NCT02676089

CCD-05993AB2-02

CLINICAL STUDY PROTOCOL

EUDRACT No.: 2015-000717-40

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 3-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 200/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS 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 ß2-AGONISTS

Version No.: 2.0
Date: 12 May 2016

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 Tel: + 39 0521 2791 *also reported as Chiesi throughout the text
CLINICAL PROJECT MANAGER:	[redacted] Tel: Fax: E-mail:
SPONSOR MEDICAL EXPERT (Clinical Research Physician)	[redacted] Tel: Mobile: Readily available in case of medical questions E-mail:
CORPORATE CARDIAC LEADER	[redacted] Tel: Mobile: E-mail:
COORDINATING INVESTIGATOR	**Prof. Giorgio Walter Canonica** Respiratory diseases & Allergy, Dept. of Internal Medicine, University of Genoa, Pad Maragliano - Lago Rosanna Benzi 10, 16132 Genoa - Italy Tel.: +39 10 3538931
MONITORING CRO	**Chiltern International SARL** 37 bis rue de Villiers 92200 Neuilly sur Seine, France Tel: + 33 (0)1 41 05 73 00
CENTRAL TECHNICAL LABORATORY OF SPIROMETRY	**Vitalograph Ltd.** Maids Moreton Buckingham MK18 1SW - UK Tel: +44 (0) 1280 827129
CENTRAL TECHNICAL LABORATORY OF ECG/HOLTER	**Vitalograph Ltd.** Maids Moreton Buckingham MK18 1SW - UK Tel: +44 (0) 1280 827129

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 3-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 200/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS 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 ß2-AGONISTS

Product: CHF 5993 200/6/12.5 µg (fixed combination of beclometasone dipropionate 200 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 [redacted] 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, 3-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 200/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS 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 ß2-AGONISTS

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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. Giorgio Walter Canonica, MD

[redacted]

23 May 2016
Date

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

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 3-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 200/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS 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 ß2-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, 3-arm parallel group trial comparing CHF 5993 200/6/12.5 µg pMDI (fixed combination of extrafine beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus 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 ß2-agonists
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 200/6/12.5µg pMDI (beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide [GB])
Centre(s)	About 250 sites
Indication	Asthma
Study design	Double-blind with an open label arm, randomized, multinational, multicentre, 3-arm parallel group study with active control group
Study phase	III
Objectives	***Primary objectives*** ▪ To demonstrate the superiority of CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in pre-dose FEV_1 at Week 26. ▪ To demonstrate the reduction of moderate and severe asthma exacerbations rate with CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI during the entire 52-week treatment period. ***Key secondary objectives*** ▪ To demonstrate the superiority of CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in peak FEV_1 within 3 hours post-dose at Week 26. ▪ To demonstrate the superiority of CHF 5993 200/6/12.5 compared to CHF 1535 200/6 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 200/6/12.5 pMDI compared to CHF 1535 200/6 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 CHF 5993 200/6/12.5 to CHF 1535 200/6 for other lung function assessments, patient's health status and clinical outcome measures. ▪ To compare CHF 5993 200/6/12.5 to CHF 1535 200/6 + Tiotropium for 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.
Treatment duration	A 2-week run-in period on CHF 1535 200/6 µg 2 puffs BID followed by a 52-week treatment period on randomized treatment.
Test product dose/route/regimen	**Treatment A: CHF 5993 200/6/12.5 µg** Fixed combination of extrafine beclometasone dipropionate 200 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose (BDP/FF/GB) **Dose regimen**: BDP/FF/GB 200/6/12.5 µg per inhalation, 2 inhalations BID, daily dose 800/24/50 µg **Administration**: pressurised metered dose inhaler (pMDI) for CHF 5993 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	▪ **Treatment B: CHF 1535 200/6 µg** Fixed combination of beclometasone dipropionate 200 µg plus formoterol fumarate 6 µg / metered dose (BDP/FF) **Dose regimen**: BDP/FF 200/6 µg per inhalation, 2 inhalations BID, daily dose 800/24 µg **Administration**: pressurised metered dose inhaler (pMDI) for CHF 1535 ▪ **Treatment C: CHF 1535 200/6 µg plus tiotropium 2.5 µg** Fixed combination of beclometasone dipropionate 200 µg plus formoterol fumarate 6 µg / metered dose (BDP/FF) + tiotropium 2.5 µg (Spiriva® Respimat®) **Dose regimen**: BDP/FF 200/6 µg per inhalation, 2 inhalations BID, daily dose 800/24 µg plus tiotropium 2.5 µg per inhalation, 2 inhalations OD (morning), daily dose 5 µg **Administration**: pressurised metered dose inhaler (pMDI) for CHF 1535 and Respimat® inhaler for tiotropium Note: Patients used to inhale their asthma pMDI medications with a spacer

<table>
<tr><td></td><td>should continue using a spacer (AeroChamber Plus Flow Vu Antistatic ™) to take the pMDI study drugs.</td></tr>
<tr><td>Number of subjects</td><td>A total of about 1435 patients will be randomised patients according to a 2:2:1 ratio to CHF 5993 200/6/12.5 pMDI (574 patients), CHF 1535 200/6 pMDI (574 patients) or CHF 1535 200/6 pMDI plus Tiotropium (287 patients)</td></tr>
<tr><td>Study population</td><td>Patients with uncontrolled asthma on high doses of inhaled corticosteroids in combination with β2 long-acting bronchodilator</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td>Inclusion Criteria
Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

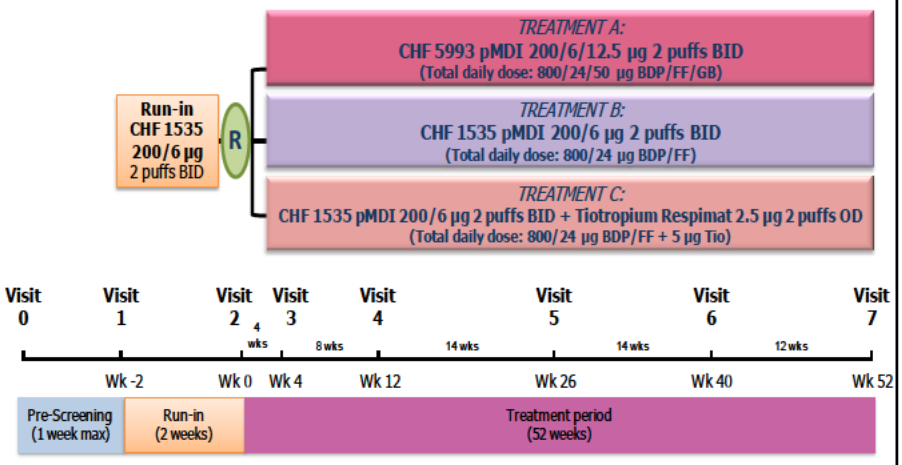
1. Patient's written informed consent obtained prior to any study-related procedures.
2. Male or female patients aged ≥18 and ≤75 years.
3. Patients must have a documented history of asthma for at least 1 year and asthma must have been diagnosed before the patient's age of 40.
4. Patients with uncontrolled asthma with double therapy only on high doses of ICS (>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>
<tr><th>Drug*</th><th>High daily dose</th></tr>
<tr><td>BDP non-extrafine</td><td>> 1000 µg</td></tr>
<tr><td>BDP extrafine</td><td>> 400 µg</td></tr>
<tr><td>Budesonide (DPI)</td><td>> 800 µg</td></tr>
<tr><td>Ciclesonide (HFA)</td><td>> 320 µg</td></tr>
<tr><td>Fluticasone (HFA/DPI)</td><td>> 500 µg</td></tr>
<tr><td>Mometasone furoate</td><td>> 440 µg</td></tr>
<tr><td>Triamcinolone acetonide</td><td>> 2000 µg</td></tr>
</table>
*(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 ΔFEV_1>12% and >200mL 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.</td></tr>
</table>

	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 the 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 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 prior to screening or slow release corticosteroids in the 12 weeks before 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 (≥ 2nd 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 ß2-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 willing to use 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 until the last study visit. 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 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. 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.
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 FEV_1 reversibility after salbutamol intake, and training for the use of inhalers and diary/peakflow meter). ▪ This visit will be followed by a 2-week ± 2 days open-label run-in period, where patients will receive CHF 1535 200/6 µg 2 inhalations BID (daily dose 800/24 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  Note: only the group C is an open-label arm (with CHF 1535 and Tiotropium Respimat®). 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 (see exception above) 10. Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs). 11. Non-selective ß-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 FEV_1 at Week 26 ▪ Moderate and severe exacerbations rate over 52 weeks of treatment **Key secondary variables** ▪ Change from baseline in peak FEV_1 (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-5993AB1-03 and CCD-05993AB2-02 **Secondary efficacy variables** ▪ Change from baseline in Peak FEV_1 (within 3 hours post dosing) at all clinical visits ▪ Change from baseline in pre-dose FEV_1 at all clinical visits ▪ FEV_1 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: o Family practitioner o Specialist outpatient setting o 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
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. ▪ Average 24-hour Heart Rate derived from ECG Holter (on a subset of 10% of the randomised patients). ▪ Standard haematology and blood chemistry.
Sample size calculation	The sample size has been calculated to demonstrate the superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in terms of both co-primary and key secondary endpoints. A total of about 1435 patients will be randomised according to a 2:2:1 ratio to CHF 5993 200/6/12.5 pMDI (574 patients), CHF 1535 200/6 pMDI (574 patients) or CHF 1535 200/6 pMDI plus Tiotropium (287 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 1198 completed patients (479 per group in each of the CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI arms, and 240 in the CHF 1535 200/6 pMDI plus Tiotropium arm) will be available for the analysis at Week 26. This sample size will ensure: ▪ approximately 99% power to detect a mean difference of 90 ml in favour of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in change from baseline in pre-dose FEV_1 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 200/6/12.5 and CHF 1535 200/6 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 200/6 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in Peak FEV_1 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 200/6/12.5 pMDI over CHF 1535 200/6 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 200/6/12,5 and CHF 1535 200/6 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 200/6 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 FEV_1 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. Superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval 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. Superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the upper limit of the confidence interval is <1. **Key Secondary efficacy variables** ▪ Change from baseline (Visit 2 pre-dose) in Peak FEV_1 (within 3 hours post-dosing) at week 26 will be analysed using a similar model as for change from baseline in pre-dose FEV_1. Superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval 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. Superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval 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. Superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the upper limit of the confidence interval is <1.

	Secondary efficacy variables ▪ Change from baseline in Peak FEV_1 at all clinical visits, and change from baseline in pre-dose FEV_1 at all clinical visits, will be analysed using the same model as for the primary efficacy analysis. ▪ FEV_1 $AUC_{0\text{-}3h}$ nornalised 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 FEV_1 endpoint, but including baseline ACQ-7 instead of baseline FEV_1. ▪ 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 at Week 52 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 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 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 signs (SBP, DBP) and 12-lead ECG parameters (HR, PR, QRS and QTcF) will be presented using descriptive statistics. ▪ Change from baseline in Average 24-hour HR and in ECG parameters will be also 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. ▪ 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

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	*Bis in die* (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
FEV_1	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
HFA	Hydrofluoroalkane
HR	Heart Rate
IC	Inspiratory Capacity
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intention to Treat
IUD	Intra Uterine Device

IUS	Intra Uterine System
L	Liter
LABA	Long-acting β2-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
OD	Once daily
P	Period
PEF	Peak Expiratory Flow
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 betwween two consecutive R waves
R&D	Research and Development
SABA	Short-Acting β2-agonist
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

CONTENTS

APPENDICES

1. BACKGROUNG INFORMATION AND STUDY RATIONALE

The goal of asthma management is to achieve and maintain disease control for prolonged periods with regard to the safety of treatment, potential for adverse effects and the treatment cost 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 recommended the addition of therapies such as antileukotrienes, theophyllines, anti-IgE, and immunosuppressants (e.g. systemic corticosteroids). However, the patients stayed remain both symptomatic and obstructed despite these therapies [(2)].

An alternative and potentially effective approach was the addition of a second bronchodilator (anticholinergics) 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/ICS combination shown lung function improvement and increased the time to 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 inadequatey 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 administerd through the Respimat inhaler) to asthma treatment (including high-dose ICS + LABA) improved lung function over 24 hours in patients with inadequatey 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 administerd 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 FEV_1 (0-3h) (all $p<0.05$) and trough FEV_1 (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 antisialogogue 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 combination of BDP/FF/GB (CHF 5993) pMDI for asthmatic patients that would benefit from ICS/LABA and LAMA combined therapy. This product will combine glycopyrronium bromide with the fixed combination CHF 1535 200/6 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, and has just been approved on 15 July 2015 with the strength 200/6 µg.

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 sever 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 has different characteristics also resistance, pMDI devices doesn'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-05993AB2-02 has been then designed to assess the efficacy and safety of the triple fixed combination CHF 5993 200/6/12.5 µg versus CHF 1535 200/6 µg and versus CHF 1535 200/6 µg plus Tiotropium 2.5µg on patients with uncontrolled asthma under high dose of ICS/LABA. A second study CCD-05593AB1-03 will be run in parallel of the study CCD-05993AB2-02 (Eudract number 2015-000716-18) with CHF 5993 at the strength 100/6/12.5 µg on patients with uncontrolled asthma under medium 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 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in pre-dose FEV_1 at Week 26.
- To demonstrate the reduction of moderate and severe asthma exacerbations rate with CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI during the entire 52-week treatment period.

2.2 Secondary Objective(s)

Key secondary objectives:

- To demonstrate the superiority of CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in peak FEV_1 within 3 hours post-dose at Week 26.
- To demonstrate the superiority of CHF 5993 200/6/12.5 compared to CHF 1535 200/6 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 200/6/12.5 pMDI compared to CHF 1535 200/6 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 CHF 5993 200/6/12.5 to CHF 1535 200/6 for other lung function assessments, patient's health status and clinical outcome measures.
- To compare CHF 5993 200/6/12.5 to CHF 1535 200/6 + Tiotropium for 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.

3. STUDY DESIGN

This is a phase III, multicentre, randomised, double-blind, with an open label arm, active-controlled, 3-arm parallel group study in asthmatic patients. Approximately 1435 randomised patients in about 250 sites will be involved.

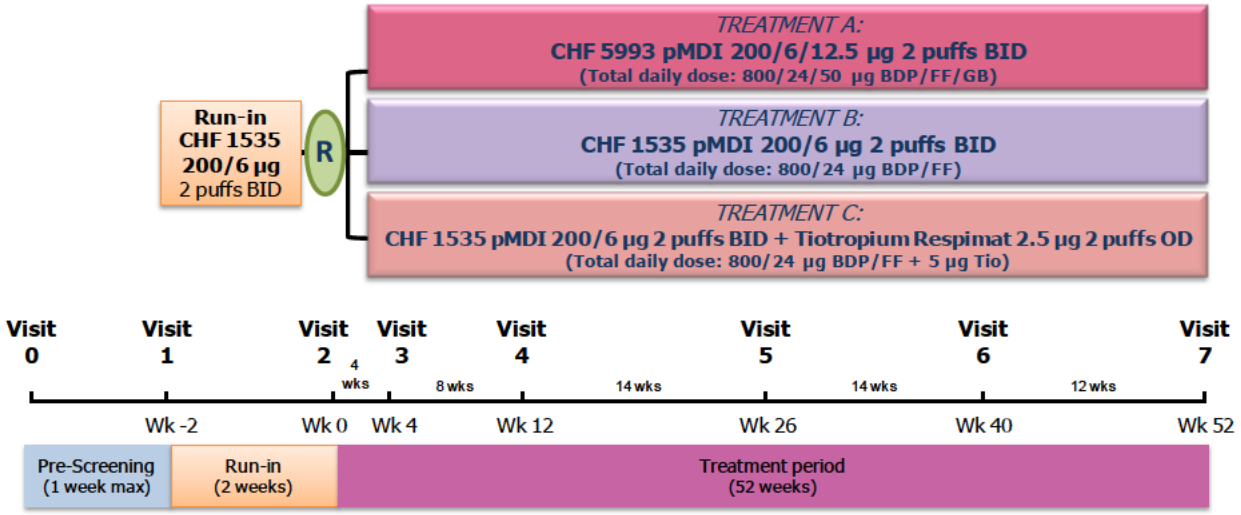
A total of 8 clinic visits (V0 to V7) will be performed during the study, as follows:

- 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 FEV_1 reversibility after salbutamol intake, and training for the use of inhalers and ediary/epeakflow meter).
- This visit will be followed by a 2-week ± 2 days open-label run-in period, where patients will receive CHF 1535 200/6 µg 2 inhalations BID (daily dose 800/24 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

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:



Note: only the group C is an open-label arm (with CHF 1535 and Tiotropium Respimat®).

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. About 250 sites will be involved.

Approximately 2208 patients will be screened and a total of about 1435 patients will be randomised according to a 2:2:1 ratio to CHF 5993 200/6/12.5 pMDI (574 patients), CHF 1535 200/6 pMDI (574 patients) or CHF 1535 200/6 pMDI plus Tiotropium (287 patients).

The assumptions for screening failure rate (about 35%) and drop-out rate (about 16.5% at Week 26 and 20% at Week 52) 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 high doses of ICS (>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.

Drug*	**High daily dose**
BDP non-extrafine	> 1000 µg
BDP extrafine	> 400 µg
Budesonide (DPI)	> 800 µg
Ciclesonide (HFA)	> 320 µg
Fluticasone (HFA/DPI)	> 500 µg
Mometasone furoate	> 440 µg
Triamcinolone acetonide	> 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 ΔFEV_1>12% and >200mL 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 the 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 prior to screening or slow release corticosteroids in the 12 weeks before 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 ($\geq 2^{nd}$ 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 $ß_2$-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 willing to use 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 until the last study visit.

    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

    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.

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.

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.

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 Visit 1 (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 (see exception above).
10. Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs).
11. Non-selective ß-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 200/6/12.5 µg - Test product***
  Active ingredient: Beclometasone dipropionate/Formoterol fumarate/Glycopyrronium bromide
  200/6/12.5 µg per metered dose
  Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: Each canister contains 120 doses

- ***CHF 1535 pMDI 200/6 µg - Reference product***
  Active ingredient: Beclometasone dipropionate/Formoterol fumarate
  200/6 µg per metered dose
  Excipient: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
  Presentation: Each canister contains 120 doses

- ***Tiotropium (Spiriva®) Respimat® 2.5 µg - Reference product***
  Active ingredient: Tiotropium 2.5 µ per dose equivalent to 3.124 microgram tiotropium bromide
  Excipient: Benzalkonium chloride, disodium edetate, hydrochloric acid
  Presentation: One Respimat inhaler and one cartridge containing 60 doses

- ***Placebo CHF 5993 pMDI*** *- used only for training*
  Excipient: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 doses

  For arms A and B: the canisters/actuators of CHF 5993 and CHF 1535 pMDI are identical to allow a complete double-blind design. The arm C with CHF 1535 and tiotropium (Spiriva® Respimat®) is an open-label arm.

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 [21,22,26].

6.2.2 Dosage

6.2.2.1 Run-in period:

- **CHF 1535 pMDI 200/6 µg**
  - 2 inhalations BID (Total daily dose : BDP 800µg/FF 24µg)

6.2.2.2 Randomised Treatment period:

- **Treatment A: CHF 5993 pMDI 200/6/12.5 µg**
  - 2 inhalations BID CHF 5993 (Total daily dose: BDP 800µg/FF 24µg/GB 50µg)
- **Treatment B: CHF 1535 pMDI 200/6 µg**
  - 2 inhalations BID CHF 1535 (Total daily dose: BDP 800µg/FF 24µg)
- **Treatment C: CHF 1535 pMDI 200/6 µg + tiotropium Respimat® (Spiriva® Respimat®)**
  - 2 inhalations BID CHF 1535 (Total daily dose: BDP 800µg/FF 24µg)
  - 2 inhalations OD tiotropium (Total daily dose: tiotropium 5 µg)

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 200/6 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 Visit 1 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 in total:

- For groups A and B: 8 treatments kits of pMDIs, each kit covering an 8-week period.
- For group C: 8 treatments kits of pMDIs and 8 kits of Respimat, each kit covering an 8-week period.

At the randomisation visit (Visit 2), after confirmation of patient's eligibility and at each subsequent visit (Visit 4, 5 and 6), the Investigator, or designee, will contact the IRT system to dispense to each patient the study treatment A (CHF 5993 pMDI), or treatment B (CHF 1535 pMDI), or treatment C (CHF 1535 pMDI + tiotropium) as follows:

- For group A and B: 2 kits of pMDIs will be dispensed at Week 0 (Visit 2), at Week 12 (Visit 4), Week 26 (Visit 5) and Week 40 (Visit 6).
- For Group C: 2 kits of pMDIs and 2 kits of Respimat will be dispensed at Week 0 (Visit 2), at Week 12 (Visit 4), Week 26 (Visit 5) and Week 40 (Visit 6).

Each treatments kit of pMDI 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.**

Each treatments kit of Respimat will consist of 1 box containing 2 inhalers (2 tiotropium). The 2 inhalers (numbered 3 and 4 and identified with a sun label) will be used in the morning only. **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) as follows:

For Groups A and B:

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

For Group C:

- **Morning administration:**
  - One inhalation from the inhaler 1 pMDI,
  - One inhalation from the inhaler 2 pMDI,
  - One inhalation from the inhaler 3 Respimat (sun inhaler),
  - One inhalation from the inhaler 4 Respimat (sun inhaler).
- **Evening administration:**
  - One inhalation from the inhaler 1 pMDI,
  - One inhalation from the inhaler 2 pMDI.

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 for groups A and B (2 in the morning and 2 in the evening **and 6 inhalations will be taken for group C** (4 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 (pMDI and Respimat), please refer to patient leaflets.

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 pMDI study treatments, 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), randomisation (Visit 2), and 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 Visit 2 after the evening dose.

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

Note: the Respimat inhaler should not be used with a spacer.

6.2.3.4 Rescue medication

The rescue medication (salbutamol 100 µg) 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 of pMDI.

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 pMDI will be checked again at randomization visit using the same training kit.

The 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

Note for patients in group C: The Investigator will instruct them how to use the Respimat inhaler by reading toghether and showing the Respimat leaflet to the patient. At each visit the morning

administration of the Respimat will be closely supervised by the Investigator to check whether it is conducted in accordance with the leaflet's instructions.

6.3 Packaging

6.3.1 Training kit

For pMDI:

- *Primary packaging:* One aluminium canister of placebo CHF 5993 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 with a tear/peel off portion.

6.3.2 Run-in kit

- *Primary packaging:* One aluminium canister of CHF 1535 200/6 µg with a study label in English only plus standard actuator.
- *Secondary packaging:* One carton box labelled with a study multi language label with a tear/peel off portion.

6.3.3 Treatment kit

For pMDI

- *Primary packaging:* Two aluminium canisters labelled with a study label in English only plus standard actuator. 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.

For Respimat:

- *Primary packaging:* Two cartridges labelled with a study label in English only plus two Respimat inhalers labelled with a study multilanguage label. The two inhalers will be numbered 3 and 4 and identified with a "SUN" label.
- *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 study multi language label 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/ cartridges 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 or of the cartridge inside the Respimat inhaler). Moreover, due to the small size of the labels on canisters/cartridges, 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 pMDI training kit will be labelled in English, as they are not dispensed to the patient.

Note: the pMDI actuators of the run-in and treatments kits will not be labelled due to the washing procedure (see patient leaflet for cleaning instructions) that would damage the label on the actuator. All the relevant information for patient will be reported on the outbox multilanguage label. It is therefore important to keep the inhalers in their own box when not used and not to discard the box until the end of the study. The use by date (after dispensation) will be handwritten on the canisters label (that are removed before washing) and on the box multilanguage label.

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 three treatment arms with a 2:2:1 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 [27] 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.

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 ediary, 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 pMDIs 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 and pMDI 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 and pMDI randomised treatments kits will be 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 randomised treatment kits** (Respimat) do not require any special storage conditions (except if required by local law). At the latest, three months after use, the Respimat inhaler should be discarded even if not all medication has been used.
- **The training kits** (pMDIs) 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 25ºC) **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 200/6 µg;
- A **randomisation visit** (**Visit 2**, Week 0) when patients will be randomised to one of thethree treatment arms (CHF 5993 200/6/12.5 µg or CHF 1535 200/6 µg or CHF 1535 200/6 µg + tiotropium 2.5µg).
- 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 (at least 10 % of randomised patients) will have a 24-hour ECG holter at V1 (screening), V2 (randomisation), V4 (Week 12), V5 (Week 26) and V7 (Week 52).

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

	Pre-screening	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
24h holter (subset of patients) [3]		X	X		X	X		X
Pre-dose spirometry [4]		X	X	X	X	X	X	X
Reversibility testing [5]		X						
Post-dose serial spirometry (0-3 hours) [6]			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
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/Respimat [8]		X	X					
Training to the use of Aerochamber Plus [8]		X	X					
Training on recognition of a developping asthma exacerbation [8]		X	X					
Training to the use of ediary/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. In a subset of at least 10 % of randomised patients
4. FEV_1, FVC at 45 min and 15 min pre-dose (only V2 to V7). IC & VC to be done before FEV_1 & FVC (only V2 to V7).
5. Reversibility after 4x100 µg salbutamol.
6. FEV_1, FVC: serial spirometry at 15 min, 30 min, 60 min, 120 min and 180 min 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:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed in order to start the Holter recorder at least 90 minutes before the salbutamol intake (see section 7.2.8).
  Note: These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration **should be at least 25 hours.**
- 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 10 minutes of rest at least (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 7.2.9):
  - 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.

- Spirometry assessment, consisting of three acceptable manoeuvres (see section 7.2.1) will be performed.
  Note: To be eligible, pre-bronchodilator FEV_1 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 FEV_1 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 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 and Respimat inhaler with the training leaflet (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 failure to screening in the IRT.
- The investigator will access IRT in order to obtain the run-in medication (CHF 1535 200/6 µg) to be taken during the run-in period (see sections 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 an AeroChamber Plus™.

Before discharge:

- **Run-in Medication (CHF 1535 200/6 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 sections 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 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).
  - **For the subset of patients performing 24h-Holter evaluation**: The Holter must be recorded before any study treatment intake. Therefore, Holter patients will be **invited to the clinic the day before the Visit 2 between 7:00am and 8:00am** in order to place the electrodes and start the Holter recorder at least 90 minutes before the run-in drug morning intake (see section 7.2.8). The total registration should be **at least 25 hours**.
- **An appointment for Visit 2 (Week 0) 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:

- **For the subset of patients performing 24h-Holter evaluation**: the Holter recorder will be stopped (before the study medication intake): the total registration should be at least **25 hours.**
- Run-in Medication (CHF 1535 200/6 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 10 minutes of rest at least (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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11)
- 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, and Respimat inhaler with the training leaflet if he/she is eligible (see sections 6.2.3.3 and 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 (FEV_1, FVC) at 45 minutes and 15 minutes prior to first dosing (see section 7.2.1).

  Note: To be eligible, pre-bronchodilator FEV_1 (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 for groups A and B and n°1&2&3&4 for group C).**

  Note: For the patient using a spacer, the study medication (pMDI only) 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 10 minutes of rest at least (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 (FEV_1, 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 of pMDI for groups A and B, and two kits of pMDI plus 2 kits of Respimat for group C) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of pMDI study medication.
  - **For groups A and B: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and in the evening (i.e. 2 puffs BID for pMDI).**
  - **For group C: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2&3&4) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID for pMDI and 2 puffs OD for Respimat).**

  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.
- **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 kits 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 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 Medications 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 10 minutes of rest at least (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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11).
- 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 (FEV_1, 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 kits (pMDI and Respimat) 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 for groups A and B and n°1&2&3&4 for group C).**

  Note: For the patient using a spacer, the study medication (pMDI only) will be taken via the AeroChamber Plus™ dipensed at Visit 2.
- 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 10 minutes of rest at least (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 (FEV_1, 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 (pMDI and Respimat kits dispensed at V2) will be redispensed** with instructions for use.
  - **For groups A and B: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and in the evening (i.e. 2 puffs BID for pMDI).**
  - **For group C: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2&3&4) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID for pMDI and 2 puffs OD for Respimat).**

  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 kits 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 ± 5 days from Visit 2 in the morning**.

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:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed in order to start the Holter recorder at least 90 minutes before the study drug intake (see section 7.2.8).

  Note: These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration **should be at least 25 hours.**
- 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 10 minutes of rest at least (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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11).
- 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 (FEV_1, 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 (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 for groups A and B and n°1&2&3&4 for group C).**

  Note: For the patient using a spacer, the study medication (pMDI only) 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 10 minutes of rest at least (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 (FEV_1, 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 of pMDI for groups A and B and two kits of pMDI plus 2 kits of Respimat for group C) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication.
  - **For groups A and B: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and in the evening (i.e. 2 puffs BID for pMDI).**
  - **For group C: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2&3&4) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID for pMDI and 2 puffs OD for Respimat).**

  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 kits 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:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed in order to start the Holter recorder at least 90 minutes before the study drug intake (see section 7.2.8).

  Note: These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration **should be at least 25 hours.**
- 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 10 minutes of rest at least (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 7.2.9):

  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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11)
- 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 (FEV_1, 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 (the time of first inhalation corresponds to Time 0 of spirometry).** Patients will be instructed to inhale **1 puff from the each inhaler (n°1&2 for groups A and B and n°1&2&3&4 for group C).**

  Note: For the patient using a spacer, the study medication (pMDI only) 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 10 minutes of rest at least (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 (FEV_1, 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 of pMDI for groups A and B and two kits of pMDI plus 2 kits of Respimat for group C) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication.
  - **For groups A and B: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and in the evening (i.e. 2 puffs BID for pMDI).**
  - **For group C: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2&3&4) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID for pMDI and 2 puffs OD for Respimat).**

  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 kits 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 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 in triplicate, after 10 minutes of rest at least (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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11)
- 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 (FEV_1, 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 (the time of first inhalation corresponds to Time 0 of spirometry).** Patients will be instructed to inhale **1 puff from the each inhaler (n°1&2 for groups A and B and n°1&2&3&4 for group C).**

  Note: For the patient using a spacer, the study medication (pMDI only) will be taken via the AeroChamber Plus™ dispensed at Visit 5.
- 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 10 minutes of rest at least (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 (FEV_1, 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 of pMDI for groups A and B and two kits of pMDI plus2 kits of Respimat for group C) will be dispensed** with instructions for use. The use-by-date must be filled-in on the label of study medication.
  - **For groups A and B: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2) in the morning and in the evening (i.e. 2 puffs BID for pMDI).**
  - **For group C: Patients will be instructed to inhale 1 puff from each inhaler (n°1&2&3&4) in the morning and 1 puff from each inhaler (n°1&2) in the evening (i.e. 2 puffs BID for pMDI and 2 puffs OD for Respimat).**

  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 kits 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 7 (Week 52) will be made in 52 weeks ± 5 days from Visit 2 in the morning**.

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:

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed in order to start the Holter recorder at least 90 minutes before the study drug intake (see section 7.2.8).

  Note: These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration **should be at least 25 hours.**
- 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 10 minutes of rest at least (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 7.2.9):
  - 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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11)
- 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 (FEV_1, 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 kits (pMDI and**

Respimat) dispensed at Visit 6 (the time of first inhalation corresponds to Time 0 of spirometry). Patients will be instructed to inhale **1 puff from the each inhaler (n°1&2 for groups A and B and n°1&2&3&4 for group C).**

Note: For the patient using a spacer, the study medication (pMDI only) 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 10 minutes of rest at least (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 (FEV_1, 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**):

- **For the subset of patients performing 24h-Holter evaluation**: The Holter electrodes will be placed in order to start the Holter recorder at least 90 minutes before the study drug intake (see section 7.2.8).

  Note: These patients will also be requested to visit the site the **next morning** in order to stop the 24-hour digital ECG Holter device. The total registration **should be at least 25 hours.**
- 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 10 minutes of rest at least (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 7.2.9):
  - 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 7.2.10).
- The investigator will collect Health economic information (see section 7.2.11)
- 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 (FEV_1, 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.** Patients will be instructed to inhale **1 puff from the each inhaler (n°1&2 for groups A and B and n°1&2&3&4 for group C) (the time of first inhalation corresponds to Time 0 of spirometry).**

  Note: For the patient using a spacer, the study medication (pMDI only) 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 10 minutes of rest at least (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 (FEV_1, 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 (FEV_1, 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 FEV_1/FVC) will be assessed by the spirometer during the visit only for information purpose of the investigator.

Predicted values of FEV_1 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 (FEV_1, FVC) as described below.**

FEV_1 and **FVC** will be recorded at each clinic visit from a forced vital capacity manoeuvre. For FEV_1 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 **FEV_1** 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)

Only uncontrolled asthmatic patients with an ACQ 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 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 FEV_1), is completed by the clinical staff.

The ACQ 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 FEV_1 % of predicted taken at -15 minutes at the visit when reversibility is met.

The ACQ 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:

- **A severe asthma exacerbations is 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) ≥ 20% decrease in PEF same from baseline on at least 2 consecutive mornings/evenings or ≥ 20% decrease in FEV_1 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°4).

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 any severe asthma exacerbation requiring systemic corticosteroid and/or use of nebuliser containing β2-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 corticosteroids, 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

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

For eligible patients, QTcF values (average) must be QTcF ≤ 450 (for males) and 470 ms (for females) (as per exclusion criterion n°13, 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.

7.2.8 24-hour digital Holter

A centralised Holter (with central reading) will be used.The sub-group of patients selected for this procedure is about 10 % of randomised patients in selected sites. Only patients without pace-maker can be included in this sub-group.

The patients will have **an ambulatory 24-hour digital Holter** on Visit 1 (screening), Visit 2 (Week 0), Visit 4 (Week 12), Visit 5 (Week 26) and Visit 7 (Week 52). The recoding will start at least 90 minutes prior to any drug administration (i.e. salbutamol at Visit 1, run-in medication the day before Visit 2, and study treatment for the subsequent visits after randomisation). Monitoring will continue for 24-hour after study drug administration till the following morning (so the actual duration of ECG Holter recording will be at least 25 hours).

The same Holter equipment will be provided to all sites. Electrodes will be twin electrodes in order to be used to record the 12-lead ECG.The specific procedures for Holter will be provided to the investigator by the centralised Holter company.

Clinically significant abnormalities at Visit 1 not due to a pre-existing condition or clinically significant changes at Visit 2, Visit 4, Visit 5 and Visit 7 in the medical opinion of the investigator will be reported as adverse events in the eCRF.

Two sets of analysis will be conducted for this trial: arrhythmia and electrocardiographic. Details of arrhythmia analysis and calculation of the Holter variables will be provided by the Holter company. From continuous 12-lead ECG recordings (Holter), 6 to 8 discrete 12-lead ECGs (of 10-sec duration each) will be extracted.

7.2.9 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 pregancy test will be performed from Visits 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).

- 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.

7.2.10 EQ-5D-3L Health Questionnaire

The EQ-5D-3L™ [33] 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.

7.2.11 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 e-CRF 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 FEV_1 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 FEV_1 (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 FEV_1 (within 3 hours post dosing) at all clinical visits
- Change from baseline in pre-dose FEV_1 at all clinical visits
- FEV_1 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 (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 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.
- Average 24-hour Heart Rate derived from ECG Holter (on a subset of at least 10% of the randomised patients).
- Standard haematology and blood chemistry.

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 CHF 1535 200/6 µg / Foster® 200/6 and Spiriva® Respimat®), 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 an 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 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	[redacted]	[redacted]	[redacted]
Chiesi Safety Contact [redacted] Global PV Operations Manager	[redacted]	[redacted]	[redacted]

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be reported if the investigator becomes aware of them.
- Up to the closure of the site, SAE reports should be reported to the Chiltern Safety Contact. New SAEs 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] (34) 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] (35) . 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 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 least once 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 meetings. 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 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, 24h Holter, 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in terms of both co-primary endpoints
- the superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in terms of the key secondary endpoints

A total of about 1435 patients will be randomised according to a 2:2:1 ratio to CHF 5993 200/6/12.5 pMDI (574 patients), CHF 1535 200/6 pMDI (574 patients) or CHF 1535 200/6 pMDI plus Tiotropium (287 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 1198 completed patients (479 per group in each of the CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI arms, and 240 in the CHF 1535 200/6 pMDI plus Tiotropium 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in change from baseline in pre-dose FEV_1 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 200/6/12.5 and CHF 1535 200/6 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 200/6 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 200/6/12.5 pMDI over CHF 1535 200/6 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 200/6/12.5 pMDI over CHF 1535 200/6 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 5993200/6/12,5 and CHF 1535 200/6 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 200/6 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 total of at least 144 patients will be selected for the Holter recording.

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.

Notes:

- When superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 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.
- 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 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 morning FEV_1 at Week 26 and Moderate and Severe exacerbation rate over 52 weeks;
2. Change from baseline in peak FEV_1 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 FEV_1 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 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 morning FEV_1 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI is >0. Adjusted means, Adjusted mean differences betwen CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI is <1. Adjusted rates, Adjusted rate ratio betwen CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

12.3.5 Key Secondary efficacy variables

- Change from baseline (Visit 2 pre-dose) in Peak FEV_1 (within 3 hours post-dosing) at week 26 will be analysed using a similar model as for change from baseline in pre-dose morning FEV_1. 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI is >0. Adjusted means, Adjusted mean differences betwen CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

- 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI is >0. Adjusted means, Adjusted mean differences betwen CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI + Tiotropium and their 95% CIs will be estimated for descriptive purposes.
- 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 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI is <1.

12.3.6 Secondary efficacy variables

- Change from baseline in Peak FEV_1 at all clinical visits, and change from baseline in pre-dose morning FEV_1 at all clinical visits will be analysed using the same model used for the primary efficacy analysis.
- FEV_1 $AUC_{0\text{-}3h}$ nornalised 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 FEV_1 endpoint, but including baseline ACQ-7 instead of baseline FEV_1.
- 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 (from Visit 3 onwards), 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.
- Change from baseline in average 24-hour HR 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. Baseline is defined as the average 24-hour HR measured the day before Visit 2.
- The number and the percentage of patients with abnormal findings (including supraventricular arrhythmias, ventricular arrhythmias and non-sustained ventricular tachycardia) in the 24-hour ECG Holter will be summarised 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 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.

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.

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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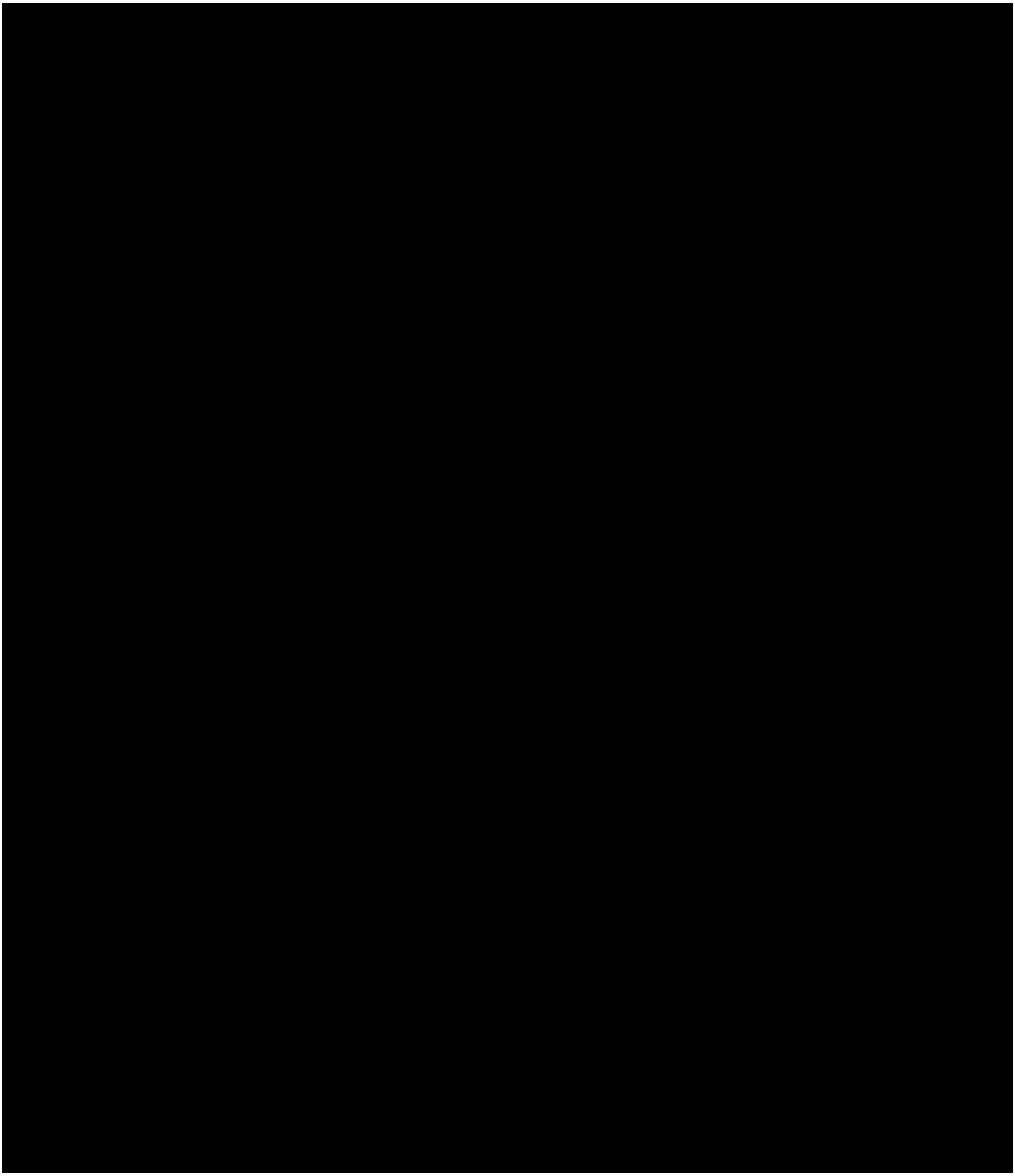
APPENDIX I

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

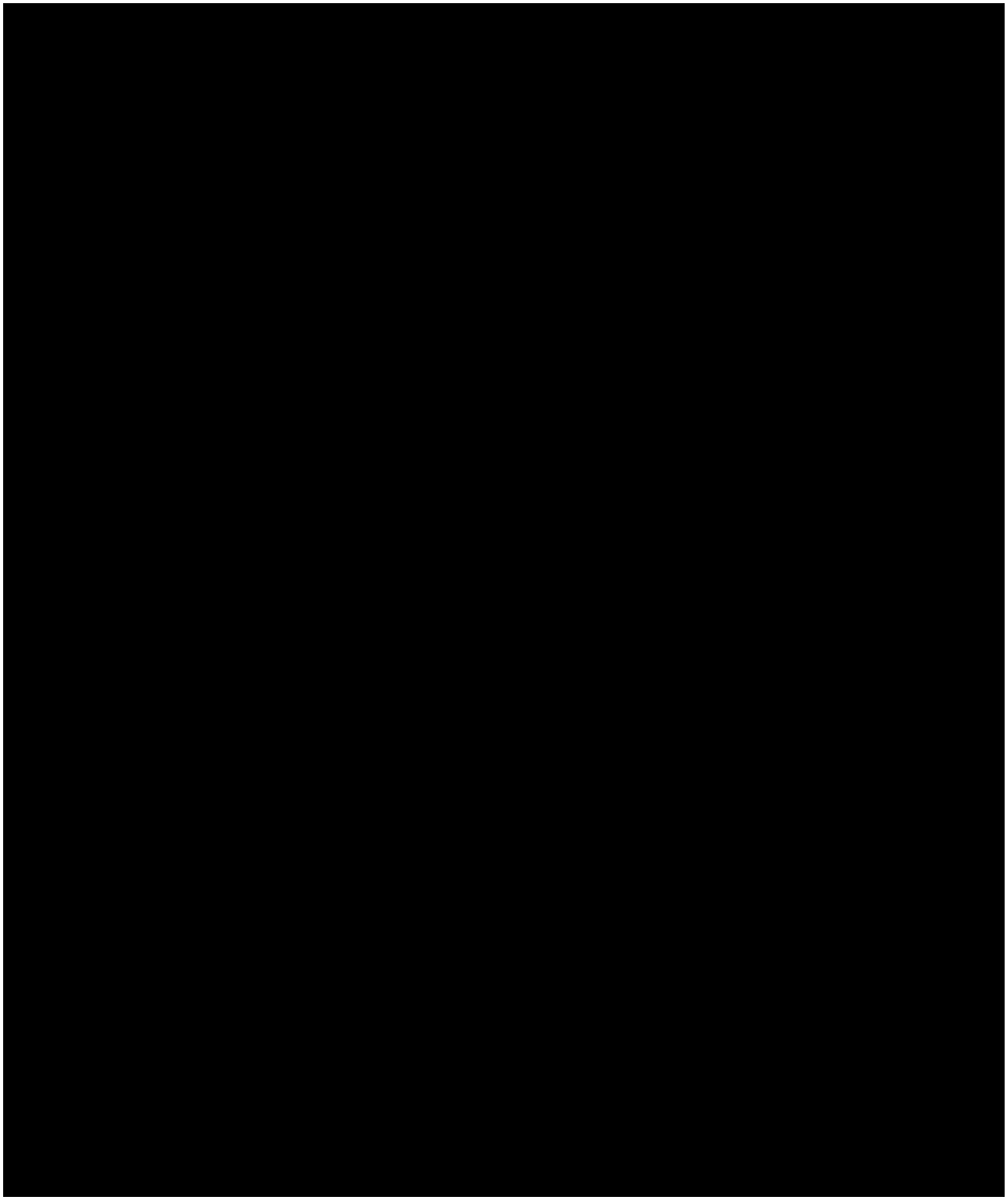
APPENDIX II

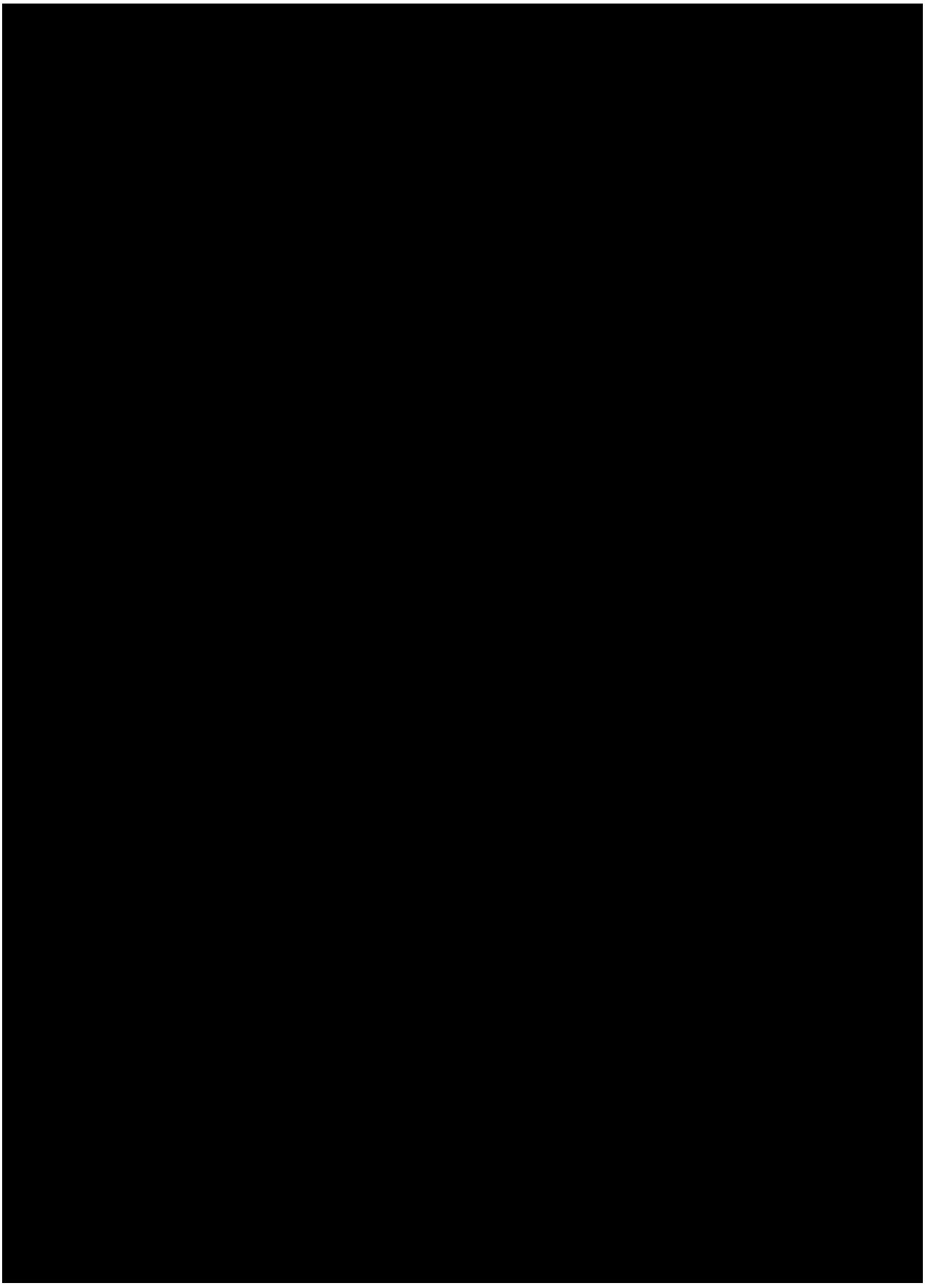
ASTHMA CONTROL QUESTIONNAIRE© (ACQ-7)



APPENDIX III

EQ-5D-3L™





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 FOR GROUPS A AND B (example)

In case of emergency or questions, please contact:

Study Doctor:
.....

.....

Name of the Hospital: (if applicable):
.....

.....

.....

Phone number:
.....

If your study Doctor is not available please contact your family Doctor

Mr/Mrs ……..……..……. is actually involved in the clinical trial CCD-05993AB2-02 (Eudract number: 2015-000717-40) concerning asthma treatment

Patient N°:

|____|____|____|____|____|____|

CRO contact details : ……..

Please keep this Card with You

Study start date: |__|__| |__|__| |__|__| (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 |__|__| : |__|__|

Study Medicines tested:
CHF 5993 200/6/12.5 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug 1 (formoterol fumarate) and bronchodilating drug 2 (glycopyrronium bromide)

CHF 1535 200/6 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug (formoterol fumarate)

Dosage
2 puffs in the morning (1 puff from each inhaler n°1 & 2)

2 puffs in the evening (1 puff from each inhaler n°1 & 2)

Please change of medicine kit after 7 weeks of use

Please remember:
- No inhalation of study & run-in medicines on the

CHIESI Farmaceutici S.p.A. ***via Palermo 26/A*** ***I-43122 Parma, Italy***	morning of the clinic visit - No rescue medicine (salbutamol) 6 hours before the clinic visit (except if absolute need) - Always bring the study/run-in medicines and the peakflowmeter / ediary with you at each clinic visit

PATIENT CARD FOR GROUP C (example)

In case of emergency or questions, please contact: **Study Doctor:** .... **Name of the Hospital:** (if applicable): .... ***Phone number:*** ..... If your study Doctor is not available please contact your family Doctor **Mr/Mrs ……..……..……. is actually involved in the clinical trial CCD-05993AB2-02 (Eudract number: 2015-000717-40) concerning asthma treatment** **Patient N°:** |____|____|____|____|____|____| ***CRO contact details : ……..*** ***CHIESI Farmaceutici S.p.A.*** ***via Palermo 26/A*** ***I-43122 Parma, Italy***	**Please keep this Card with You** ***Study start date****:* |__|__| |__|__| |__|__| (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 |__|__| : |__|__| Study Medicines tested: CHF 5993 200/6/12.5 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug 1 (formoterol fumarate) and bronchodilating drug 2 (glycopyrronium bromide) CHF 1535 200/6 micrograms = combination of corticosteroid (beclomethasone dipropionate) and bronchodilating drug (formoterol fumarate) Tiotropium Respimat 2.5 micrograms = bronchodilating drug Dosage 4 puffs in the morning (1 puff from each inhaler n°1 & 2 and 1 puff from each inhaler 3 & 4) 2 puffs in the evening (1 puff from each inhaler n°1 & 2) **Please change of medicine kit after 7 weeks of use** Please remember: - No inhalation of study & run-in 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/run-in medicines and the peakflowmeter / ediary with you at each clinic visit