Key Secondary efficacy variables ▪ Change from baseline (Visit 2 pre-dose) in Peak FEV₁ (within 3 hours post-dosing) at week 26 will be analysed using a similar model as for change from baseline in pre-dose FEV₁. ▪ Change from baseline in the average morning PEF at Week 26 will be analysed using a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, Country as fixed effects, and baseline value and baseline by period interaction as covariates. ▪ The number of severe exacerbations during the 52-week treatment period will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset. Secondary efficacy variables ▪ Change from baseline in Peak FEV₁ at all clinical visits, and change from baseline in pre-dose FEV₁ at all clinical visits, will be analysed using the same model as for the primary efficacy analysis. ▪ FEV₁ AUC_{0-3h} normalised by time at all clinical visits will be analysed using the same model used for the primary efficacy analysis. ▪ Change from baseline (Visit 2) in the ACQ-7 score at all clinical visits will be analysed using the same models as for the primary efficacy analysis on FEV₁ endpoint, but including baseline ACQ-7 instead of baseline FEV₁. ▪ Change from baseline (run-in period) in morning and evening PEF over the 52-week treatment period and to each inter-visit period will be analysed using the same model as for the PEF at 26 weeks. ▪ Change from baseline (run-in period) in the average use of rescue medication over the 52-week treatment period and to each inter-visit period will be analysed using the same model as for the PEF at 26 weeks. ▪ Time to first moderate or severe exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.
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	▪ Time to first severe exacerbation will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented. ▪ The number of moderate exacerbations during the 52-week treatment period will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset. ▪ The time to first moderate exacerbation will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented. ▪ The number of moderate exacerbations during the 52-week treatment period will be analysed using a negative binomial model including treatment, Country and number of exacerbations in the previous year as fixed effects (1 or >1), and log-time on study as an offset. ▪ The time to first moderate exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented. ▪ Daily (morning and evening) Asthma Symptoms and Percentage of asthma control days in each inter-visit period and over 52 weeks will be analysed using a linear mixed model for repeated measures including treatment, period, treatment by period interaction, Country as fixed effects, and baseline value and baseline by period interaction as covariates. Exploratory variables ▪ Absolute values and change from baseline in pre-dose morning FVC, IC and VC at all clinical visits will be analysed using descriptive statistics. Safety variables ▪ The number and percentage of patients who experienced at least one TEAE, drug-related TEAE, serious TEAE, serious related TEAE, TEAE leading to study discontinuation, and TEAE leading to death will be summarized by treatment group. Summaries will be presented overall and by System Organ Class and Preferred Term using the MedDRA dictionary. ▪ An similar analysis will be presented for Treatment-Emergent MACEs. ▪ Mean absolute values and mean changes from baseline for vital
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	signs (SBP, DBP) and 12-lead ECG parameters (HR, PR, QRS and QTcF) will be presented using descriptive statistics. ▪ For haematology and chemistry parameters, shift tables from Week 26 to Screening and from Week 52 to Screening with reference to normal ranges will be presented Pharmacokinetic variables ▪ The plasma concentration data of B17MP, FF and GB will be subjected to a population PK analysis. For this analysis the data may be combined with results from previous studies (or analysis). The aim of the population PK analysis is to develop a compartmental model of the plasma concentration vs. time profiles, which will provide a good understanding of the inter-subject and intra-subject (if possible) variability in the drug exposure. In addition the effects of selected covariates on PK parameters will be evaluated, e.g. age, sex, race, smoking status, BMI, concomitant medications, renal and hepatic impairment.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Adjudication Committee
ACQ[®]	Asthma Control Questionnaire [®]
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification)
AUC	Area Under the Curve
AV	Atrial Ventricular
BDP	Beclometasone Dipropionate
BID	<i>Bis in die</i> (twice a day)
BPH	Benign Prostatic Hyperplasia
bpm	Beats Per Minute
BTPS	Body Temperature and Pressure, Saturated (conditions)
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FF	Formoterol Fumarate
FEV₁	Forced Expiratory Volume in the first second
FPFV	First Patient First Visit
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
γ-GT	Gamma-glutamyl transpeptidase
IRT	Interactive Response Technology
Hb	Haemoglobin
Hct	Haematocrit
HE	Hepatic encephalopathy
HFA	Hydrofluoroalkane
HR	Heart Rate
IC	Inspiratory Capacity
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Standards Organization
ITT	Intention to Treat

IUD	Intra Uterine Device
IUS	Intra Uterine System
L	Liter
LABA	Long-acting β 2-agonist
LAMA	Long-Acting Muscarinic Antagonist
LMA	Leukotriene-Modifying Agent
LTRA	Leukotriene receptor antagonist
MACE	Major Adverse Cardiac Events
MAOI	Monoamine Oxidase Inhibitor
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
ml	milliliter
ms	millisecond
NYHA	New York Heart Association
P	Period
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PLT	Platelet
pMDI	Pressurized Metered Dose Inhaler
PP	Per-Protocol
PR	Time interval between the beginning of the P wave and the beginning of the QRS complex in the ECG
PV	Pharmacovigilance
QTc	Time Interval Between the Q and T wave in the ECG (corrected for heart rate)
QTcF	Fridericia - Corrected QTc
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
RR	Time interval between two consecutive R waves
R&D	Research and Development
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
μg	microgram
V	Visit
VAS	Visual Acuity Scale
VC	Vital Capacity
WBC	White Blood Cell
WHO	World Health Organization

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APPENDICES

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Appendix V	Patient Card

1. BACKGROUND INFORMATION AND STUDY RATIONALE

The goal of asthma management is to achieve and maintain disease control for prolonged periods with due regard to the safety of treatment, potential for adverse effects and the cost of treatment required to achieve this goal⁽¹⁾. However, for a substantial proportion of patients asthma remains uncontrolled despite upward titration of combination (ICS plus LABA) therapy^(1,2). This is a crucial point as poorly controlled asthma increases the risk of severe asthma exacerbations⁽³⁾.

Before the April 2015 Global Initiative for Asthma (GINA) guidelines recommend the addition of therapies such as antileukotrienes, theophyllines, anti-IgE, and immunosuppressants (eg, systemic corticosteroids). However, they may remain both symptomatic and obstructed despite these therapies⁽²⁾.

An alternative potentially effective approach was the addition of a second bronchodilator with a different mode of action. Cholinergic tone is an independent mechanism resulting in contraction of airway smooth muscle and release of mucus from submucosal glands⁽⁴⁾. Muscarinic receptors blockade (third subtype – M3) is resulting in bronchodilation effect.

The use of anticholinergics in asthma is well known:

- Inhaled ipratropium bromide, a short-acting anticholinergic, was found to improve lung function and respiratory symptoms⁽⁵⁾.
- Compared with non-smokers, smokers with asthma demonstrated a better disease control when treated with inhaled ipratropium than with salbutamol⁽⁶⁾.
- Inhaled tiotropium bromide, a long-acting anticholinergic, produces a rapid onset, sustained bronchodilation and reduced airways hyperresponsiveness⁽⁷⁾.

Tiotropium bromide decreases airways remodelling in animal models of ovalbumin-induced asthma. These effects were comparable to those of the budesonide^(8,9).

Indeed, the addition of tiotropium to LABA/steroid combination inhalers has been shown to improve lung function and increase the time to the first severe exacerbation in patients with inadequately controlled asthma^(10,11).

Tiotropium has been used off-label as an add-on bronchodilator in patients with severe asthma for some time, but this has recently been supported by controlled clinical trials:

- In 210 patients with inadequately controlled asthma, the addition of tiotropium to inhaled corticosteroids improved symptoms and lung function. The effect was equivalent to the addition of salmeterol and more effective than doubling the dose of inhaled corticosteroids⁽¹²⁾.
- The addition of tiotropium (5 µg administered through the Respimat inhaler) to asthma treatment (including high-dose ICS + LABA) improved lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma⁽¹⁰⁾.
- In two parallel studies of 912 patients with poorly controlled asthma (despite ICS + LABA) the addition of tiotropium (5 µg administered through the Respimat inhaler) increased the

time to the first severe exacerbation and provided sustained, though modest, bronchodilatation ⁽¹¹⁾.

- In two parallel studies lasting for 24 weeks, 2103 symptomatic asthma patients (despite of medium ICS dose) were added with tiotropium 5µg or 2,5µg OD, BID 50µg of salmeterol or placebo. Study results showed that OD tiotropium addition to medium-dose of ICS reduces airflow obstruction and improves asthma control in patients with moderate symptomatic asthma. Patterns of response with both tiotropium doses were similar to those of salmeterol, and all active compounds had good safety and tolerability ⁽¹³⁾.
- Pooled analysis of above mentioned trials data was published in 2015: it has included 3 012 patients and showed that tiotropium provided statistically significant and sustained improvements in both peak FEV₁ (0-3h) (all p<0.05) and trough FEV₁ (all p<0.01) responses compared with placebo, risk of asthma worsening significantly reduced. Author's conclusion was that once-daily tiotropium add-on to at least medium-dose ICS±LABA provided significant and sustained improvements in lung function, improved asthma control, and reduced risk of asthma worsening in adults with moderate or severe symptomatic asthma ⁽¹⁴⁾.

In September 2014, tiotropium was registrated for the asthma patients treatment. Above-mentioned trials convinced GINA scientific board that regardless of ICS dose – medium or high, LAMA addition to asthmatic patients is safe and provide significant clinical effect. GINA guideline was revised and tiotropium was included into the guidelines as add-on to the patients receiving LABA/ICS on the treatment Steps 4 and 5 ⁽²⁾.

Glycopyrronium bromide is a quaternary ammonium, anticholinergic agent used orally to control gastric acidity, parenterally as an antispasmodic and to reverse neuromuscular blockade, and studied inhaled in asthma and COPD. Inhaled glycopyrronium bromide has been shown to induce prolonged bronchodilation in patients with asthma ^(15,16,17) and has been found to be an effective bronchodilator in COPD ^(18,19,20).

Glycopyrronium bromide (GB) CHF 5259 as single component has been already assessed as single dose in a dose range of 12.5 µg to 200 µg and as multiple dose (1 week treatment) in a dose range of 25 µg to 100 µg in comparison with placebo in COPD patients. In asthma, a dose finding study has shown that the efficient dose for uncontrolled asthmatic patients is 50 µg GB after a period of 6 weeks of treatment. No safety risk has been raised during these studies ^(21, 22).

Chiesi intends to develop a fixed triple dose combination of BDP/FF/GB (CHF 5993) for asthmatic patients that would benefit from ICS/LABA and LAMA combined therapy. This product will be combined glycopyrronium bromide with the fixed combination CHF 1535 100/6 µg (Beclomethasone Dipropionate [BDP] plus Formoterol Fumarate [FF]). This fixed combination is already licensed under the trade name Foster[®] with the strength 100/6 µg approved for asthmatic patients.

Chiesi believes that new fixed triple combination in one pMDI device will provide additional benefit for asthma patients:

- First fixed triple LAMA/LABA/ICS combination for severe asthma patients is in line with modern asthma guidelines
- Twice daily regimen provides additional asthma symptoms control during the nighttime.
- Better treatment effect and overall treatment results due to the pMDI device inhalation technique.
- DPI devices have different characteristics also resistance, pMDI devices don't need any additional patient effort to make an inhalation.

A significant advantage of a triple inhaler in asthma is convenience for the patient as this reduces the need for using separate inhalers that are often of a differing type and therefore need to be used differently ⁽²³⁾. This is critical since most patients with poorly controlled asthma show poor adherence with regular inhaled therapy ^(24, 25).

The study CCD-05993AB1-03 has been then designed to assess the efficacy and safety of the triple fixed combination CHF 5993 100/6/12.5 µg versus CHF 1535 100/6 µg on patients with uncontrolled asthma under medium dose of ICS/LABA. A second study CCD-05593AB2-02 will be run in parallel of the study CCD-05993AB1-03 ⁽²⁶⁾ (Eudract number 2015-000717-40) with CHF 5993 at the strength 200/6/12.5 µg on patients with uncontrolled asthma under high dose of ICS/LABA

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

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

- To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI in terms of change from baseline in pre-dose FEV₁ at Week 26.
- To demonstrate the reduction of moderate and severe asthma exacerbations rate with CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI during the entire 52-week treatment period.

2.2 Secondary Objective(s)

Key secondary objectives:

- To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI in terms of change from baseline in peak FEV₁ within 3 hours post-dose at Week 26.
- To demonstrate the superiority of CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI in terms of change from baseline in morning PEF averaged over 26-week treatment period.
- To demonstrate the reduction of severe asthma exacerbations rate with CHF 5993 100/6/12.5 pMDI compared to CHF 1535 100/6 pMDI during the entire 52-week treatment period in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 trials.

Other secondary objectives:

- To compare the study treatments for other lung function assessments, patient's health status and clinical outcome measures.
- To collect data in order to assess the impact of study treatments on health economic outcomes.
- To assess the safety and the tolerability of the study treatments.
- To perform a population PK analysis in a subset of patients treated with CHF 5993 investigating the inter- and intra-subject variability in the drug exposure and the effect of selected covariates on PK beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide.

3. STUDY DESIGN

This is a phase III, multicentre, randomised, double-blind, active-controlled, 2-arm parallel group study with active control group in asthmatic patients. Approximately 1148 randomised patients in about 200 sites will be involved.

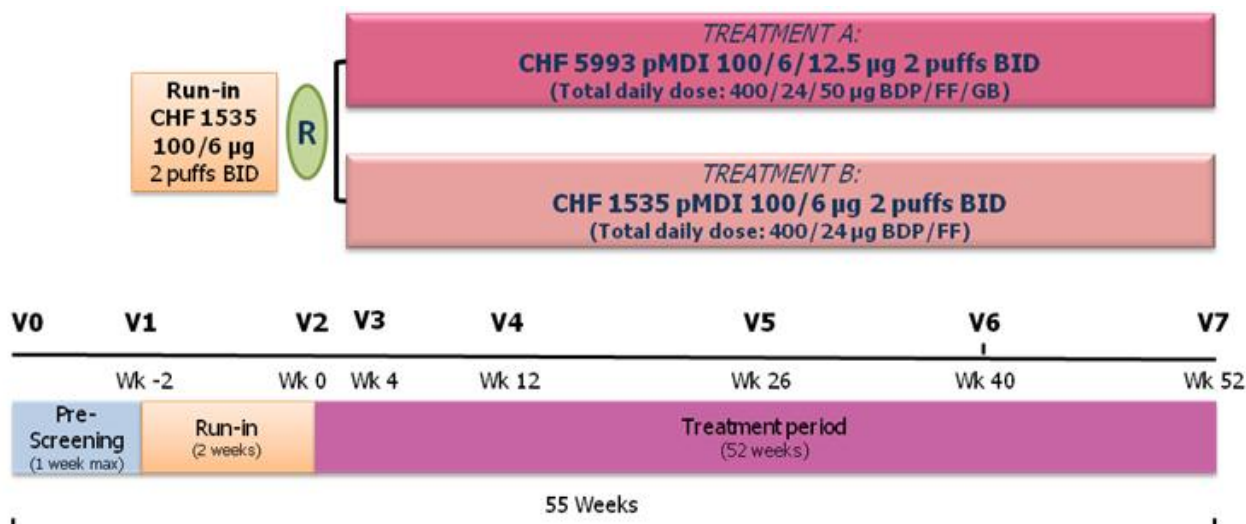
A total of 8 clinic visits (V0 to V7) will be performed during the study, as follows:

- A pre-screening visit (V0) will be carried out in order to fully explain the study to potential patients and to obtain the written informed consent from the patient and instruct the patient on screening visit procedures (such as medication restrictions).
- A screening visit (V1) will help establishing the eligibility of patients for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead ECG, ACQ-7, spirometry including FEV₁ reversibility after salbutamol intake, and training for the use of inhalers and epeakflow meter/ediary).
- This visit will be followed by a 2-week $\pm$ 2 days open-label run-in period, where patients will receive CHF 1535 100/6 μ g 2 inhalations BID (daily dose 400/24 μ g).
- After the randomisation visit (V2), patients will be assessed after 4, 12, 26, 40 and 52 weeks of treatment (from V3 to V7) at clinic/hospital. At each visit from V2 to V7, spirometry pre-dose and 3-hour post dose (serial test during 3 hours), as well as ACQ-7 and EQ-5D-3L, will be performed in addition to other safety tests.
- AEs and SAEs will be monitored throughout the study.

Total study duration (V0 to V7) = 55 weeks

The end of the trial is defined as the last visit (Visit 7) of the last subject in the trial.

General flow chart of the study:



During the visits of the randomised treatment period (V2 to V7), patients will undergo serial spirometry assessments under supervision (over 3-hour post-dose):

- Time "0" (T-0) is defined as the time of first inhalation of study medication.
- The 7 time points are: -45min; -15min; 15min; 30min; 60min; 120min and 180min.

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Patients attending the hospital clinics/study centres will be recruited. Adults asthmatic patients (males and females), 18 to 75 years of age will be selected.

Approximately 1766 patients will be screened in order to reach a total of 1148 randomised and evaluable patients at week 52 (574 per group); estimating a drop-out rate of 16.5% at Week 26, approximately 958 evaluable patients (479 per group) will be available for the analysis at that time point.

A subset of patients (about 450) will be selected in order to reach about 200 evaluable patients in the PK analysis (CHF 5993 pMDI group).

The assumptions for screening failure rate and drop-out rate may be refined during the study.

Financial compensation fees may be given to the patients according to local law and regulations to compensate patients' time, travel expenses, and for any inconvenience caused by the study.

4.2 Inclusion Criteria

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

1. Patient's written informed consent obtained prior to any study-related procedures.

2. Male or female patients aged ≥ 18 and ≤ 75 years.
3. Patients must have a documented history of asthma for at least 1 year and asthma must have been diagnosed before the patient's age of 40.
4. Patients with uncontrolled asthma with double therapy only on medium doses of ICS (>500 - 1000 μg daily dose BDP non-extrafine or estimated clinical comparable dose) in combination with a β_2 long-acting bronchodilator (LABA) at a stable dose for at least 4 weeks prior to screening. LABA daily dose: patients under formoterol 24 μg or salmeterol 100 μg or vilanterol 25 μg or other approved dose of LABA as clinically comparable to the others in the list can be included.

Drug*	Medium daily dose
BDP non-extrafine	>500 - 1000 μg
BDP extrafine	>200 - 400 μg
Budesonide (DPI)	>400 - 800 μg
Ciclesonide (HFA)	>160 - 320 μg
Fluticasone (HFA/DPI)	>250 - 500 μg
Mometasone furoate	>220 - 440 μg
Triamcinolone acetonide	>1000 - 2000 μg

*(Table adapted from GINA 2015)

5. Patients with a pre-bronchodilator FEV_1 $<80\%$ of their predicted normal value, after appropriate washout from bronchodilators, at the screening and randomization visits.
6. Patients with a positive response to a reversibility test at screening, defined as $\Delta\text{FEV}_1 >12\%$ and $>200\text{mL}$ over baseline 10-15 minutes after inhaling 400 μg of salbutamol pMDI.
Note: In case the reversibility threshold is not met at screening, the test can be performed once before randomisation.
7. Patients with uncontrolled asthma evidenced by a score at the Asthma Control Questionnaire 7[®] (ACQ-7) ≥ 1.5 (this criterion must be met at screening and at the end of the run-in period).
8. A documented history of one or more asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalization in previous 12 months.
9. A co-operative attitude and ability:
 - to be trained to correctly use the pMDI inhalers;
 - to perform all trial related procedures including technically acceptable pulmonary function tests;
 - to correctly use the electronic diary/peak flow meter.

At screening visit (Visit 1), all inclusion criteria will be checked.

If at Visit 1 the inclusion criterion 6 is not met, the following criteria will be re-checked prior the randomisation visit: 5, 6 and 7.

At randomisation visit (Visit 2), the following criteria will be re-checked: 5, 7 and 9.

4.3 Exclusion Criteria

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

1. Inability to carry out pulmonary lung function testing, to comply with study procedures or with study treatment intake.
2. Run-in compliance < 50% at randomisation.
3. History of near fatal asthma or of a past hospitalisation for asthma in intensive care unit which, in the judgement of the investigator, may place the patient at undue risk.
4. Hospitalisation, emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period.
5. Patients with any asthma exacerbation or respiratory tract infection in the 4 weeks prior to the screening visit or during run-in period.
6. Any change in dose, schedule or formulation of the combination ICS plus LABA in the 4 weeks prior to screening visit.
7. Patients using systemic corticosteroid medication in the 4 weeks or slow release corticosteroids in the 12 weeks, prior to screening.
8. Patients who suffer from COPD as defined by the current GOLD guidelines.
9. History of a diagnosis of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease which may interfere with study evaluations.
10. Current smokers or ex-smokers with total cumulative exposure equal or more than 10 pack-years or having stopped smoking one year or less prior to screening visit.
11. Patients who have clinically significant cardiovascular condition according to investigator's judgement, such as but not limited to: congestive heart failure (NYHA class > 3), acute ischemic heart disease in the last year prior to study screening, history of sustained cardiac arrhythmias or sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months (sustained means lasting more than 30 seconds or ending only with external action, or leads to hemodynamic collapse; non-sustained means > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), high degree impulse conduction blocks ($\geq 2^{\text{nd}}$ degree AV block type 2). Similarly, patients affected by persistent, long standing or paroxysmal atrial fibrillation will not be considered for enrolment.

*Note: Patients with **Permanent Atrial Fibrillation** (for at least 6 months) with a resting ventricular rate < 100/min, controlled with a rate control strategy (i.e., selective β -blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) can be considered for the enrolment.*

12. An abnormal and clinically significant 12-lead ECG that results in active medical problem which may impact the safety of the patient according to investigator's judgement.
13. Patients whose electrocardiogram (12-lead ECG) shows QTcF >450 ms for males or QTcF >470 ms for females at screening or at randomisation visits (criterion not applicable for patient with pacemaker or permanent atrial fibrillation).

14. Patients with a medical history or current diagnosis of narrow-angle glaucoma, symptomatic prostatic hypertrophy, urinary retention bladder neck obstruction that, in the opinion of the investigator, would prevent use of anticholinergic agents.

Note: Benign Prostatic Hyperplasia (BPH) patients who are stable under treatment can be considered for inclusion.

15. Other severe acute or chronic medical or malignancy or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
16. Patients having received a vaccination within 2 weeks prior to screening or during the run-in.
17. Patients mentally or legally incapacitated, or patients accommodated in an establishment as a result of an official or judicial order.
18. Patients with a history of alcohol or drug abuse within two years prior to the start of the study.
19. Patients with known intolerance/hypersensitivity or contra-indication to treatment with β_2 -agonists, inhaled corticosteroids, anticholinergics or propellant gases/excipients.
20. Patients with major surgery in the 3 months prior to screening visit or planned surgery during the trial.
21. Patients treated with non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening), non-selective beta-blocking drugs, quinidine, quinidine-like anti arrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation.
22. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants.
23. Patients being treated with monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs.
24. Patients who are receiving any therapy that could interfere with the study drugs according to investigator's opinion.
25. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS are using one or more of the following highly effective contraceptive measures:
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
 - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
 - Bilateral tubal occlusion
 - Vasectomised partner.

Reliable contraception should be maintained throughout the study.

Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized

(e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study.

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

26. Patients who have received an investigational drug within 2 months or six 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.

Only for patients included in the subset for PK assessment

27. Patients with unsuitable veins for repeated venipuncture.
28. Blood donation (equal or more than 450 mL) or blood loss in the 4 weeks before randomization.

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

At randomisation visit (Visit 2), the following criteria will be verified: 1, 2, 3, 4, 5, 12, 13, 15, 16, 20, 24, and 25. In addition, for patients included in the subset for PK assessment, the criterion 28 will be verified.

4.4 Subject Withdrawals

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

- An adverse event occurs that, in the opinion of the investigator, makes it unsafe for the subject to continue in the study. In this case, the appropriate measures will be taken.
- The subject is lost to follow-up.
- The subject withdraws consent.
- The subject's safety is affected by violation of inclusion or exclusion criteria or use of not-permitted concomitant medication.
- The subject is unwilling or unable to adhere to the study requirements, i.e, non-compliance.
- The sponsor or the regulatory authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided.

However, should a subject discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible.

All the assessments foreseen at Visit 7 (Week 52) should be done at early termination to the extent possible, providing there is no safety issue for the patient (see [section 7.1.9](#) for more details).

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

In order to collect as complete as possible information in the clinical study database, all Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs) ongoing at the time the subject’s study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as “ongoing” in the eCRF.

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

The following medications are allowed during the study:

1. Inhaled salbutamol administered as rescue medication. A minimum wash-out period of 6 hours between the use of rescue salbutamol and the start of the spirometric study assessments is required. If a patient needs rescue medication within this time window, the visit must be postponed.
2. Short courses (≤ 14 days each) of systemic corticosteroid and/or brief uses of nebuliser containing β_2 -agonists and/or corticosteroids, and/or antibiotics therapy for severe asthma exacerbation are permitted.
3. Antihistamines and nasal corticosteroids 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).
4. Treatment for desensitisation 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). Sublingual immunotherapy started before the study can be continued at a stable dose.
5. In case of concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluations and it is not listed below under the section "non-permitted medications".

5.2 Non-permitted concomitant Medications

The following medications are not permitted during the total study period starting from Visit1 (run-in and treatment period). Intake of these medications during run-in constitutes a non eligibility criterion and the patient will not be randomised into the study. **If any of these medications is taken during the randomised treatment period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest.**

1. Inhaled corticosteroids other than the study drugs.
2. Inhaled LABA other than the study drugs.
3. Inhaled fixed combinations ICS/LABAs (e.g. Seretide[®], Symbicort[®]) other than the study drugs.

4. Inhaled Short-Acting Muscarinic Antagonists (SAMAs) and Inhaled Long-acting Muscarinic Antagonists (LAMAs).
5. Inhaled free combinations of ICS/LABAs and/or LAMA other than the study drugs.
6. Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers).
7. Theophylline.
8. Systemic anticholinergics.
9. Systemic corticosteroids (except short courses for severe asthma exacerbations).
10. Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs).
11. Non-selective β -blocking drugs (including eye drops).
12. Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening).
13. Quinidine and Quinidine-like anti arrhythmics.
14. Any medication with a QTc prolongation potential.
15. Monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs.
16. Any medication that could interact with the study drug, according to Investigator's judgement.

Prior to screening (Visit 1), the following wash-out periods apply:

- Inhaled/nebulized SABA: 6 hours,
- Inhaled/nebulized SAMA: 8 hours,
- Inhaled/nebulized combination of SABA/SAMA fixed combination: 8 hours,
- Inhaled LABA for BID administration: 12 hours,
- Inhaled LABA for once daily administration (e.g. indacaterol): 72 hours,
- Inhaled fixed combination of LABA/ ICS for BID administration: 12 hours,
- Inhaled fixed combination of LABA/ ICS for once daily administration: 72 hours
- ICS: 12 hours,
- Theophylline and leukotriene modifiers: 72 hours.

6. TREATMENT(S)

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

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.

6.1 Appearance and Content

- **CHF 5993 pMDI 100/6/12.5 μ g - Test product**
 - Active ingredient:* Beclometasone dipropionate/Formoterol fumarate/ Glycopyrronium bromide
100/6/12.5 μ g per metered dose
 - Excipient:* HFA-134a propellant, ethanol anhydrous, hydrochloric acid
 - Presentation:* Each canister contains 120 doses

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

Active ingredient: Beclometasone dipropionate/Formoterol fumarate
100/6 µg per metered dose

Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid

Presentation: Each canister contains 120 doses

- **Placebo CHF 5993 pMDI - used only for training**

Excipient: HFA-134a propellant, ethanol anhydrous

Presentation: Each canister contains 120 doses

All the inhalers are identical so it will allow a complete double-blind design.

Note: salbutamol (rescue medication 100 µg/puff) will be purchased locally and provided by Investigator site to patients. The rescue medication will be reimbursed by the Sponsor.

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

The dose of CHF 5993 has been selected based on available relevant literature and a previous Chiesi dose-finding study in asthma showing that the daily dose 50 µg of Glycopyrronium bromide tested in this trial has a good pharmacological profile both in terms of efficacy and safety [\(21, 22, 27\)](#).

6.2.2 Dosage

6.2.2.1 Run-in period:

- **CHF 1535 pMDI 100/6 µg**

- 2 inhalations BID (Total daily dose : BDP 400µg/FF 24µg)

6.2.2.2 Randomised Treatment period:

- **Treatment A: CHF 5993 pMDI 100/6/12.5 µg**

- 2 inhalations BID (Total daily dose: BDP 400µg/FF 24µg/GB 50µg)

- **Treatment B: CHF 1535 pMDI 100/6 µg**

- 2 inhalations BID (Total daily dose: BDP 400µg/FF 24µg)

6.2.3 Administration

6.2.3.1 Run-In kits

During the run-in period, each patient will receive 1 run-in kit (containing 1 inhaler of CHF 1535) covering the 2-week run-in period.

At screening visit (Visit 1), the Investigator, or designee, will contact the IRT system to dispense to each patient one run-in kit of CHF 1535 100/6 µg, **to be taken with 2 inhalations BID**, in replacement of the patient's current asthma therapy.

The run-in medication will be administered twice a day in the morning (between 7 and 9 am preferably) and in the evening (between 7 and 9 pm preferably). To the extent possible, the time of dosing must remain constant for each patient for the whole duration of the study

Note: the first dose of run-in medication must be administered at clinic at the end of Visit 1 (the run-in kit should be dispensed at V1 even if the reversibility test needs to be re-performed before the randomisation).

For more details regarding the instructions for use of run-in treatment, please refer to patient leaflet.

6.2.3.2 Study Treatment kits

During the randomised treatment period, each patient will receive 8 treatments kits in total, each one covering an 8-week period.

At the randomisation visit (Visit 2), after confirmation of patient's eligibility, the Investigator, or designee, will contact the IRT system to dispense to each patient two treatment kits of study treatment A (CHF 5993 pMDI) or treatment B (CHF 1535 pMDI), as follows:

- The first 2 kits will be dispensed at Week 0 (Visit 2);
- The others 6 kits will be dispensed respectively at Week 12 (Visit 4), Week 26 (Visit 5) and Week 40 (Visit 6).

Each treatment kit will consist of 1 box containing 2 inhalers (2 CHF 5993 pMDI or 2 CHF 1535 pMDI). The 2 inhalers (numbered 1 and 2) will be used in the morning and in the evening. **As each kit can cover a period of 8 weeks, the patient will be instructed to change the kit after 7 weeks of use maximum.**

The study drug will be administered twice a day in the morning (between 7 and 9 am preferably) and in the evening (between 7 and 9 pm preferably):

- **Morning administration:**
 - One inhalation from the inhaler 1
 - One inhalation from the inhaler 2
- **Evening administration:**
 - One inhalation from the inhaler 1
 - One inhalation from the inhaler 2

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

Per day, 4 inhalations will be taken (2 in the morning and 2 in the evening). After each inhalation, the patient must hold his/her breath for as long as possible. For more details regarding the instructions for use of Study Treatments, please refer to patient leaflet.

Note: the first morning dose of study medication must be administered at Time “0” at clinics before the serial spirometry on Visits 2 to 7. The evening dose on Visits 2 to 6 must be administered at home.

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

6.2.3.3 Use of AeroChamber Plus™

In case patients are used to inhale their pMDI asthma medications with a spacer device, they should continue using a spacer for both run-in and study treatment medications' inhalations.

The spacer device to be used in the study is the **AeroChamber Plus™ Flow-Vu antistatic Valved Holding Chamber** (referred as AeroChamber Plus™ in the rest of the document).

For these patients, **each inhalation** (for the run-in and randomisation periods) **must be performed via AeroChamber Plus™. For each puff, the patient must inhale slowly and deeply and hold his breath as long as possible.**

One spacer will be assigned to the patient by the Investigator at screening (Visit 1), at randomisation (Visit 2), and at Week 26 (Visit 5).

Note: At Visit 1, an AeroChamber Plus™ will be dispensed to the patient for training purposes at site and will be also used for the run-in period. There is no need to wash the spacer between the training and the start of the run-in medication.

From Visit 1, the spacer must be washed every week until the end of the study, including the night before V2 after the evening dose.

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

6.2.3.4 Rescue medication

The rescue medication (salbutamol 100 µg/puff) must be used only in case of absolute need. **The maximum dose allowed is 8 puffs per day. In case the patients' needs exceed 4 puffs/day for more than 2 consecutive days, he/she must contact the investigator.**

A minimum period of 6 hours should elapse between the use of rescue salbutamol and the spirometric measurements.

6.2.4 Subject Training

At screening visit (Visit 1), the Investigator, or designee, will contact the IRT system to get to each patient one training kit.

The patient will be instructed by the Investigator on how to use the pressurised Meter Dose Inhalers (pMDIs), on the method of inhalation and duration of breath holding after inhalation, according to

the instructions for use. The proper use of the inhalers will be checked again at randomization visit using the same training kit.

This training kit will be kept at the site by the Investigator and can be re-used for subsequent trainings.

If the patient is used to take asthma pMDI medications via a spacer, he/she will be trained on the use of pMDI with an Aerochamber Plus™.

At screening and at randomization visits, the patient will be trained with the same Aerochamber Plus™ dispensed at Visit 1.

For more details concerning the use of the pMDI with spacer and the Aerochamber Plus™, please refer to the corresponding patient leaflets.

6.3 Packaging

6.3.1 Training kit

- Primary packaging: One aluminium canister of CHF 5993 placebo plus standard actuator both labelled with a study label in English only
- Secondary packaging: One carton box labelled with a study label in English only label with a tear/peel off portion.

6.3.2 Run-in kit

- Primary packaging: One aluminium canister of CHF 1535 100/6 µg with a study label in English only plus standard actuator labelled with a study multi language label.
- Secondary packaging: Carton box labelled with a study multi language label with a tear/peel off portion.

6.3.3 Treatment kit

- Primary packaging: Two aluminium canisters labelled with a study label in English only plus standard actuator labelled with a study multilanguage label. The two inhalers will be numbered 1 and 2.
- Secondary packaging: Carton box labelled with a study multi language label with a tear/peel off portion.

6.3.4 AeroChamber Plus™ Spacer

- Primary packaging: Spacer AeroChamber Plus™ Flow-Vu antistatic VHC.
- Secondary packaging: One box containing 1 spacer AeroChamber Plus™ Flow-Vu antistatic VHC with a tear/peel off portion.

6.4 Labelling

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

the exclusion of canisters that will be in English (indeed, a multilanguage booklet label, due to its thickness, could interfere with the proper movement of the canister inside the actuator). Moreover, due to the small size of the labels on the canisters, some information are reported on the secondary packaging as per Annex 13.

In addition, for all the labels, the patient identification is expressed by the kit number. This number is assigned by the IRT System which allows the full traceability of essential details such as: site identification, investigator's name, visit number, randomization number. Therefore, the presence of this kit number allows the exclusion of the above mentioned specifics terms from the labeling (except if required by local law).

The training kits will be labelled in English, as they are not dispensed to the patient.

6.5 Treatment allocation

A balanced block randomisation scheme stratified by Country will be prepared via a computerised system. Patients will be centrally assigned to one of the two treatment arms with a 1:1 ratio.

An Interactive Response Technology (IRT) system will be used at each visit (from pre-screening to follow-up call) to record patient status.

Patient number will be centrally assigned, through the IRT, during the pre-screening visit (Visit 0).

Patient numbers will consist of a 9 digit-number:

- the 6 first digits correspond to the centre number (first 3 digits for the country number corresponding to the ISO country codes and 3 last progressive for the site);
- the 3 last digits to the screening number (allocated in a chronological way in each site).

The Investigator, or designee, at the sites will call the IRT system to screen, randomise patients and assign treatment kits according to the sequence described in the randomisation list. The IRT will track also patient screen failures and discontinuations from the study.

6.6 Treatment Code

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

The randomization list will be provided to the labelling facility but will not be available to subjects, Investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency. The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list.

As the study foresees PK assessment on biological samples, an additional copy of the Master Randomization List will be provided to the analytical laboratory performing the PK analyses, that will be unblinded.

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

Users from Chiesi Global Pharmacovigilance will have their own passwords to unblind patients in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees/IRB.

6.7 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the subject in the diary, as well as the information recorded in the eCRF during the treatment visits.

The evaluation of study medication 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 of 65-135 % will be taken into account for a satisfactory level of compliance to the study medication, while a level of compliance equal or superior to 50 % will be considered as satisfactory for the run-in medication.

Note: at the end of the 2-week run-in period, if the compliance is below 50%, the run-in period will be extended of one week to achieve this level. If this level is not achieved within this week, the patient will be screened failed as per exclusion criterion n°2.

To optimize patients' compliance to study medication, a compliance check will be periodically done by means of phone calls to the patients during the study.

6.8 Drug Storage

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

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

Once delivered to patients, the run-in/randomised treatments kits must be stored at room temperature (not above 25°C) **at home**.

At this temperature condition, the actual use-by-date of the run-in treatments kits will be five months (150 days) and the use-by-date of the randomised treatments kits four months (**120 days**). Therefore, the Pharmacist/Investigator at the hospital must write the use-by-date on the kit labels once the kits are removed from the refrigerator, before assigning to the patients.

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

The patient should never inhale a cold medication

After usage, the training kit must be stored at room temperature (not above 25°C) **at the clinics**.

At this temperature condition the actual use-by-date of the training kits will be four months (**120 days**) from the date of removal from refrigerator. The Pharmacist/Investigator at the hospital must write the use-by-date on the kit labels once the kits are removed from the refrigerator, before assigning to the patients.

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

6.9 Drug Accountability

The Investigator, or the designated/authorized representative, is responsible for the management of all the study medications to be used for the study. Study medications that should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study medications.

An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study medication(s) received, dispensed and returned by each subject during the trial.

At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies.

All the study medications supplied, used or unused, will be returned to Chiesi or to the designated CRO under Sponsor's responsibility. Return and destruction will not occur until authorized by Chiesi.

6.10 Provision of additional care

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

7. STUDY PLAN

7.1 Study Schedule

The study plan includes a total of 8 clinic visits (Visit 0 to Visit 7), as follows:

- A **pre-screening visit (Visit 0)** to explain the aim of the study to the patients, to obtain their informed written consent and to prepare patients for V1;
- A **screening visit (Visit 1)**, no more than 7 days after V0 (Week - 2 before randomisation), to verify the patients' eligibility. This visit will be followed by a 2-week run-in period, where the patients will receive open-label CHF 1535 100/6 µg;
- A **randomisation visit (Visit 2, Week 0)** when patients will be randomised to one of the two treatment arms (CHF 5993 100/6/12.5 µg or CHF 1535 100/6 µg).
- Five **subsequent visits** scheduled during the treatment period after 4 (**Visit 3**), 12 (**Visit 4**), 26 (**Visit 5**), 40 (**Visit 6**) and 52 (**Visit 7**) weeks of treatment.

The visits shall be performed with appropriate wash-out of medications. In case the wash-out of medications is not respected:

- at Visit 1 and Visit 2, the visit can be rescheduled once within 2 days. If, in the morning of the rescheduled visit, the wash-out is still not respected the patient will be discontinued;
- at Visit 3 to Visit 7, the visit will be rescheduled within 3 days in order to obtain proper medication wash-out.

Note:

- Unscheduled visits/tests can be performed during the study at the discretion of the Investigator. The relevant information will be collected in the eCRF.
- In case the reversibility test is negative at Visit 1, it should be performed again during run-in period (once before randomisation), after an appropriate wash-out from bronchodilators (6 hours) and run-in medication (12 hours). The relevant information will be collected in the eCRF.

In addition:

- A subset of patients will undergo blood sample collection in order to perform pharmacokinetic evaluations. The sampling will take place during **V3 (Week 4)**, at steady state and **V6 (Week 40)**.

The study plan and scheduled tests are summarised in the following flow-chart:

	Pre-screenin	Run-in	Treatment Period					
Visit	V0	V1	V2	V3	V4	V5	V6	V7/ET*
Time (Wks)	-3	-2	0	4	12	26	40	52
Windows (Days)			±2d	±3d	±5d	±10d	±5d	±5d
Assessments								
Informed consent procedures	X							
Instructions for the screening visit	X							
Demographic data collection	X							
Inclusion/Exclusion criteria		X	X					
Medical history/Previous medications		X						
Concomitant medications		X	X	X	X	X	X	X
Adverse Events/Serious adverse events		X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X
Weight & Height		X						
Vital signs (BP) pre-dose/post-dose ¹		X	X	X	X	X	X	X
12-lead ECG (single) pre-dose/post-dose ²		X	X	X	X	X	X	X
Pre-dose spirometry ³		X	X	X	X	X	X	X
Reversibility testing ⁴		X						
Post-dose serial spirometry (0-3 hours) ⁵			X	X	X	X	X	X
ACQ-7		X	X	X	X	X	X	X
EQ-5D-3L questionnaire			X	X	X	X	X	X
Health Economics			X	X	X	X	X	X
Pharmacokinetic evaluations (subset of patients) ⁶				X			X	
Haematology and blood chemistry		X				X		X
Serum pregnancy test		X						X
Urinary pregnancy test		X	X	X	X	X	X	
Home PEF (predose)		X (daily am/pm)						
Electronic diary completion (asthma symptoms, treatment compliance, rescue intake)		X (daily am/pm)						
Electronic diary review ⁷			X	X	X	X	X	X
Assessment of asthma exacerbations		X	X	X	X	X	X	X
Training to the use of pMDI ⁸		X	X					
Training to the use of Aerochamber Plus ⁸		X	X					
Training on recognition of a developing asthma exacerbation ⁸		X	X					
Training to the use of ed diary/epeakflowmeter ⁸		X	X					
IRT	X	X	X	X	X	X	X	X
Run-in dispensation (D) /Collection (C)		D	C					
Study drug dispensation (D) /Collection (C)			D		D/C	D/C	D/C	C
Spacer dispensation (D) /Collection (C) ⁹		D	D/C			D/C		C

* ET stands for Early Termination (pre-dose assessments will be performed/ post-dose assessments only if appropriate)

1. SBP and DBP after 10 min rest in sitting position. Pre-dose at V1. Pre and post-dose (45 min) from V2 to V7.
2. ECG in single. Pre-dose at V1. Pre and post-dose (45 min) from V2 to V7.
3. FEV₁, FVC at 45 min and 15 min pre-dose (only V2 to V7). IC and VC to be done before FEV₁ & FVC (only V2 to V7).
4. Reversibility after 4x100 µg salbutamol.
5. FEV₁, FVC: serial spirometry at 15 min, 30 min, 60 min, 120 min and 180 min post-dose.
6. PK blood collection: pre-dose (within 30 min before drug administration) and 5 minutes, 25 minutes, 1 hour, 4 hours and 8 hours post-dose.
7. Regular check by the investigator and/or designee. Phone call(s) to the patient will be done in case of bad compliance and/or asthma control worsening.
8. Re-trainings can be done during the study if need be. Training for spacer only for patients who use it.
9. Spacer (Aerochamber) only dispensed for patients who use it.

7.1.1 Visit 0: Pre-screening visit

A pre-screening visit (Visit 0) will be carried out in order to fully explain the study to potential eligible asthmatic patients.

The following procedures will take place:

- The investigator or his/her designee will explain the study to the patient and written informed consent will be obtained from the patient and/or legal representatives (if applicable). 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 (including the race for spirometry purpose);
- Instructions will be given to the patient for the next visit (Visit 1) such as **concomitant medications to be withdrawn** prior to the visit in accordance with [section 5.2](#);
Note: In case the patient has not taken his/her usual asthma treatment when he/she arrives at the clinic and that the wash-out period is respected (according to [section 5.2](#)), as well as he/she has fasted overnight (at least 10 hours), Visit 0 and Visit 1 can be combined.
- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to allocate a unique patient number. This number will be sequentially assigned.

Before discharge:

- **A patient card** with the Investigator's contact details will be handed out to the patient (see [Appendix V](#)).
- **Patients will be instructed:**
 - To fast overnight (at least 10 hours) before the next visit in order to perform blood sampling (only water is allowed);
 - Not to take salbutamol or other SABA in the 6 hours preceding the next visit, unless absolutely necessary;
 - Not to take SAMA or combination of SABA / SAMA in the 8 hours preceding the next visit, unless absolutely necessary;
 - Not to take his/her usual medication for asthma (ICS/LABA, LTRA, Theophylline) in accordance with [section 5.2](#).
- **An appointment for Visit 1 will be made within 1 week (maximum) in the morning.**

7.1.2 Visit 1: Screening visit

A screening visit (1 week maximum after Visit 0) will be carried out in the morning in order to identify eligible consenting patients in the study.

If any of the wash-out for asthma medications has not been respected, the visit needs to be re-scheduled within 2 days. This is allowed only once. If any of the relevant wash-out is not respected again before the rescheduled visit, the patient will be discontinued and recorded in the IRT as screening failure.

The following procedures will take place:

- The medical history including smoking status, as well as all medications taken by the patient in the last 3 months, will be recorded. Intake of non-permitted medication constitutes non-eligibility criterion for enrolment in the study.
- AEs occurred since the signature of the informed consent will be recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the patient's medical history, unless its start date is after the informed consent signature date and it is not due to a pre-existing condition. In this case it will be recorded as an adverse event.
- Asthma control will be evaluated by the completion of the Asthma Control Questionnaire[®] (ACQ-7) to verify the eligibility of the patient (see [section 7.2.2](#) and [Appendix II](#)). Only patients with uncontrolled asthma with an ACQ-7 score ≥ 1.5 are eligible.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#)). A documented history of at least one exacerbation in the 12 months preceding screening should be checked (according to inclusion criterion n°8). Eligible patients should remain free of exacerbation requiring systemic steroids within 4 weeks prior to screening.
- A full physical examination will be performed.
- Weight and height will be recorded.
- Vital signs (systolic [SBP] and diastolic [DBP] blood pressure) will be measured before salbutamol administration, after 10 minutes of rest, in resting position (see [section 7.2.7](#)).
- A 12-lead ECG will be performed before salbutamol administration, after at least 10 minutes of rest (see [section 7.2.6](#)).
- A blood sample will be collected before salbutamol administration and after an overnight fasting for the assessments of (see [section 7.2.8](#)):
 - standard haematology and blood chemistry;
 - serum β -HCG tests 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 (randomisation visit).

In addition, a urine pregnancy test will be performed in women of childbearing potential.

- For the subset of patients performing the PK assessment, the renal and hepatic impairment will be assessed (see [section 7.2.9](#))
- Spirometry assessment, consisting of three acceptable manoeuvres (see [section 7.2.1](#)) will be performed.

Note: To be eligible, pre-bronchodilator FEV₁ must be < 80% of the patient's predicted normal values.

- Reversibility test will be performed: the patients shall receive four inhalations of salbutamol 100 µg (total dose of 400 µg) via a metered-dose inhaler. Post-bronchodilator spirometry, consisting of three acceptable manoeuvres (see [section 7.2.1](#)), is to be performed 10 to 15 min after inhalation of salbutamol.

Positive reversibility test is defined as **an increase of >12% (percent increase) and >200 mL (absolute increase) from pre-dose FEV₁ 10-15 minutes after salbutamol intake.**

Note: In case this reversibility threshold is not met, it should be performed again during run-in period (once before randomisation), after an appropriate wash-out from bronchodilators (6 hours) and run-in medication (12 hours) in order to recheck the inclusion criterion n°6, as well as n°5 and n°7 (the ACQ-7 will be re-evaluated).

Patients will be trained to the proper use of the pMDI device (and AeroChamber Plus™ if applicable) with the training kit (see sections [6.2.3.3](#) and [6.2.4](#)) if he/she is eligible.

- Patients will be also trained in the early recognition of a developing asthma exacerbation and on appropriate early actions needed (see [Appendix IV](#)).
- Patient will be instructed and trained on how to daily record the PEF, the medications intake (run-in and rescue) as well as the asthma symptoms in the electronic peak flow meter/electronic diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening during the run-in period, before the intake of run-in medication. The assessment of asthma symptom scores and of number of rescue/run-in medication puffs will always precede the PEF measurements. The recording will start in the evening of Visit 1 at home.
- The patient's eligibility for entry into the study will be assessed according to the inclusion and exclusion criteria, and confirmed, recording the screening or the failure to screening in the IRT.
- The investigator will access IRT in order to obtain the run-in medication (CHF 1535 100/6 µg) to be taken during the run-in period (see [section 6.2.2](#) and [6.2.3](#)).
- **The morning dose of run-in medication (first administration) will be administered at the clinic visit under medical supervision. Patients will be instructed to inhale 2 puffs from the run-in inhaler.**

Note: For the patient using a spacer, the run-in medication will be taken via the AeroChamber Plus™.

Before discharge:

- **Run-in Medication (CHF 1535 100/6 µg / one kit) for the run-in period will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication. **Patients will be instructed to inhale 2 puffs in the morning and 2 puffs in the evening.** In addition, patient will be also instructed to take salbutamol as rescue if necessary (see [section 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, the AeroChamber Plus™ used for the training will be dispensed to the patient for the run-in treatment period.

- **The electronic peak flow meter/electronic diary will be dispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site.**

Note: the investigator should check the patient's compliance/PEF/asthma symptoms regularly through a dedicated web portal.

▪ **Patients will be instructed:**

- To record daily (morning and evening) PEF, the medications intake (run-in and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
- To perform the morning PEF measurement before coming to the next visit and to answer questions in the peak flow meter.
- Not to take the morning dose of the run-in medication before coming to the clinic visit.
- Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
- To bring back the electronic peak flow meter/diary and the run-in medication/ AeroChamber Plus™ (in their boxes).

▪ **An appointment for Visit 2 (randomisation) will be made in 14 ± 2 days from Visit 1 (screening) in the morning.**

7.1.3 Visit 2: Randomisation (Week 0)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or run-in medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. Only one re-schedule is allowed. If rescue medication intake occurs again in the previous 6 hours before the re-scheduled visit or the run-in medication has been inhaled in the morning of the visit, the patient will be discontinued and recorded as screen failure in the IRT.

The following procedures will take place:

- Run-in Medication (CHF 1535 100/6 µg) taken during the run-in period will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the run-in medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance. **In case of lack of compliance, appropriate instructions will be given to the patient**

Note: if the compliance to run-in medication is below 50%, the run-in period will be extended of 1 week in order to achieve a satisfactory compliance. If at the end of this extension, the compliance is still below 50%, the patient will be screen failed.

- Patient will be re-instructed and trained on how to daily record the PEF, the medication intake (rescue and study medications) as well as the asthma symptoms in the electronic peak flow meter/diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening before the intake of study medication. The assessment of asthma symptom scores and of number of rescue/study medication puffs will always precede the PEF measurements. The recording will start in the evening of Visit 2 at home.

- Changes of concomitant medications being taken by the patient will be recorded. In the case of intake of any non-permitted concomitant medication, the patient will be withdrawn from the study (see [section 5.2](#)).
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma control will be evaluated again by the completion of the Asthma Control Questionnaire[®] (ACQ-7) as at Visit 1, to confirm the eligibility of the patient (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A urine pregnancy test will be performed in women of childbearing potential.
- Eligibility criteria will be reviewed.
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#))
- The patient will be retrained to the proper use of the pMDI (and AeroChamber Plus[™] if applicable) with the training kit assigned at Visit 1, if he/she is eligible (see [section 6.2.4](#)).

Note: this training can be repeated during the study if need be.

- Patients will be also retrained in the early recognition of a developing asthma exacerbation and on appropriate early actions needed (see [Appendix IV](#)).

Note: this training can be repeated during the study if need be.

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose inspiratory and vital capacities (IC and VC) at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).

Note: To be eligible, pre-bronchodilator FEV₁ (both at 45 and 15 minutes) must be < 80% of the patient's predicted normal values.

- The investigator will access IRT in order to obtain the appropriate kit numbers of study medication.
- **The morning dose of study medication (first administration) will be administered at the clinic visit under medical supervision (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale 1 puff from each inhaler (n°1&2).**

Note: For the patient using a spacer, the study medication will be taken via a new AeroChamber Plus[™].

- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).

- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

Before discharge:

- **Study medication (two kits) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication. **Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID).** The evening dose of Week 0 will be administered at home. Patient will be also instructed to take salbutamol as rescue if necessary (see [sections 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, a new AeroChamber Plus™ will be dispensed to the patient.

- **The electronic peak flow meter/electronic diary will be redispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site.**

Note: the investigator (or designee) should check regularly the patient's compliance/PEF/asthma symptoms through a dedicated portal.

- **Patients will be instructed:**
 - To record daily (morning and evening) PEF, the medications intake (study medications and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
 - To perform the morning PEF measurement and to answer questions in the peak flow meter before coming to the next visit.
 - To change of study medication kit after 7 weeks of use.
 - Not to take the morning dose of the study medication before coming to the next visit.
 - Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
 - To bring back the electronic peak flow meter/diary and study medication/AeroChamber Plus™ (in their boxes) at the next visit.
 - **For the subset of patients with PK assessment:** To fast overnight (at least 10 hours) before the next visit in order to perform blood sampling (only water is allowed) and to not take alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food starting from 48 hour before the next visit.
- **An appointment for Visit 3 (Week 4) will be made in 4 weeks ± 3 days from Visit 2 in the morning.**

7.1.4 Visit 3 (Week 4)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or study medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 3 days.

The following procedures will take place:

- Study Medication will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance. **In case of lack of compliance, appropriate instructions will be given to the patient.**
- Patient will be re-instructed and trained on how to daily record the PEF, the medication intake (rescue and study medications) as well as the asthma symptoms in the electronic peak flow meter/diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening before the intake of study medication. The assessment of asthma symptom scores and of number of rescue/study medication puffs will always precede the PEF measurements.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.5](#)).
- A urine pregnancy test will be performed in women of childbearing potential.
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#))
- **In a subset of patients (for PK assessment)**, pre-dose (corresponding to 12 hours after drug intake the evening before the visit) blood sample collection will be done (after vital signs) in order to perform the pharmacokinetic evaluations (see below and [section 7.2.10](#)).

Note: Before drug administration, **it is important to reinstruct the patient on how to use pMDI, on the method of inhalation and on the duration of breath holding after inhalation** (according to the instructions for use).

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).
- **The morning dose of study medication will be administered at the clinic visit (before 10.00 am) under medical supervision from the kit dispensed at Visit 2 (the time of first**

inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale **1 puff from each inhaler (n°1&2)**.

Note: For the patient using a spacer, the study medication will be taken via the AeroChamber Plus™ dispensed at Visit 2.

- The Investigator will access the IRT to register the status the patient.
- **For the subset of patients (for PK assessment)**, post-dose blood sample collections at 5 minutes, 25 minutes, 1 hour, 4 hours and 8 hours will be done in order to perform the pharmacokinetic evaluations (see below and [section 7.2.10](#)).
- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

Before discharge:

- **Study medication (kit dispensed at V2) will be redispensed** with instructions for use. **Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID)**. The evening dose of Week 4 will be administered at home. Patient will be also instructed to take salbutamol as rescue if necessary (see [sections 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, the AeroChamber Plus™ (dispensed at Visit 2) will be redispensed.

- **The electronic peak flow meter/electronic diary will be redispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site**.

Note: the investigator (or designee) should check regularly the patient's compliance/PEF/asthma symptoms through a dedicated portal.

- **Patients will be instructed:**
 - To record daily (morning and evening) PEF, the medications intake (study medications and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
 - To perform the morning PEF measurement and to answer questions in the peak flow meter before coming to the next visit.
 - To change of study medication kit after 7 weeks of use.
 - Not to take the morning dose of the study medication before coming to the next visit.
 - Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.

- To bring back the electronic peak flow meter/diary and study medication/AeroChamber Plus™ (in their boxes) at the next visit.
- **An appointment for Visit 4 (Week 12) will be made in 12 weeks $\pm$ 5 days from Visit 2 in the morning.**

Important Notes for the visit for the subset of patients selected to perform PK assessment:

- ✓ Patient will have to be at the clinical centre in the morning at least **1 hour before drug administration in fasting conditions** (fasting from at least 10 hours).
- ✓ Patient will remain fasted until 2 hour post-dose. Breakfast and lunch will be served approximately 2 and 4 hour post-dose.
- ✓ Fluid intake will be forbidden for 1 hour post-dose, then, in order to maintain an adequate hydration, patients should take at least 240 mL of mineral water every 2 hours for the following 6 hours.
- ✓ No alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food will be allowed starting from 48 hour before the drug administration on the day of blood sampling for PK assessments until the end of blood sampling.
- ✓ Time 0 is defined as the moment when the first inhalation of the drug takes place. Patients will take the medication in an upright position. Additionally, the patients will be instructed to hold their breath as long as possible following each inhalation and to wait 30 sec before taking the next inhalation.
- ✓ Patient will not be allowed to lie down or sleep for 2 hours after administration, except when undergoing clinical assessments. They must rest in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) as much as possible and avoid strenuous activities. Patient will be required to stay in the ward area until at least 2 hours after dosing.
- ✓ In order to prevent any kind of blood samples contamination, the administration of the study drug will take place in a room well separated from the blood sampling station. Patients will remain in the room of administration only for the time strictly needed for the administration. Furthermore, during study drug inhalation, patient and investigator assistant will wear special protective coats and gloves, which will be removed before blood sampling. The assistant administering the inhalations will not be allowed to participate in the blood sampling procedures

7.1.5 Visit 4 (Week 12)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or study medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 3 days.

The following procedures will take place:

- Study Medication will be collected.

- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance. **In case of lack of compliance, appropriate instructions will be given to the patient.**
- Patient will be re-instructed and trained on how to daily record the PEF, the medication intake (rescue and study medications) as well as the asthma symptoms in the electronic peak flow meter/diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening before the intake of study medication. The assessment of asthma symptom scores and of number of rescue/study medication puffs will always precede the PEF measurements.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- **A urine pregnancy test will be performed** in women of childbearing potential.
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health **economic information** (see [section 7.2.12](#))
- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).
- The investigator will access IRT in order to obtain the appropriate kit numbers of study medication.
- **The morning dose of study medication will be administered at the clinic visit under medical supervision from the kit dispensed (the time of first inhalation corresponds to Time 0 of spirometry).** Patients will be instructed to inhale **1 puff from each inhaler (n°1&2).**
Note: For the patient using a spacer, the study medication will be taken via the AeroChamber Plus[™] dispensed at Visit 2.
- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

Before discharge:

- **Study medication (two kits) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication. **Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID).** The evening dose of Week 12 will be administered at home. Patient will be also instructed to take salbutamol as rescue if necessary (see [sections 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, the AeroChamber Plus™ (dispensed at Visit 2) will be redispensed.

- **The electronic peak flow meter/electronic diary will be redispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site.**

Note: the investigator (or designee) should check regularly the patient's compliance PEF/asthma symptoms through a dedicated portal.

- **Patients will be instructed:**
 - To fast overnight (at least 10 hours) before the next visit in order to perform blood sampling (only water is allowed);
 - To record daily (morning and evening) PEF, the medications intake (study medications and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
 - To perform the morning PEF measurement and to answer questions in the peak flow meter before coming to the next visit.
 - To change of study medication kit after 7 weeks of use.
 - Not to take the morning dose of the study medication before coming to the next visit.
 - Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
 - To bring back the electronic peak flow meter/diary and study medication/AeroChamber Plus™ (in their boxes) at the next visit.
- **An appointment for Visit 5 (Week 26) will be made in 26 weeks ± 10 days from Visit 2 in the morning.**

7.1.6 Visit 5 (Week 26)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or study medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 3 days.

The following procedures will take place:

- Study Medication will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance. **In case of lack of compliance, appropriate instructions will be given to the patient.**
- Patient will be re-instructed and trained on how to daily record the PEF, the medication intake (rescue and study medications) as well as the asthma symptoms in the electronic peak flow meter/diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening before the intake of study medication. The assessment of asthma symptom scores and of number of rescue/study medication puffs will always precede the PEF measurements. The recording will start in the evening of Visit 2 at home.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A blood sample will be collected after an overnight fasting for the assessments of standard haematology and blood chemistry (see [section 7.2.8](#)):
 - standard haematology and blood chemistry;The blood samples must be collected **after vital signs and 12-lead ECG recording**.
In addition, a urine pregnancy test will be performed in women of childbearing potential.
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#))
- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).
- The investigator will access IRT in order to obtain the appropriate kit numbers of study medication.
- **The morning dose of study medication will be administered at the clinic visit under medical supervision from the kit dispensed (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale 1 puff from each inhaler (n°1&2).**

Note: For the patient using a spacer, the study medication will be taken via a new AeroChamber PlusTM

- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

Before discharge:

- **Study medication (two kits) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication. **Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID).** The evening dose of Week 26 will be administered at home. Patient will be also instructed to take salbutamol as rescue if necessary (see [sections 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, a new AeroChamber Plus™ will be dispensed.

- **The electronic peak flow meter/electronic diary will be redispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site.**

Note: the investigator (or designee) should check regularly the patient's compliance PEF/asthma symptoms through a dedicated portal.

- **Patients will be instructed:**
 - To record daily (morning and evening) PEF, the medications intake (study medications and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
 - To perform the morning PEF measurement and to answer questions in the peak flow meter before coming to the next visit.
 - To change of study medication kit after 7 weeks of use.
 - Not to take the morning dose of the study medication before coming to the next visit.
 - Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
 - To bring back the electronic peak flow meter/diary and study medication/AeroChamber Plus™ (in their boxes) at the next visit.
 - **For the subset of patients with PK assessment:** To fast overnight (at least 10 hours) before the next visit in order to perform blood sampling (only water is allowed) and to not take alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food starting from 48 hour before the next visit.
- **An appointment for Visit 6 (Week 40) will be made in 40 weeks ± 5 days from Visit 2 in the morning.**

7.1.7 Visit 6 (Week 40)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or study medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 3 days.

The following procedures will take place:

- Study Medication will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance. **In case of lack of compliance, appropriate instructions will be given to the patient.**
- Patient will be re-instructed and trained on how to daily record the PEF, the medication intake (rescue and study medications) as well as the asthma symptoms in the electronic peak flow meter/diary (see [sections 7.2.3](#) and [7.2.4](#)). The measurements will take place every morning and every evening before the intake of study medication. The assessment of asthma symptom scores and of number of rescue/study medication puffs will always precede the PEF measurements. The recording will start in the evening of Visit 2 at home.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A urine pregnancy test will be performed in women of childbearing potential.
- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#)).
- **In a subset of patients (for PK assessment),** pre-dose (corresponding to 12 hours after drug intake the evening before the visit) blood sample collection (after vital signs) will be done in order to perform the pharmacokinetic evaluations (see below and [section 7.2.9](#)).

Note: Before drug administration, **it is important to reinstruct the patient on how to use pMDI, on the method of inhalation and on the duration of breath holding after inhalation** (according to the instructions for use).

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).

- The investigator will access IRT in order to obtain the appropriate kit numbers of study medication.
- **The morning dose of study medication will be administered at the clinic visit under medical supervision from the kit dispensed (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale 1 puff from each inhaler (n°1&2).**

Note: For the patient using a spacer, the study medication will be taken via the AeroChamber Plus™ dispensed at Visit 5.

- **For the subset of patients (for PK assessment),** post-dose blood sample collections at 5 minutes, 25 minutes, 1 hour, 4 hours and 8 hours will be done in order to perform the pharmacokinetic evaluations (see below and [section 7.2.10](#)).
- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres ([see section 7.2.1](#)).

Before discharge:

- **Study medication (two kits) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication. **Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID).** The evening dose of Week 40 will be administered at home. Patient will be also instructed to take salbutamol as rescue if necessary (see [sections 6.2.2](#) and [6.2.3](#)).

Note: For the patient using a spacer, the AeroChamber Plus™ (dispensed at Visit 5) will be redispensed.

- **The electronic peak flow meter/electronic diary will be redispensed** with instructions for use. In case of bad compliance to study medication and/or worsening of asthma control, **phone call(s) to the patient will be done by the site.**

Note: the investigator (or designee) should check regularly the patient's compliance PEF/asthma symptoms through a dedicated portal.

- **Patients will be instructed:**
 - To fast overnight (at least 10 hours) before the next visit in order to perform blood sampling (only water is allowed);
 - To record daily (morning and evening) PEF, the medications intake (study medications and rescue) as well as the asthma symptoms in the electronic peak flow meter/diary.
 - To perform the morning PEF measurement and to answer questions in the peak flow meter before coming to the next visit.

- To change of study medication kit after 7 weeks of use.
 - Not to take the morning dose of the study medication before coming to the next visit.
 - Not to take salbutamol in the 6 hours preceding the next visit, unless absolutely necessary.
 - To bring back the electronic peak flow meter/diary and study medication/AeroChamber PlusTM (in their boxes) at the next visit.
- **An appointment for Visit 7 (Week 52) will be made in 52 weeks $\pm$ 5 days from Visit 2 in the morning.**

Important Notes for the visit for the subset of patients selected to perform PK assessment:

- ✓ Patient will have to be at the clinical centre in the morning at least **1 hour before drug administration in fasting conditions** (fasting from at least 10 hours).
- ✓ Patient will remain fasted until 2 hour post-dose. Breakfast and lunch will be served approximately 2 and 4 hour post-dose.
- ✓ Fluid intake will be forbidden for 1 hour post-dose, then, in order to maintain an adequate hydration, patients should take at least 240 mL of mineral water every 2 hours for the following 6 hours.
- ✓ No alcohol or xanthine (coffee, tea, chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food will be allowed starting from 48 hour before the drug administration on the day of blood sampling for PK assessments until the end of blood sampling.
- ✓ Time 0 is defined as the moment when the first inhalation of the drug takes place. Patients will take the medication in an upright position. Additionally, the patients will be instructed to hold their breath as long as possible following each inhalation and to wait 30 sec before taking the next inhalation.
- ✓ Patient will not be allowed to lie down or sleep for 2 hours after administration, except when undergoing clinical assessments. They must rest in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) as much as possible and avoid strenuous activities. Patient will be required to stay in the ward area until at least 2 hours after dosing.
- ✓ In order to prevent any kind of blood samples contamination, the administration of the study drug will take place in a room well separated from the blood sampling station. Patients will remain in the room of administration only for the time strictly needed for the administration. Furthermore, during study drug inhalation, patient and investigator assistant will wear special protective coats and gloves, which will be removed before blood sampling. The assistant administering the inhalations will not be allowed to participate in the blood sampling procedures

7.1.8 Visit 7 (Week 52)

The patient will visit the clinical centre and begin the procedures in the morning, preferably **between 7.00-9.00 am.**

If rescue medication has been inhaled in the previous 6 hours, or study medication has been taken the morning of the visit, the visit needs to be re-scheduled to take place within 3 days.

The following procedures will take place:

- Study Medication will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A blood sample will be collected after an overnight fasting for the assessments of standard haematology and blood chemistry (see [section 7.2.8](#)):
 - standard haematology and blood chemistry;
 - serum β -HCG tests in women of childbearing potential.

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

- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#))
- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).
- **The morning dose of study medication (last administration) will be administered at the clinic visit (before 10.00 am) under medical supervision from the kit dispensed at Visit 6 (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale 1 puff from each inhaler (n°1&2).**

Note: For the patient using a spacer, the study medication will be taken via the AeroChamber Plus[™] dispensed at Visit 5.

- The Investigator will access the IRT to register the status the patient.
- Vital signs (SBP and DBP) will be measured 45 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

- The last visit completion shall be recorded in the IRT.

Before discharge:

- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer to the General Practitioner.
- The patient must be informed that he/she cannot participate in another clinical study for 4 weeks after this visit.
- The patient is exited from the study (providing that all her/his safety assessments are satisfactory).

7.1.9 Early Termination Visit (for a patient withdrawn before Week 52)

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

All the assessments foreseen at Visit 7 (Week 52) should be done at early termination to the extent possible, providing there is **no safety issue for the patient**. The post-dose assessments will be performed only if appropriate.

The following procedures will be performed (in the morning if possible, preferably **between 7.00-9.00 am**):

- Study Medication will be collected.
- The investigator (or designee) will collect and check the electronic peak flow meter/diary to verify the study medication compliance, rescue medication intake, asthma symptoms scores and PEF data, in order to check the correct use of the device, to detect any clinical abnormality and to check patient's compliance.
- Changes of concomitant medications being taken by the patient will be recorded.
- Adverse events will be recorded if any.
- The asthma exacerbation assessment will be done (see [section 7.2.5](#))
- Asthma Control Questionnaire[®] (ACQ-7) will be completed (see [section 7.2.2](#) and [Appendix II](#)).
- A full physical examination will be performed.
- Pre-dose vital signs (SBP and DBP) will be measured, after 10 minutes of rest (see [section 7.2.7](#)).
- A pre-dose 12-lead ECG will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A blood sample will be collected after an overnight fasting for the assessments of standard haematology and blood chemistry (see [section 7.2.8](#)):
 - standard haematology and blood chemistry;
 - serum β -HCG tests in women of childbearing potential.

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

- The EQ-5D-3L questionnaire will be completed by the patient (see [section 7.2.11](#)).
- The investigator will collect Health economic information (see [section 7.2.12](#))

- Pre-dose spirometry measurement will be performed: the patient will have to perform a SVC manoeuvre to assess pre-dose IC and VC at 45 minutes prior to first dosing, followed by a FVC manoeuvre for other pre-dose parameters (FEV₁, FVC) at 45 minutes and 15 minutes prior to first dosing (see [section 7.2.1](#)).
- **The morning dose of study medication will be administered at the clinic (before 10.00 am) under supervision of the Investigator from the kit dispensed at the last visit (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale 1 puff from each inhaler (n°1&2).**

Note: For the patient using a spacer, the study medication will be taken via the AeroChamber Plus™ dispensed at the previous visit.

- Vital signs (SBP and DBP) will be measured 10 minutes post-dose, after 10 minutes of rest (see [section 7.2.7](#)).
- A post-dose 12-lead ECG (45 minutes after study drug intake) will be performed after at least 10 minutes of rest (see [section 7.2.6](#)).
- A **3 hours** post-dose serial spirometry assessment will be performed starting 15 minutes after study drug intake. Post-dose lung function (FEV₁, FVC) during 3 hours will be evaluated and recorded at the following times: 15, 30, 60, 120 and 180 min after administration.

For each time point, spirometry consists in three acceptable manoeuvres (see [section 7.2.1](#)).

- The Investigator will access IRT to register the discontinuation of the patient from the study.

Before discharge:

- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer to the General Practitioner.
- The patient must be informed that he/she cannot participate in another clinical study for 4 weeks after this visit.
- The patient is exited from the study (providing that all her/his safety assessments are satisfactory).

7.2 Investigations

7.2.1 Spirometry

Lung function measurements will be done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society ⁽²⁸⁾. All sites will be provided with the same spirometer. Centralised spirometry (with central reading) will be used. The specific procedures for centralised spirometry will be provided to the investigator by the centralised spirometry company.

Lung function measurements will be done with patients either standing or sitting (for each patient, this should be consistent throughout the study) with the nose clipped after at least 10 minutes rest. Values will be corrected for BTPS conditions. **Calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to any spirometry manoeuvres and the reports must be kept with the source study documents.**

Throughout the study (after randomisation), the clinic visits and the lung function measurements will start in the morning between 7:00 and 09:00 a.m. preferably, approximately at the same time of the day for each patient.

The following parameters will be recorded:

- Forced Expiratory Volume in the 1st second (FEV₁, L) from Visit 1 to Visit 7,
- Forced Vital Capacity (FVC, L) from Visit 1 to Visit 7,
- Inspiratory capacity (IC, L) from Visit 2 to Visit 7.
- Vital capacity (VC, L) from Visit 2 to Visit 7

Note: some additional standard parameters (for instance PEF or ratio FEV₁/FVC) will be assessed by the spirometer during the visit only for information purpose of the investigator.

Predicted values of FEV₁ will be calculated according to formulas reported by Quanjer et al ([29](#), [30](#)). The predicted values will be adjusted for race.

IC, which is the volume change recorded at the mouth when taking a slow full inspiration with no hesitation, from a position of passive end-tidal expiration, i.e. functional residual capacity (FRC), to a position of maximum inspiration, and **VC**, which is the volume change at the mouth between the positions of full inspiration and complete expiration, will be recorded at each clinic visit (from Visit 2).

Patients 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 manoeuvres). They are then urged to take a deep breath to TLC (Total Lung Capacity) with no hesitation.

The **average** of at least 3 acceptable **slow vital capacity (SVC) manoeuvres** will be recorded for **IC and VC**. **These SVC manoeuvres must be performed before the forced vital capacity manoeuvres used to assess other lung function parameters (FEV₁, FVC) as described below.**

FEV₁ and FVC will be recorded at each clinic visit from a forced vital capacity manoeuvre. For FEV₁ and FVC, **the highest value from three technically satisfactory attempts** will be recorded (irrespective of the curve they come from). The chosen value should not exceed the next one by more than 150 mL. If the difference is larger, up to 8 measurements will be made and the largest value be reported.

During the randomised treatment period at each clinic visits (V2 to V7), patients will undergo serial spirometry assessments under supervision (over 3 hours post-dose) for **FEV₁ and FVC**:

- Time “0” (T-0) is defined as the time of first inhalation of study medication;
- The 7 time points are: -45min; -15min; 15min; 30min; 60min; 120min and 180min.

Note: The following time tolerances from theoretical post-dose times will **be allowed**:

< 60 min post-dose:	± 5 min
60 min post-dose:	± 10 min
120 and 180 min post-dose:	± 15 min

The rescue medication (salbutamol) must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit. If the patient requires rescue

medication within this timeframe, the visit should be rescheduled once within the three next days.

During the 3-hour serial spirometry, rescue use should be limited as much as possible and rescue intake must be under medical control. The serial spirometry will continue after the salbutamol intake, if there is no safety risk for the patient. Details on intake of rescue medication during the visits will be recorded in the eCRF.

The run-in medication CHF 1535 or the study medication should not be taken in the morning of the visit. If taken, in both cases, the measurements should be deferred (i.e. the visit needs to be re-scheduled to take place within 3 days).

7.2.2 Asthma control Questionnaire (ACQ-7)

Only uncontrolled asthmatic patients with an ACQ-7 score ≥ 1.5 are eligible for randomisation (the criteria must be met at screening and at the end of the run-in period).

Asthma control will be evaluated by the completion of the Asthma Control Questionnaire[®] (ACQ-7) ⁽³¹⁾ (see [Appendix II](#)). The ACQ-7 is able to identify the adequacy of asthma control in individual patients. The first 6 items of the questionnaire refer to symptoms and rescue use in the previous 7 days while the 7th item (related to FEV₁), is completed by the clinical staff.

The ACQ-7 is administered from Visit 1 to Visit 7. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment).

The item 7 should be populated considering the pre-dose FEV₁ % of predicted taken at -15 minutes at the visit when reversibility is met.

The ACQ-7 is provided on paper and should be completed by the patient in a quiet place before the pulmonary function testing, only question 7 will be completed after the testing.

The investigator (or designated site-personnel) should check that all items have been completed by the patient, but the response to each item should not be questioned.

The scores will then be transcribed into the eCRF by the Investigator (or designated site personnel).

7.2.3 Daily PEF measurements with Electronic Peak Flow Meter

PEF (L/min) will be monitored twice daily in the morning and in the evening (during the run-in and the treatment periods, i.e. from V1 to V7) by patients using a portable electronic peak flow meter.

The device will be customised with a specific program, according to the parameters required by the study protocol. Patients will be educated on the purpose and technique of PEF home monitoring. Specific instructions for use will be made available to the patients.

During each measurement session (morning or evening before the intake of the run-in medication or study medication) the patient will perform 3 blows. 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 patients 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 patient's compliance. In case of bad compliance and/or worsening of asthma control during the study, phone call(s) to the patient will be done by the site and instructions will be given again to the patient if appropriate.

7.2.4 Asthma symptom scores and use of rescue medication

The asthma symptom scores and the use of rescue medication (number of salbutamol puffs) will be recorded in the electronic diary twice daily in the morning and in the evening, before the PEF measurements (during the run-in and treatment periods, i.e. from V1 to V7). **The data will be automatically transmitted from home to the Vendor's database on a daily basis, and checked by the Investigator on a regular basis.**

- **Asthma symptoms** (overall symptoms, cough, wheeze, chest tightness and breathlessness) will be scored, as occurred respectively during the night and during the day, 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
- **Rescue medication**

The daily use of rescue medication will be recorded 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.
- **Asthma control day**

The derived variable of asthma control days will be calculated according to the following definition:

 - Days (night-time plus daytime) with a total asthma score = 0

- No rescue medication use.

7.2.5 Asthma exacerbation

Asthma exacerbations (as per ATS/ERS guidelines and Virchow paper ⁽³²⁾) are defined as follows:

- **Severe asthma exacerbations are defined by an asthma worsening requiring the initiation of treatment with systemic corticosteroids for at least 3 days.**

Note: Courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations. A severe exacerbation requiring an emergency room visit or a hospitalisation will be documented accordingly.

- **A moderate exacerbation is defined as ≥ 1 of criteria a)-d) fulfilled and leading to a change in treatment:**
 - a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights or increase of ≥ 0.75 from baseline in daily symptom score on 2 consecutive days
 - b) Increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day)
 - c) $\geq 20\%$ decrease in PEF same from baseline on at least 2 consecutive mornings/evenings or $\geq 20\%$ decrease in FEV1 from baseline
 - d) Visit to the emergency room/trial site for asthma treatment not requiring systemic corticosteroids

To be eligible at screening (Visit 1), the patient should have experienced at least one asthma exacerbation in the 12 months preceding screening (according to inclusion criterion n°8). However, eligible patients should remain free of exacerbation requiring systemic steroids within 4 weeks prior to screening (according to exclusion criterion n°2).

During the run-in period, if the patient experiences any asthma exacerbation the patient will not be randomised in the study.

In this case, the patient could be re-selected at a later stage (one month minimum should elapse) with a new patient number (the patient should sign a new informed consent), providing the medical conditions of the patient is appropriate with the inclusion in the study according to the investigator.

After the randomisation, if the patient experiences a severe asthma exacerbation requiring systemic corticosteroid and/or use of nebuliser containing β_2 -agonists and/or corticosteroids and/or antibiotics therapy, hospitalization or emergency care visit, **the following study visit should only occur after patient's stabilization. In addition, a minimum timeframe of 2 weeks between the start of the exacerbation and the clinic visits should elapse. Otherwise, the clinic visit should be delayed.**

In case of repeated severe asthma exacerbations during the study which may jeopardize the safety of the patient, **it is up to the investigator to decide to withdraw or not the patient.**

At each visit (starting Visit 1), the investigator will assess the occurrence of any asthma exacerbation since the last visit. If not already notified by the patient, the investigator will also

check whether the patient has taken systemic corticosteroids meeting the **criteria for a severe exacerbation** or whether the patient has been in the emergency room or been hospitalised due to asthma.

In addition, the investigator will be also automatically notified via the electronic diary if a criterion for a **moderate exacerbation** has been met. The physician will be directed to diagnose the cause of the worsening symptoms and decide whether to ask the patient to come to the clinic for an unscheduled visit and whether additional treatment is required.

If an asthma exacerbation occurs, the physician will be asked to record it in the dedicated eCRF form the following information:

- Onset and End date of the event;
- Corticosteroids used or any other medications taken to treat the event;
- Hospitalisation/Emergency Room details;
- Worsening of respiratory symptoms;
- Medical procedures performed (i.e. Lung function tests, Blood oxygen levels, Chest X-ray, ECG, other);
- Assessment of the exacerbation aetiology;
- Assessment of the Asthma exacerbation as Adverse Event (seriousness, outcome, relationship with study drug, intensity, action taken on the study drug).

Patient will be also instructed on recognition of signs and symptoms signalling a developing asthma exacerbation (as reported in [Appendix IV](#)) and to call the investigator in this case.

In case of severe asthma exacerbations during the study, the patients will be allowed to receive **short courses (≤ 14 days each)** of systemic corticosteroid and/or brief uses of nebuliser containing β_2 -agonists and/or steroids, and/or antibiotics therapy (see [section 5.1](#)). If the patient will need more courses, he will be discontinued from the study.

The intake of study medication should be maintained in case of asthma exacerbation to the extent possible. Only in case of absolute need, a temporary discontinuation of study treatment intake no longer than 2 weeks is allowed (if longer, the patient will be withdrawn). The investigators will carefully record all additional treatments taken for the exacerbation. Any necessary unscheduled visit will be performed in order to evaluate the patient's clinical conditions. **A minimum timeframe of 2 weeks between the start of the exacerbation and the clinic visits should elapse. Otherwise, the clinic visit should be delayed.**

In the recovery period after exacerbation episode, if the condition of the patient allows, any possible effort should be made to remove all additional medications used in the treatment of the exacerbation and to restart the treatment of the patient according to the protocol as early as possible.

An asthma exacerbation is not a reason to withdraw the patient from the study, unless the investigator deems it necessary.

Asthma exacerbations interpreted as due to lack of efficacy of the study medication should not be classified drug related.

7.2.6 12-lead ECG

A local ECG will be used. The 12-lead ECG measurement will be done only pre-bronchodilator at screening (Visit 1), and pre-dose plus 45 min post-dose at all visits from Visit 2 (Week 0) to Visit 7 (Week 52). The 12-lead ECG will be recorded in **single**.

Before recording, patients should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and lay in a resting position for 10 minutes at least before ECG. **The ECG must be performed before the blood sampling.**

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

ECGs with computerized protocol interpretation are considered normal if

- $45 \leq \text{Heart rate} \leq 110 \text{ bpm}$,
- $120 \text{ ms} \leq \text{PR} \leq 210 \text{ ms}$,
- $\text{QRS} \leq 120 \text{ ms}$.

For eligible patients, QTcF values (average) must be $QTcF \leq 450$ (for males) and 470 ms (for females) (as per exclusion criterion n°12, not applicable for patients with pacemaker).

In case of relevant ECG abnormalities, the inclusion of the patient will be judged by the investigator (values are in a range of 5% higher or lower than the established normal ones, considering the normal variability and a possible mistake in measurements due to artefacts, the ECG can be repeated according to the investigator's judgment). For any doubts the Investigator may consult the Chiesi Cardiac Leader. The final decision for enrolment would be documented in the Medical File of the patient.

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

7.2.7 Vital signs

Systolic and diastolic blood pressure (SBP, DBP) will be measured after 10 min rest in sitting position at pre-dose and 45 min post-dose from Visit 1 to Visit 7.

Note: the vital signs should be assessed before the blood sample withdrawal for PK.

7.2.8 Blood Haematology and Chemistry

Blood samples of about 10 mL will be collected at Visit 1 (screening), Visit 5 (Week 26) and Visit 7 (Week 52) in the morning, after an overnight fasting of at least 10 hours (only water is allowed during the night). The blood withdrawal should be performed **after vital signs and 12-lead ECG recording**.

An additional blood sample will be collected for serum pregnancy test in women of childbearing potential at Visits 1 and 7 only. In addition, a urine pregnancy test will be performed from Visit 1 to 6.

The following evaluation will be performed **locally**:

- Haematology: red blood cells count (RBC), white blood cells count (WBC) and differential, total haemoglobin (Hb), haematocrit (Hct), platelets count (PLT) and prothrombin time (PT).
- Serum chemistry: fasting glucose, 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, sodium, potassium, calcium, and chloride electrolytes.
- Serum & urine pregnancy tests.

Blood collection and sample preparation will be performed according to procedures provided by **the local laboratory** which will be in charge to transmit the results to the Investigator.

7.2.9 Renal and hepatic impairment assessments

The renal and hepatic impairment assessments will be performed only in the subset of patients who undergo the PK assessments.

7.2.9.1 Renal impairment

The renal function will be assessed and classified accordingly to the table below (EMA/83874/2014).

Group	Description	GFR (ml/min)
1	Normal renal elimination capacity	≥ 90
2	Mildly decreased renal elimination capacity	60-89
3	Moderately decreased renal elimination capacity	30-59
4	Severely decreased renal elimination capacity	15-29
5	End stage renal disease (ESRD)	<15 or requiring dialysis treatment

The determination of glomerular filtration rate (GFR) is based on creatinine measurement accordingly to the following MDRD equation:

$$\text{eGFR} = \alpha \times (\text{Serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

where α can equal 175 or 186 depending on whether the method used for creatinine assessment is calibrated or not.

GFR is expressed in mL/min per 1.73 m² and should be recalculated to the absolute GFR in mL/min in each individual. Serum creatinine is expressed in mg/dL and age in years.

7.2.9.2 Hepatic impairment

The hepatic impairment will be assessed using the Child-Pugh classification (EMA, CPMP/EWP/2339/02) as follows:

Assessment	Degree of abnormality	Score
Encephalopathy	None	1
	Moderate	2
	Severe	3
Ascites	Absent	1
	Slight	2
	Moderate	3
Bilirubin (mg/dL)	<2	1
	2.1-3	2
	>3	3
Albumin (g/dL)	>3.5	1
	2.8-3.5	2
	<2.8	3
Prothrombin Time (seconds > control)	0-3.9	1
	4-6	2
	>6	3

The method for encephalopathy and ascites assessments is described in more details in the following paragraph.

a) Hepatic encephalopathy

HE may be defined as a disturbance in central nervous system function because of hepatic insufficiency. This broad definition reflects the existence of a spectrum of neuropsychiatric manifestations related to a range of pathophysiological mechanisms. HE can cause mental and physical symptoms. They can vary person to person, and may progress slowly or occur suddenly ([33](#), [34](#)).

The grading of hepatic encephalopathy will be done accordingly to the West Haven Criteria for Semi-quantitative Grading of Mental Status, as follows:

Grade 1

Trivial lack of awareness

Euphoria or anxiety

Shortened attention span

Impaired performance of addition

Grade 2

Lethargy or apathy

Minimal disorientation for time or place

Subtle personality change

Inappropriate behavior

Impaired performance of subtraction

Grade 3

Somnolence to semi-stupor, but responsive to verbal stimuli

Confusion

Gross disorientation

Grade 4

Coma (unresponsive to verbal or noxious stimuli)

b) Ascites

Ascites is an abnormal accumulation of fluid in the abdomen. The most common cause of ascites is elevated pressure in the liver circulation (portal hypertension) due to liver disease such as cirrhosis. Ascites can be graded as follows:

Grade 1 (mild)

Ascites is only detectable by ultrasound examination.

Grade 2 (moderate)

Ascites causing moderate symmetrical distens

Grade 3 (large)

Ascites causing marked abdominal distension.

Based on the scores attributed to the patient by the investigator, the grade for hepatic impairment severity will be determined accordingly to the table below:

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

7.2.10 Pharmacokinetic evaluations: FF, GB and BDP/B17MP analysis

The pharmacokinetic evaluation will be performed via a **central Laboratory** only in a subset of patients in specific selected centres.

A subset of patients (about 450) will be selected in order to reach about 200 evaluable patients in the PK analysis (CHF 5993 pMDI group).

Blood sampling will be performed for all the patients included in the selected subset, but only the samples from patients in the CHF 5993 pMDI group will be submitted to PK analysis by the analytical laboratory. The blood sampling will be collected at Visit 3 and Visit 6 (4 and 40 weeks after randomisation, respectively), both at the steady state of BDP, B17MP, formoterol and GB⁽²¹⁾.

The blood samples will be collected in the morning of Visit 3 and Visit 6, after an overnight (at least 10 hours) fasting (only water is allowed during overnight). No alcohol or xanthine (coffee, tea,

chocolate, cola, etc) containing beverages or food as well as xanthine derivatives, nor grapefruit containing beverages or food will be allowed starting from **48 hours before the drug administration on the days of blood sampling for PK assessments** until the end of blood sampling.

The following blood sample will be collected in order to perform the analysis: 4 ml per time point for the formoterol analysis, 4 ml per time point for the GB analysis and 6 ml per time point for the BDP/B17MP analysis, at the six following times:

- Pre-dose (always after vital signs) , corresponding also to 12 hours after drug intake the evening before Visit 3 and Visit 6
- 5 min post dose,
- 25 min post dose,
- 1 hour post dose,
- 4 hour post dose,
- 8 hours post dose.

This scheme is based on a previous population pharmacokinetic analysis performed on B17MP, formoterol and glycopyrrolate data, an optimal time sampling strategy was conducted in order to select the best combination of sampling times. PK analyses showed that for the 3 compounds, a 3-compartment model was necessary to best describe the data. Therefore, blood samples at six different time points have to be taken in the current study (2 samples per elimination phase) (^{35, 36, 37}).

Note: The following time tolerances from theoretical post-dose times will **be allowed**:

Pre-dose	± 45 min referring to 12 hours after drug intake the evening before Visit 3 and Visit 6
5 min post dose:	± 1 min
25 min post dose:	± 5 min
1 and 4 hours post dose:	± 10 min
8 hours post dose:	± 20 min

In case activities are scheduled together with blood collection, these will be performed in a sequence allowing for blood sampling exactly at the scheduled time point. The exact time of each activity will be recorded in the CRF. In addition, the time of blood sample collection should be recorded in the eCRF, as well as the times of administration the day before the PK visit and the time of administration the day of the PK visit.

To minimise the discomfort during blood sampling the following procedures will be followed:

- Topical anaesthesia to place IV catheters/cannula (e.g. lidocain cream) may be used,
- Indwelling catheters/cannulas rather than repeated venipunctures for blood sampling where possible.

Pre-printed bar-coded labels (with identification of study number, drug name, patient's number, theoretical collection time, study period and sample number) will be provided by the bioanalysis laboratory SGS.

- **Determination of formoterol in human plasma**

Blood samples of 4 mL per timepoint in the 0-8h interval (pre-dose, 5min, 25 min, 1h, 4h and 8 hours post morning dose) will be collected.

Samples will be collected into tubes containing lithium heparin (Venoject green top or equivalent) and will be immediately chilled (ice bath). The blood will be centrifuged within 20 min after blood collection.

The plasma will be separated in a refrigerated centrifuge (about +4°C) at circa 2500 x g for 15 min and transferred into polypropylene tubes with exactly 500 µL of plasma per tube. For stabilizing the compound, polypropylene tubes will be pre-filled with 50 µL of citric acid 1M by the PK analysis laboratory before sending to the clinical centre. Those pre-filled tubes with 50 mL of citric acid need to be centrifuged before opening tubes in order to ensure that citric acid is at the bottom of the tube. After each blood collection, a volume of exactly **500 µL** plasma will be dispensed in two tubes containing the citric acid buffer (500 µl plasma in each tube), and any remaining plasma (regardless which amount) will be dispensed in a third tube containing the citric acid buffer.

The plasma samples will have appropriate labels and will be stored at, or below, -65°C in the clinical centre. Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -65°C until submitted for analysis with a validated method.

- **Determination of Glycopyrronium Bromide (GB) in human plasma**

Blood samples of 4 mL in the 0-8 h interval (pre-dose, 5min, 25 min, 1h, 4h and 8 hours post morning dose) will be collected.

Samples will be collected into tubes containing lithium heparin (Venoject green top or equivalent) and will be immediately chilled (ice bath). The blood will be centrifuged within 20 min after blood collection.

The plasma will be separated in a refrigerated centrifuge (about +4°C) at circa 2500 x g for 15 min and transferred into polypropylene tubes. After each blood collection, a volume of **500 µL** plasma will be dispensed in the first tube; the remaining plasma will be dispensed in the second tube.

The plasma samples will have appropriate labels and will be stored at, or below, -65°C in the clinical centre. Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -65°C until submitted for analysis with a validated method.

- **Determination of BDP/B17MP in human plasma**

Beclometasone dipropionate (BDP) is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B17MP), which has potent topical anti-inflammatory activity.

Blood samples of 6 mL assay in the 0-8 hours (pre-dose, 5min, 25min, 1h, 4h and 8 hours post morning dose) will be collected.

Samples will be collected into vacuum tubes containing K₂EDTA. The samples will be immediately chilled (ice bath) and plasma preparation will be done within 20 min after blood collection.

The plasma will be separated in a **refrigerated centrifuge** (+4°C) at ca 2500 g for 15 min and two aliquots of **at least 1.2 ml** will be transferred into 2 polypropylene tubes (1.2 ml each).

The plasma samples will have appropriate labels and will be stored at, or below, -20°C in the clinical centre. Thereafter the plasma samples will be transported in dry ice to the PK analysis laboratory, where they will be stored at, or below, -65°C until submitted for analysis with a validated method.

7.2.11 EQ-5D-3L Health Questionnaire

The EQ-5D-3L⁽³⁸⁾ essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

The questionnaire will be completed by patients at each visit from randomisation (Visit 2) until the end of treatment (Visit 7). The questionnaire will be checked for completeness and collected before the patient leaves the center.

At each visit, the data collected on the paper questionnaire will be entered by the Investigator in the eCRF.

7.2.12 Health Economic information

Information on the total use of healthcare resources and absence from work associated with the patients's condition will be collected during the trial. Whether the patient has a job, it will be recorded in the eCRF as well as patient work information.

Professional status will be collected at Visit 2. Health Economic information will be collected in the eCRF by the Investigator based on medical records and patient interviews at each visit from Visit 3 until end of treatment (Visit 7).

8. EFFICACY ASSESSMENTS

8.1 Primary efficacy variables

- Change from baseline in pre-dose FEV₁ at Week 26
- Moderate and severe exacerbations rate over 52 weeks of treatment

8.2 Secondary efficacy variables

Key Secondary Variables:

- Change from baseline in peak FEV₁ (within 3 hours post dosing) at Week 26

- Change from baseline in morning PEF measured by patients at home over the 26-week treatment period.
- Severe exacerbations rate over 52 weeks of treatment in a pre-specified pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

Secondary variables:

- Change from baseline in Peak FEV₁ (within 3 hours post dosing) at all clinical visits
- Change from baseline in pre-dose FEV₁ at all clinical visits
- FEV₁ AUC normalised by time at all clinical visits
- Change from baseline in ACQ-7 at all clinical visits
- Change from baseline in morning and evening PEF over the 52-week treatment period
- Change from baseline in the average use of rescue medication (number of puffs/day) over the 52-week treatment period
- Time to first moderate or severe exacerbation
- Time to first severe exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate exacerbations rate over 52 weeks of treatment in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Time to first moderate exacerbation in the pooled analysis of the two pivotal studies of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate exacerbations rate over 52 weeks of treatment
- Time to first moderate exacerbation
- Daily (morning and evening) asthma symptoms over the 52-week treatment period
- Percentage of asthma control days over the 52-week treatment period

Exploratory variables

- Pre-dose morning FVC, IC and VC at all clinical visits

Health economic variables

- EQ-5D-3L VAS score and EQ-5D-3L index at all clinical visits
- Number of hospital admissions due to asthma
- Number of days in hospital due to asthma
- Number of emergency room visits due to asthma
- Number of unscheduled contacts with health care providers due to asthma:
 - Family practitioner
 - Specialist outpatient setting
 - Specialist hospital outpatient setting
- Unplanned diagnostic tests or instrumental tests due to asthma
- Concomitant medications
- Lost productivity (sick leave days from work, anticipated retirement) due to asthma

9. SAFETY & PHARMACOKINETIC ASSESSMENTS

Safety variables

- Adverse events (AEs) and adverse drug reactions (ADRs).
- Vital signs (systolic and diastolic blood pressure).
- 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS.
- Standard haematology and blood chemistry.

Pharmacokinetic variables

- Clearances and volumes of distribution will be estimated by population PK analysis starting from B17MP, formoterol and GB plasma levels measured in a subset of patients in the CHF 5993 100/6/12.5 pMDI group at steady state (Week 4 and Week 40).
- Other pharmacokinetic parameters of interest could also be reported like for example AUCtau (AUC during a dosing interval at steady state).

10. ADVERSE EVENT REPORTING

10.1 Definitions

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

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

An **Adverse Drug Reaction** is an “untoward and unintended responses to an investigational medicinal product related to any dose administered”.

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

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

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

- Results in death

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

- **Is life-threatening**

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

- **Requires hospitalisation or prolongation of existing hospitalisation**

Hospitalization refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an “elective” or “scheduled” basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as a AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

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

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

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

- **Is a medically significant adverse event**

This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the subject’s health or may require intervention to prevent one of the above outcomes.

Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction

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

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (Investigator’s Brochure CHF 5993 or Summary of Product Characteristics or approved Package Insert for Foster®), 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 labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

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

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

10.4 Causality Assessment

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

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

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

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

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

10.5 Action taken with the study drug due to the AE

- Dose not changed
- Drug Withdrawn
- Drug Interrupted
- Not applicable
- Unknown

10.6 Other actions taken

- Specific therapy/medication
- Surgical/medical procedures
- (Prolonged) Hospitalization

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.

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the subject's study participation ends should be evaluated up to 14 days

after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as “ongoing” in the eCRF.

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 Chiltern 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 Chiltern 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
Chiltern Safety Contact [REDACTED] Senior PV Officer	+44 [REDACTED]	[REDACTED]	GlobalSAEInbox@Chiltern.com
Chiesi Safety Contact [REDACTED] Global PV Operations Manager	+39 [REDACTED]	+39 [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 Chiltern Safety Contact. New serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported in compliance with the timelines and standards for reporting SUSARs set out in the EU Directive 2001/20/EC [Directive 2001/20/EC of the European parliament and of the council of 4/April/2001] ⁽³⁹⁾ and linked guidance [European Commission, Enterprise and Industry Directorate General: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use, latest version] ⁽⁴⁰⁾. The EMA and the concerned national health authority (if applicable) will be informed through Eudravigilance, while the Ethics Committees and

the investigators by CIOMS I form or by periodic line- listings produced by Chiesi Global Pharmacovigilance.

With regard to regulations in force for Pharmacovigilance, the Investigator must fulfil his/her obligation according to the law in force in his country.

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Chiltern Safety Contact by fax together with the Serious Adverse Event form, retaining a copy on site with the case report form;
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Chiltern Safety Contact as soon as available, retaining a copy on site with the case report form;
- 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 Chiltern Safety Contact using the paper Pregnancy Report Form. The Chiltern 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 Chiltern 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 medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.
-

10.12 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) is being established, in order to have an independent scrutiny of the study and a better safety insurance of those subjects who will be recruited in the trial.

Through the involvement of external expert advisors, an unbiased evaluation of the overall safety will be provided, with particular regard to:

- the incidence of major adverse health outcomes (i.e. Serious Adverse Events) during the whole duration of the study including the run-in period,
- any occurring differential risk for major adverse health outcomes (as previously defined) in the different treatment arms during the study,
- any other relevant study data/assessments.

The DSMB will be composed by independent Clinicians and one independent Biostatistician.

A document with the DSMB procedures will be established by the members during the first meeting. The DSMB will have periodical face-to-face and telephone meetings, as appropriate, and a Safety Assessment Report will be issued after each meeting.

The Monitoring of Safety will be accomplished through the evaluation of the rate of Adverse Events (AEs), Serious Adverse Events (SAEs) and asthma exacerbations in the overall study population and in each treatment arm, with a specific attention to the occurrence of SAEs of particular concern for the study patient population, if any.

All relevant listings will be transmitted for evaluation to the DSMB according to the agreed timelines.

The DSMB will have access to the relevant modules of the study IRT with the authorization to:

- unblind the study treatment (if necessary)
- evaluate the trial status (e.g. number of screened patient, screening failures, randomized patients, drop-outs, completers) on an ongoing basis.

Any additional information will be promptly made available by the Sponsor upon request of the DSMB members, as well as any request for additional clinical/instrumental/ laboratory evaluations deemed appropriate by the DSMB will be transmitted to the Investigator and followed-up by the Sponsor.

The Sponsor (and other study personnel) may be involved in some parts of the DSMB meetings, however, they will never have access to unblinded data and/or unblinded/coded comparisons.

All DSMB members will keep as confidential all information and data deriving from the DSMB activity, without disclosing them to others.

10.13 Adjudication Committee for MACE

An Adjudication Committee (AC) will be established, in order to have a particular scrutiny of some potentially relevant adverse events to perform a MACE evaluation.

An unbiased evaluation of the following adverse events will be provided:

- **Acute MI** (acute coronary syndrome, non-fatal myocardial infarction);
- **Stroke** (non-fatal stroke);
- **Cardiovascular death**(cardiac arrest, sudden death);
- **Arrhythmias**: New-Sustained Supraventricular and Sustained Ventricular;
- **Heart Failure** (change in the status)

The AC will be composed by three independent cardiologists and will meet at the end of the study to adjudicate the data in blinded condition. Some additional meetings may be planned during the course of the study.

Any additional available information will be promptly made available by the Sponsor upon request of the AC members, as well as any request for additional clinical/instrumental/ laboratory

evaluations deemed appropriate by the AC will be transmitted to the Investigator and followed-up by the Sponsor. If the data available will be insufficient by the Committee to permit a definitive diagnosis, then the original reporter's diagnosis will be accepted

The Sponsor Corporate Cardiac Leader and other study personnel will be involved in this AC meeting. However, they will never have access to unblinded data and/or unblinded/coded comparisons as the other AC members.

All AC members will keep as confidential all information and data deriving from the AC activity, without disclosing them to others.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.

All patients who will sign the informed consent will be databased. For patients who are screened but not randomized a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, adverse events and concomitant medications if taken due to an adverse event or if they are the reason of discontinuation.

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

Medical history, Adverse Events and Concomitant Procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC) up to 5th level.

ACQ-7 and EQ-5D-3L will be entered in the eCRF by the site and databased.

Laboratory normal ranges will be collected prior to FPFV at each site and provided to data management via the CRO. Laboratory results collected at V1, V5 and V7 will be entered in the eCRF by the investigator.

External data (Spirometry, PK assessments, data from electronic diary/peakflowmeter) will be processed centrally and results will be sent electronically to the designated CRO. External data will be reconciled against data recorded in the eCRF as part of the cleaning activities.

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

12. STATISTICAL METHODS

12.1 Sample Size

The sample size has been calculated to demonstrate:

- the superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in terms of both co-primary endpoints
- the superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in terms of the key secondary endpoints

A total of 1148 patients will be randomised to CHF 5993 100/6/12.5 pMDI (574 patients) or CHF 1535 100/6 pMDI (574 patients).

A log-normal distribution is assumed for drop-out time, estimating approximately 13% drop-out rate at week 12, 16.5% at week 26 and 20% at week 52.

Approximately 958 completed patients (479 per arm) will be available for the analysis at Week 26.

This sample size will provide:

- approximately 99% power to detect a mean difference of 90 ml in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in change from baseline in pre-dose FEV₁ at Week 26 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 311 ml;
- approximately 93% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI at a two-sided significance level of 0.05 using a negative binomial model and assuming a rate of 2.70 moderate and severe exacerbations per patient per year in the CHF 1535 100/6 group and an overdispersion parameter of the negative binomial distribution of 0.56.

The same number of patients will provide:

- approximately 99% power to detect a mean difference of 100 ml in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in Peak FEV₁ change from baseline at Week 26 at a two-sided significance level of 0.05, assuming a SD of 338 ml.
- at least 99% power to detect a mean difference of 20 L/min in favour of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI in morning PEF change from baseline at Week 26 at a two-sided significance level of 0.05, assuming a SD of 45 L/min.
- approximately 86% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI at a two-sided significance level of 0.05, in the pooled analysis, using a negative binomial model and assuming a rate of 0.60 severe exacerbations per patient per year in the CHF 1535 100/6 pMDI group and an overdispersion parameter of the negative binomial distribution of 0.56.

Since each patient with a follow-up of non-null duration provides a contribution to the analysis of exacerbation rates, all randomized patients are considered to be evaluable, irrespective of whether they withdraw from the study prematurely.

Notes:

A subset of patients (about 450) will be selected in order to reach about 200 evaluable patients in the PK analysis (CHF 5993 pMDI group).

This sample size is based on an evaluation of historical PK data and it is considered sufficient to properly conduct the planned population PK analysis.

12.2 Populations for analysis

- **Intention-to-Treat population (ITT):** all randomized subjects who receive at least one dose of the study treatment 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 deviations (i.e., wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Blind Review Report.
- **Safety population:** all randomized subjects who receive at least one dose of study treatment.
- **PK population:** all subjects from the safety population excluding subjects without any valid PK measurement or with major protocol deviations significantly affecting PK, for example: incorrect inhalation, change in subject condition (cold), failure in delivery of the device, use of non-permitted medications. Exact definition of major protocol deviations concerning PK will be discussed by the clinical team and described in a specific document before bioanalytical data are disclosed. Subjects will not be excluded on the basis of statistical analysis or for pharmacokinetic reasons, except in the cases defined in the EMA "Guideline on the Investigation of Bioequivalence" ⁽⁴¹⁾.

Notes:

- When superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI is tested, the primary analysis population for efficacy will be the ITT. Analysis on the primary variables and key secondary variables will be repeated in the PP population for sensitivity purposes.
- Secondary efficacy variables and Health Economics variables will be analysed in the ITT population.
- PK variables will be analysed in the PK population.
- The Safety population will be used in the analysis of all safety variables.
- In case of deviation between as-randomised treatment and treatment actually received, the treatment actually received will be used in the PK and safety analyses (i.e. an as-treated analysis will be performed).
- Analyses stratified by relevant factors may be performed for selected efficacy or safety variables; these analyses will be defined a priori in the Statistical Analysis Plan (SAP).

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.

The test of co-primary and key secondary endpoints will be conducted according to a hierarchical testing procedure. The variables will be considered in the following order:

1. Change from baseline in pre-dose FEV₁ at Week 26 and Moderate and Severe exacerbation rate over 52 weeks;
2. Change from baseline in peak FEV₁ at Week 26;
3. Change from baseline in morning PEF at Week 26;
4. Severe exacerbation rate over 52 weeks in the pooled analysis;

At step 1, both superiority tests on the two co-primary endpoints must be significant. At each of the next steps of the procedure, no confirmatory claims will be made unless all the preceding steps have been demonstrated.

12.3.1 Descriptive Statistics

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

General descriptive statistics for continuous variables will include n (number of observed values), mean, standard deviation, median, minimum and maximum. The 1st and the 3rd quartiles will be also presented for the EQ-5D-3L data. The rate (number of events per year or number of days per year) may also be presented for health economic variables.

For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented.

12.3.2 Missing data

- The validity of the negative binomial model planned for the primary and secondary efficacy analyses relies on the Missing At Random (MAR) assumption. Sensitivity analyses to explore the impact of departures from the expected missing pattern may be used to investigate the robustness of the conclusions of the study: these will be defined a priori in the SAP.
- Only asthma exacerbations with onset during the randomised treatment period (i.e. before study completion or discontinuation) will be included in the analyses.
- If one of the lung function 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.
- In case of less than two missing values among post-dose lung function measurements at 15 min, 30 min, 1 h, 2 h, 3 h, the peak value will be calculated as the maximum of the available values. In case of two or more missing values, the peak value will be considered as missing.
- In the calculation of AUC_{0-3h} normalised by time, missing values will be replaced as follows:
 - If the pre-dose value is not available, the entire curve will be considered as missing
 - Single, isolated missing values (not pre-dose or last value) will be replaced by linear interpolation using the adjacent values

- If two or more consecutive time points have a missing observation, the entire FEV₁ AUC_{0-3h} will be missing.
- If in total three or more of the time points have missing values, the entire curve will be considered as missing.
- A minimum of 7 days with available measurements will be required in each inter-visit period (including run-in period) and in the entire treatment period to consider the following variables as non-missing: morning and evening PEF, use of rescue medication, daily asthma symptoms, percentage of asthma control days.
- 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 Patient demographics and baseline characteristics

The following variables will be summarised by treatment group on the ITT population (and in case also in the PP population): 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 (Visit 2 pre-dose) in pre-dose FEV₁ at week 26 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) and p-value will be estimated by the model. Superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI is >0.
- The number of moderate and severe exacerbations during the 52-week treatment period will be analysed using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model. Superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI is <1.

12.3.5 Key Secondary efficacy variables

- Change from baseline (Visit 2 pre-dose) in Peak FEV₁ (within 3 hours post-dosing) at week 26 will be analysed using a similar model as for change from baseline in pre-dose FEV₁. The

adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs and p-value at Week 26 will be estimated by the model. Superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI is >0 .

- Change from baseline in the average morning PEF at Week 26 will be analysed using a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, Country as fixed effects, and baseline value and baseline by period interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) and p-value will be estimated by the model. Superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI is >0 .
- The number of severe exacerbations during the 52-week treatment period will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model. Superiority of CHF 5993 100/6/12.5 pMDI over CHF 1535 100/6 pMDI will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 100/6/12.5 pMDI and CHF 1535 100/6 pMDI is <1 .

12.3.6 Secondary efficacy variables

- Change from baseline in Peak FEV₁ at all clinical visits, and change from baseline in pre-dose FEV₁ at all clinical visits will be analysed using the same model used for the primary efficacy analysis.
- FEV₁ AUC_{0-3h} normalised by time at all clinical visits will be analysed using the same model used for the primary efficacy analysis.
- Change from baseline (Visit 2) in the ACQ-7 score at all clinical visits will be analysed using the same models as for the primary efficacy analysis on FEV₁ endpoint, but including baseline ACQ-7 instead of baseline FEV₁.
- Change from baseline (run-in period) in morning and evening PEF over the 52-week treatment period and to each inter-visit period will be analysed using the same model as for the PEF at 26 weeks.
- Change from baseline (run-in period) in the average use of rescue medication over the 52-week treatment period and to each inter-visit period will be analysed using the same model as for the PEF at 26 weeks.
- Time to first moderate or severe exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.
- Time to first severe exacerbation will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a Cox proportional hazards model

including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.

- The number of moderate exacerbations during the 52-week treatment period will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a negative binomial model including treatment, Country, and number of exacerbations in the previous year (1 or >1) as fixed effects, and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model.
- The time to first moderate exacerbation will be analysed in the pooled data of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.
- The number of moderate exacerbations during the 52-week treatment period will be analysed using a negative binomial model including treatment, Country and number of exacerbations in the previous year as fixed effects (1 or >1), and log-time on study as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with its 95% CI will be estimated by the model.
- The time to first moderate exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.

Daily (morning and evening) Asthma Symptoms and Percentage of asthma control days in each inter-visit period and over 52 weeks will be analysed using a linear mixed model for repeated measures including treatment, period, treatment by period interaction, Country as fixed effects, and baseline value and baseline by period interaction as covariates. An unstructured covariance matrix will be assumed. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) and p-value will be estimated by the model.

Exploratory variables

- Absolute values and change from baseline in pre-dose morning FVC, IC and VC will be analysed using descriptive statistics.

Health Economics variables

- Health economic variables will be summarised by treatment group using descriptive statistics. Further details on additional analyses of health economic data will be provided in a separate analysis plan; these analyses will not be part of the Clinical Study Report: a dedicated report will be generated.

12.3.7 Safety variables

- The number and percentage of patients who experienced at least one TEAE, drug-related TEAE, serious TEAE, serious related TEAE, TEAE leading to study discontinuation, and TEAE leading to death will be summarized by treatment group. Summaries will be presented overall and by System Organ Class and Preferred Term using the MedDRA dictionary.

- An analysis similar to the one performed on TEAEs will be presented for Major Adverse Cardiovascular Events (MACEs).
- Mean absolute values and mean changes from baseline (Visit 2 pre-dose) for vital signs (SBP, DBP) will be calculated with their 95% CIs by treatment group.
- At each time point after the first study drug intake, 12-lead ECG parameters (HR, PR, QRS and QTcF) will be analysed using descriptive statistics as follows:
 - mean absolute values, with two-sided 95% confidence intervals;
 - mean change from baseline with two-sided 90% confidence intervals.

Baseline is defined as the average of the pre-dose triplicates recorded at Visit 2.

- Change from baseline (Visit 2 pre-dose) in pre-dose 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, Country, as fixed effects, and baseline value and baseline by visit interaction as covariates. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 90% CIs. The same analysis will be performed for change from baseline (Visit 2 pre-dose) in post-dose 12-lead ECG parameters.
- At each visit when ECG is performed the change from pre-dose to post-dose in the 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using an ANCOVA model including treatment, Country as fixed effects and the pre-dose value at the visit as a covariate. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 90% CIs.
- The number and the percentage of patients with a
 - QTcF >450 ms (>470 ms for females), >480 ms (for males only) and >500 ms
 - change from baseline (Visit 2 pre-dose) in QTcF >30 ms and >60 ms
 - only for post-dose time points: change from pre-dose at the same visit in QTcF >30 ms and >60 ms

at each time point after the first study drug intake and at any time point after the first study drug intake will be presented by treatment group.

- For haematology and chemistry parameters, shift tables from Week 26 to Screening and from Week 52 to Screening with reference to normal ranges will be presented

12.3.8 Pharmacokinetic variables

Individual plasma concentration data of BDP, B17MP, formoterol and GB will be tabulated vs. the scheduled sampling times. Concentrations will be summarized by scheduled sampling time using descriptive statistics. Mean plasma concentration vs. time profiles will be presented in linear/linear and log/linear scales.

The plasma concentration data of B17MP, formoterol and GB will be subjected to a population PK analysis. For this analysis the data may be combined with results from previous studies (or analysis). The aim of the population PK analysis is to develop a compartmental model of the plasma concentration vs. time profiles, which will provide a good understanding of the inter-subject and intra-subject (if possible) variability in the drug exposure. In addition the effects of selected covariates on PK parameters will be evaluated, e.g. age, sex, race, smoking status, BMI, concomitant medications, renal and hepatic impairment.

Information regarding the population PK analysis will be described in the separate population PK Analysis Plan. The results and the model development will be described in detail in a separate PK Report.

12.3.9 Interim analysis

Interim analysis not planned.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Ethics Committee/Institutional Review Board in accordance with the requirements of each country.

The EC/IRB shall give its opinion in writing -clearly identifying the study number, study title and informed consent form approved-, before the clinical trial commences.

A copy of all communications with the EC/IRB will be provided to the Sponsor.

The Investigator should provide written reports to the EC/IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the subjects (according to the requirements of each country).

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.

Selection of the subjects will not start before the approval of the Ethics Committee/Institutional Review Board has been obtained and the study notified to Health Authorities (or authorized by).

The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

15. INFORMED CONSENT

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

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

Consent must be documented by the subject's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.

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

16. DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

The Investigators 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 Chiltern who has been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data (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 CRFs for accuracy and completeness;
- to validate the contents of the CRFs against the source documents;
- to assess the status of drug storage, dispensing and retrieval.
- Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
- It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

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

19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.

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

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.

The conditions that may warrant early termination of the trial include, but are not limited to:

- safety concerns (e.g. new findings that could pose at risk the patients enrolled in the trial)
- sponsor's decision to stop the development of the study product
- difficulties in the patients' recruitment

The conditions that may warrant early termination of a trial site include, but are not limited to:

- failure of the Investigator to comply with the protocol requirements and/or regulatory requirements
- the investigator is unable to continue the study

Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

The Sponsor should submit a written notification to the Regulatory Authority concerned and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to Co-ordinating International Investigator for agreement and signature.

At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to the Competent Authority 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.

25. REFERENCES

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formoterol fumarate) alone or on top of open-label tiotropium 2.5 µg Respimat® in patients with asthma uncontrolled on high doses of inhaled corticosteroids in combination with long-acting β_2 -agonists

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APPENDIX I

MINIMUM LIST OF SOURCE DATA REQUIRED

- Subjects demography file
- Subjects medical file
- Study number
- Subject identity/number
- Randomisation number
- Medical and surgery history
- Previous and concomitant medications
- Weight, height
- Date of informed consent signature
- Date of specific study visits
- Examination or assessments carried out during the study (including spirometry reports, spirometry calibration reports, ECG, holter)
- Laboratory reports (blood analysis)
- Study drugs (labels, intake, training)
- Adverse events / serious adverse events
- If subject is withdrawn, reason
- Study start and end dates

APPENDIX II

ASTHMA CONTROL QUESTIONNAIRE® (ACQ-7)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

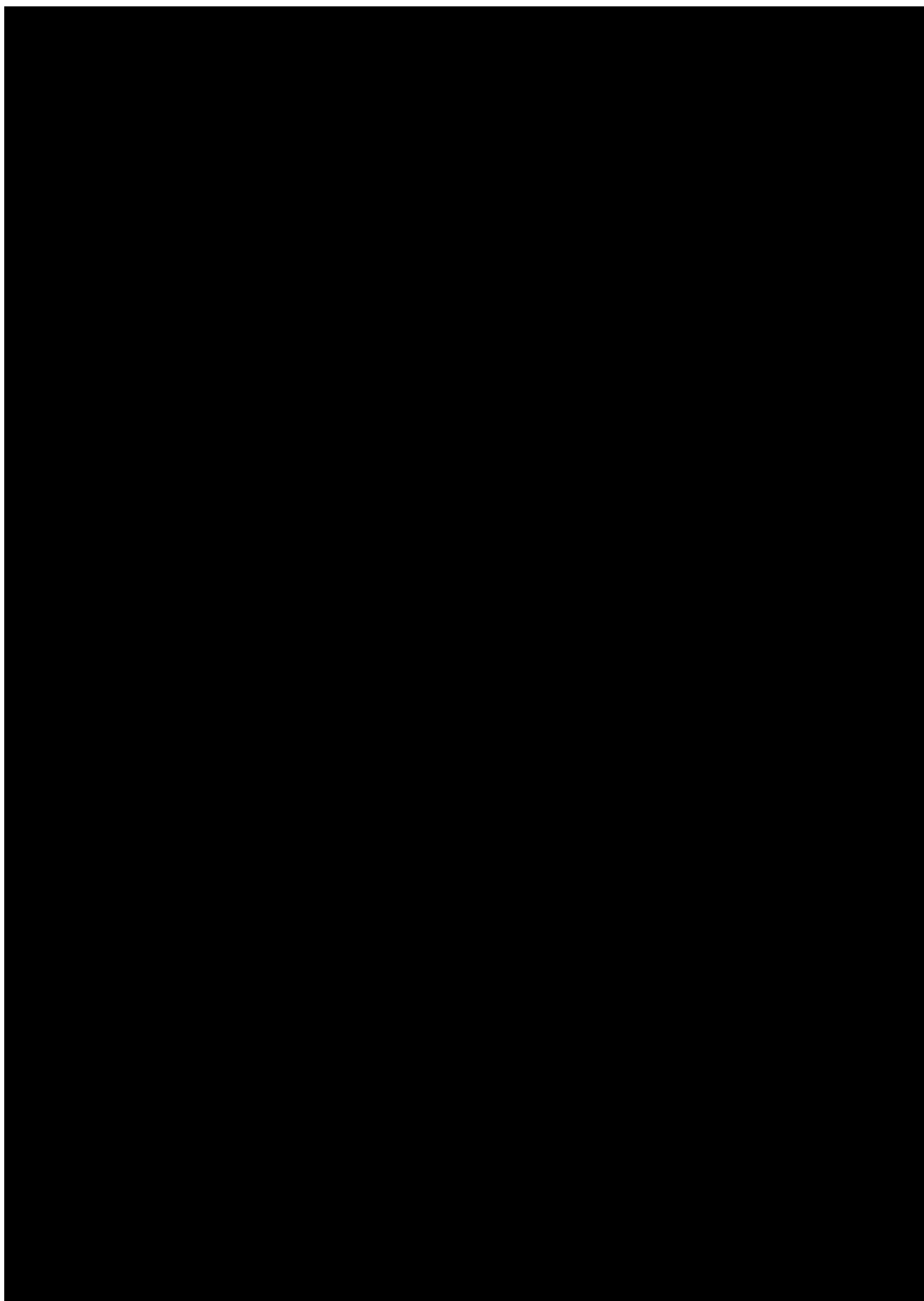
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Category	Value	Percentage
Category 1	100	100%
Category 2	40	40%
Category 3	10	10%
Category 4	40	40%
Category 5	45	45%
Category 6	20	20%
Category 7	10	10%
Category 8	35	35%
Category 9	55	55%
Category 10	40	40%
Category 11	100	100%
Category 12	60	60%
Category 13	65	65%
Category 14	45	45%
Category 15	15	15%
Category 16	25	25%
Category 17	35	35%
Category 18	35	35%
Category 19	25	25%
Category 20	15	15%
Category 21	30	30%
Category 22	45	45%
Category 23	40	40%



APPENDIX IV**SIGNS AND SYMPTOMS OF A
DEVELOPING ASTHMA EXACERBATION***

Sign/Symptom	Moderate Exacerbation	Severe Exacerbation
Breathless	Prefers sitting	Hunched forward
Talks in	Phrases	Words
Agitated	No	Yes
Respiratory rate	Increased	Often > 30/minute
Pulse/min	100-120	>120

* Modified from Box 4.3 (Management of Asthma exacerbations in primary care) of the Global Initiative for Asthma Document (GINA 2015) [www.ginasthma.org]

APPENDIX V

PATIENT CARD (example)

In case of emergency or questions, please contact: <u>Study Doctor:</u> <u>Name of the Hospital:</u> (if applicable): <u>Phone number:</u> If your study Doctor is not available please contact your family Doctor Mr/Mrs is actually involved in the clinical trial CCD-05993AB1-03 (Eudract number: 2015-000716-18) concerning asthma treatment Patient N°: CRO contact details : CHIESI Farmaceutici S.p.A. via Palermo 26/A I-43122 Parma, Italy	 Chiesi Please keep this Card with You <u>Study start date:</u> (deciding visit) Planned visits: Visit 1: at : Visit 2: at : Visit 3: at : Visit 4: at : Visit 5: at : Visit 6: at : Visit 7: at : <u>Study Medicines tested:</u> CHF 5993 100/6/12.5 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug 1 (formoterol fumarate) and bronchodilating drug 2 (glycopyrronium bromide) CHF 1535 100/6 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug (formoterol fumarate) <u>Dosage</u> 2 puffs in the morning (1 puff from inhalers n°1 & 2) 2 puffs in the evening (1 puff from inhalers n°1 & 2) <u>Reminder: Inhalers must be changed after 7 weeks of use.</u> <u>Please remember:</u> - No inhalation of any study medicines on the morning of the clinic visit - No rescue medicine (salbutamol) 6 hours before the clinic visit (except if absolute need) - Always bring the study medicines and the peakflowmeter / diary with you at each clinic visit
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