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CLINICAL STUDY PROTOCOL

STUDY CODE No.: CLI-05993AB1-06

EUDRACT No.: 2021-002391-39

A 26 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN SUBJECTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS (**MiSTIC**)

Version No.: 2.0
Date: 28 September 2021

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

GENERAL INFORMATION

SPONSOR:	**Chiesi Farmaceutici S.p.A.*** Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
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Clinical Study Code No.: CLI-05993AB1-06	Version No.: 2.0
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VERSION HISTORY

Version	Date	Change History
1.0	24 June 2021	First version
2.0	28 September 2021	Second version - The post-dose spirometry assessment will be performed at 2 hours instead of 3 hours, because in previous analysis the bronchodilation peak appears to occur at 2 hours post-dose. This is updated accordingly for the post-dose spirometry as well as the Oscillometry post-dose assessments. - At screening, the subjects will be defined as having Persistent Airflow Limitation (PAL) (instead of Airflow Obstruction (AO+)) or No Persistent Airflow Limitation (NPAL) (instead of No Airflow Obstruction (AO-)), in order to use a terminology who better suits with the real patient/disease condition and for consistency with the definitions used in previous studies. - Stratification factors for the treatment allocation are now detailed in section 6.5: Patient stratification will be done by Persistent Airflow Limitation (PAL), age and Region (Western and Eastern Europe) status at screening. - Wash-out of 7 months for the monoclonal antibodies is now specified in the part "Non-permitted Concomitant Medications". - The whole WBC differential should be performed in order to have the EOS count at V2 & V6. This is corrected accordingly in the study flow chart in section 7.1, in the section 7.2.8.1 for Haematology and Chemistry investigations. Furthermore, no fasting conditions are needed before assessment of EOS count and biobanking samples. - Additional Quality Checks with an automatic algorithm will be performed for home spirometry. - Moderate and severe exacerbation definitions were clarified in section 7.2.13. - The Chiesi sponsor medical expert changed, this was updated accordingly in the general information part. - Some typos were corrected.

PROTOCOL OUTLINE

Study title	A 26 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN SUBJECTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS (**MiSTIC**)
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF 5993 100/6/12.5µg pMDI (beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide)
Centre(s)	Multiple centres (about 200 sites)
Indication	Asthma
Study design	Randomized (1:1 ratio), Double-blind, Multinational, Multicenter, Active controlled, 2-arm parallel group study
Study phase	Phase IV
Objectives	**Primary Objective:** To demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) compared to high-dose BDP/FF pMDI (200/6 pMDI µg, 2 puffs bid) in terms of the proportion of subjects exhibiting on average no Persistent Airflow Limitation (NPAL) over 26 weeks of treatment in the study sub-population with Persistent Airflow Limitation (PAL) at screening. • A subject is defined as having PAL at screening if their post-bronchodilator (salbutamol) FEV1/FVC ratio is < 0.7. • A subject is defined as having NPAL during the treatment period if the mean of their 2h post-dose FEV1/FVC ratios collected during the 26-week treatment period (i.e. from Week 0 to Week 26) is ≥ 0.7. **Key secondary Objective:** To demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) compared to high dose BDP/FF pMDI (200/6 µg, 2 puffs bid) in terms of change from baseline in pre-dose FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening.

	<u>Other secondary Objectives:</u> • To compare the study treatments on other lung function assessments, clinical outcomes, risk of exacerbations in the study sub-population meeting PAL criterion at screening and in the overall study population. • To assess the safety and tolerability of the study treatments in the study sub-population meeting PAL criterion at screening and in the overall study population.
Treatment duration	One week of pre-screening period, 2 weeks of run-in period, 26 weeks of randomized treatment, one week of follow-up.
Test product dose/route/regimen	**Treatment A: CHF 5993 100/6/12.5 µg** Fixed combination of extrafine beclometasone dipropionate 100 µg plus formoterol fumarate 6 µg plus glycopyrronium bromide 12.5 µg / metered dose (BDP/FF/GB) **Dose regimen**: BDP/FF/GB 100/6/12.5 µg per inhalation, 2 inhalations BID, daily dose 400/24/50 µg **Administration**: pressurized metered dose inhaler (pMDI) Note: Subjects used to inhale their asthma pMDI medications with a spacer should continue using a spacer 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**: pressurized metered dose inhaler (pMDI) Note: Subjects used to inhale their asthma pMDI medications with a spacer should continue using a spacer to take the pMDI study drugs.
Number of subjects	A total of about 1400 subjects will be randomised according to a 1:1 ratio to BDP/FF/GB 100/6/12.5 pMDI (700 subjects) and BDP/FF 200/6 pMDI (700 subjects)
Study population	Adult subjects with asthma uncontrolled on medium dose of inhaled corticosteroids in combination with a long acting β2-agonist (ICS/LABA) who have had at least one asthma exacerbation in the last 3 years. Patients with PAL and NPAL status at screening after salbutamol intake will constitute 65% and 35% of the randomized patients, respectively.
Inclusion/exclusion criteria	**<u>Inclusion criteria:</u>** 1. **Informed consent:** Subject's written informed consent obtained prior to any study related procedures; 2. **Gender and age:** Male or female subjects aged ≥ 18 and ≤ 75 years;

3. **Diagnosis of asthma:** A documented diagnosis of permanent asthma for at least 1 year according to GINA recommendations (Box 1-2, GINA report 2021), and with diagnosis before the subject's age of 40 years;

4. **Stable asthma therapy:** a stable treatment with medium dose of Inhaled corticosteroids (ICS) (extrafine BDP daily dose > 200 and ≤400 µg or estimated clinically comparable dose, as described in GINA 2021 box 3-6) plus a long-acting ß2-agonist (LABA) (formoterol 24 µg or salmeterol 100 µg or vilanterol 25 µg or other approved dose of LABA as clinically comparable to the others) for at least 4 weeks prior to screening;

Drug*	**Medium daily dose (µg)**
BDP non extrafine (pMDI, HFA)	> 500-1000 µg
BDP extrafine (pMDI, HFA)	> 200-400 µg
Budesonide (DPI)	> 400-800 µg
Ciclesonide (pMDI, HFA)	> 160-320 µg
Fluticasone furoate (DPI)	100 µg
Fluticasone propionate (DPI)	> 250-500 µg
Fluticasone propionate (pMDI, HFA)	> 250-500 µg
Mometasone furoate (DPI)	200-400 µg
Mometasone furoate (HFA/pMDI)	200-400 µg

*Table adapted from box 3-6 GINA 2021
BDP = Beclometasone dipropionate; DPI = Dry powder inhaler;
HFA = Hydrofluoroalkane; pMDI = Pressurized metered dose inhaler.

5. **Lung function:** A prebronchodilator FEV_1 < 80% of the predicted normal value, after appropriate washout from bronchodilators, at the screening and randomisation visits;

6. **Reversibility of bronchoconstriction:** A demonstrated increase in FEV_1 > 12% *and* > 200 mL over baseline within 30 minutes after inhaling 400 µg of salbutamol pMDI (based on ATS/ERS guidelines);

7. **A Post-bronchodilator FEV_1/FVC ratio ≥ 0.5** within 30 minutes after inhaling 400 µg of salbutamol pMDI at screening (based on ATS/ERS guidelines);

8. **Poor Asthma control:** Evidence of poorly controlled or uncontrolled asthma as based on an Asthma Control Questionnaire© (ACQ-7) score ≥ 1.5 at screening and at randomisation;

9. **History of exacerbations:** A documented history of one or more asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or inpatient hospitalisation in the last 3 years prior to screening;

10. **A cooperative attitude and ability**:
- to correctly use the pMDI inhalers;

- to perform all trial related procedures including technically acceptable pulmonary function tests;
- to correctly use the e-Diary/e-Peak flow meter and home-spirometry device.

11. Female subjects:

a. Woman of Childbearing Potential (WOCBP) fulfilling one of the following criteria:
   i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up call *or*
   ii. WOCBP with non-fertile male partners (contraception is not required in this case).

For the definition of WOCBP and of fertile men and the list of highly effective birth control methods, refer to Appendix 4.

or

b. Female patient of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile, as per definitions given in Appendix 4). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

In case one of the inclusion criteria #5, #6, or #7 (#5: Pre-bronchodilator FEV_1 value, #6: Reversibility threshold, #7: Post-bronchodilator FEV_1/FVC ratio) is not met at screening, they can be repeated together with ACQ-7 (inclusion criterion #8) once, no later than 5 days before randomisation.

Inclusion criteria #5 (Lung function), #8 (Poor Asthma control) and #10 (Co-operative attitude and ability) should be re-checked at the randomisation visit.

Exclusion criteria:

1. **Pregnant or lactating woman** where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive pregnancy test (serum pregnancy test to be performed at screening visit and urine pregnancy test to be performed prior to randomisation);

2. **Run-in compliance** to study drug and e-Diary completion < 50% at randomisation;

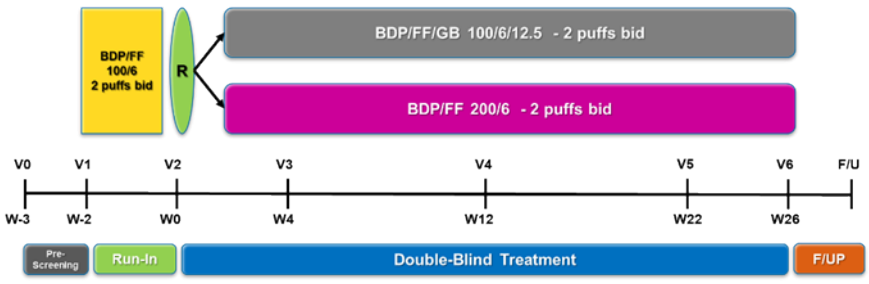
3. **History of "at risk" asthma:** History of near fatal asthma or of a past hospitalisation for asthma in intensive care unit which, in the judgement of the Investigator, may place the subject at undue risk;

4. **Recent exacerbation:** 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;

	Note: Subjects experiencing an exacerbation during the run-in period may be re-screened once, at least 4 weeks after recovery. 5. **Non-permanent asthma:** exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine; 6. Subjects using **systemic corticosteroid** medication in the 4 weeks or slow release corticosteroids in the 12 weeks, prior to screening; 7. **Asthma requiring use of biologics:** Subjects receiving asthma treatment with an injectable biologic drug such as monoclonal antibodies; 8. **Respiratory disorders other than asthma:** Subjects with known respiratory disorders other than asthma. This can include but is not limited to: diagnosis of COPD as defined by the current guidelines (e.g. GOLD Report), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease; 9. **Lung cancer or history of lung cancer**: Subjects with an active diagnosis of lung cancer or a history of lung cancer; 10. **Lung resection**: Subjects with a history of lung volume resection; 11. **Respiratory tract infection**: Subjects with respiratory tract infection within 4 weeks prior to screening or during the run-in period; *Note: Subjects experiencing a respiratory tract infection during the run-in period may be re-screened once, at least 4 weeks after recovery.* 12. **Smoking status:** Current smoker or ex-smoker with a smoking history of ≥ 10 pack-years (pack-years = the number of cigarette packs per day times the number of years). Ex- smokers must have stopped smoking for ≥1 year (≥ 6 months for e-cigarettes). 13. **Cancer or history of cancer (other than lung):** Subjects with active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g. basal cell carcinoma, in situ carcinoma of the cervix adequately treated, …) is acceptable; 14. **Cardiovascular diseases:** Subjects who have clinically significant (CS) cardiovascular condition according to Investigator's judgement, such as but not limited to: congestive heart failure (NYHA class IV), unstable or acute ischaemic heart disease in the last year prior to screening, history of sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months prior to screening (sustained meant lasting more than 30 seconds or ending only with external action, or led to haemodynamic collapse; non-sustained meant > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), high degree impulse conduction blocks (> 2nd degree atrioventricular

	block type 2),persistent, long standing or paroxysmal atrial fibrillation (AF); *Note: Subjects with permanent AF (for at least 6 months prior screening) 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 enrolment;* 15. **ECG criteria:** Any abnormal and clinically significant 12-lead ECG that in the investigator's opinion would affect efficacy or safety evaluation or place the subjects at risk. 16. **ECG QTcF:** Male subjects with a Fridericia's corrected QT interval (QTcF) >450 msec and female subjects with a QTcF >470 msec at screening are not eligible (not applicable for subjects with permanent atrial fibrillation and for subjects with pacemaker); 17. Subjects 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 subjects who are stable under treatment can be considered for inclusion.* 18. **CNS disorders:** Subjects with a history of symptoms or significant neurological disease such as but not limited to transient ischemic attack (TIA), stroke, seizure disorder or behavioural disturbances according to the investigator's opinion; 19. **Other medical conditions**: Subjects with other severe acute or chronic medical or malignancy or psychiatric condition or clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease, that might in the judgment of the Investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study; 20. **Other concurrent diseases:** Subjects with historical or current evidence of uncontrolled concurrent disease such as but not limited to hyperthyroidism, diabetes mellitus or other endocrine disease; haematological disease; autoimmune disorders (e.g. rheumatoid arthritis,), gastrointestinal disorders (e..; poorly controlled peptic ulcer, GERD), significant renal and hepatic impairment or other disease or condition that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study; 21. **Liver diseases:** Subjects with severe hepatitis, chronic active hepatitis or evidence of uncontrolled chronic liver disease according to the investigator's opinion; 22. **Vaccination:** Subjects who receive a vaccination within 2 weeks prior to screening or during the run-in;

	23. Subjects mentally or legally incapacitated, or subjects accommodated in an establishment as a result of an official or judicial order; 24. **Contra-indications to IMPs**: Contra-indications to IMPs constitute an exclusion criterion. For warnings, eligibility will be judged by the investigator; 25. **Alcohol/drug abuse:** Subjects with a history of alcohol or drug abuse within two years prior to the start of the study; 26. **Hypersensitivity:** Subjects with known intolerance/hypersensitivity or contraindication to treatment with $ß_2$-agonists, ICS, anticholinergics or propellant gases/excipients. For warnings/precaution for use, eligibility will be judged by the investigator; 27. **Surgery:** Subjects with major surgery in the 3 months prior to screening visit or planned surgery during the trial; 28. **Subjects treated** with non-potassium sparing diuretics (unless administered as a fixed dose combination [FDC] with a potassium conserving drug or changed to potassium sparing before the screening), nonselective beta blocking drugs, quinidine, quinidine like anti-arrhythmics, or any medication with a corrected QT interval (QTc) prolongation potential or a history of QTc prolongation; 29. Subjects treated with **monoamine oxidase inhibitors** (MAOIs) and tricyclic anti-depressants; 30. Subjects receiving any therapy that could interfere with the study drugs according to Investigator's opinion; 31. **Participation to investigational trial:** Subjects who have received an investigational drug within 2 months or six half-lives (whichever is greater) prior to screening visit, or have been previously randomised in this trial, or are currently participating in another clinical trial; 32. Documented **COVID-19 diagnosis or its complication** which has not resolved within 14 days prior to screening. *Exclusion criterion #2 (Run-in compliance), will be checked only at randomisation visit.* *Exclusion criteria #1 (Pregnancy/contraception), #4 (Recent exacerbation), #11 (Respiratory tract infection), #19 (Other medical conditions), #21 (Liver diseases), #22 (Vaccination), #27 (Surgery,) #30 (any therapy) will be re-checked at randomisation visit.*
Study plan	A total of 7 clinic visits (V0 to V6) plus a follow-up call 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 subjects and to obtain the written informed consent

	from the subject and instruct the subject on screening visit procedures (such as medication or procedure-linked restrictions). • A screening visit (V1) will help establish the eligibility of subjects 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 and Persistent Airflow Limitation status after salbutamol intake, and training on the use of inhalers and e-diary/peak flow meter). This visit will be followed by a 2-week ± 2 days open-label run-in period, where subjects will receive BDP/FF 100/6 µg 2 inhalations BID (daily dose 400/24 µg). • After the randomization visit (V2), subjects will be assessed after 4, 12, 22, and 26 weeks of treatment (from V3 to V6) at clinic/hospital. At each visit from V2 to V6, spirometry pre-dose and 2-hours post dose, in addition to other efficacy and safety tests. ACQ-7, AQLQ will be completed at V2, V4 & V6. • A safety follow-up phone call will be done by the investigator 1 week after the V6 or Early Treatment Discontinuation visit to check the status of unresolved adverse events and to record any new AEs that have occurred after the last visit as well as the related concomitant medications. • Subject who discontinues study treatment should not be considered automatically withdrawn from the study (except if the reason is consent withdrawal or lost to follow up). The investigator and study staff must discuss with the subject who will be asked to continue attending the remaining study visits while off investigational treatment. • AEs and SAEs will be monitored throughout the study. Total study duration = 30 weeks 
Most relevant permitted concomitant medications	• 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 subject needs rescue medication within this time window, the visit must be postponed. • Short courses (≤ 14 days each) of systemic corticosteroid and/or brief uses of nebulized treatment containing β2-agonists and/or

	corticosteroids, and/or antibiotics therapy for severe asthma exacerbation. • Antihistamines (oral, ocular, intranasal) and intranasal corticosteroids for the treatment of allergy or rhinoconjunctivitis symptoms). • Allergen immunotherapy for the treatment of respiratory allergy, if already started before the study • Appropriate treatment for concomitant diseases, seasonal influenza and SARS-CoV-2 vaccination (1 week should elapse from vaccination and the post-randomization study visits) will be permitted if it does not interfere with the study drugs or the study evaluations and it is not listed under the section "Non-permitted concomitant medications".
Most relevant non-permitted concomitant medications	• Inhaled corticosteroids other than the study drugs. • Inhaled LABA other than the study drugs. • Inhaled fixed or free combinations ICS/LABAs (e.g. Seretide®, Symbicort®) or ICS/LABA/LAMA other than the study drugs. • Inhaled Short-Acting Muscarinic Antagonists (SAMAs). • Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers). • Theophylline. • Systemic anticholinergics. • Systemic corticosteroids (see exception above) • Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs). • Non-selective ß-blocking drugs (including eye drops). • Quinidine and Quinidine-like anti arrhythmics. • Monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs used for the treatment of respiratory conditions, and for any other condition if impact on respiratory outcomes cannot be excluded, for more than 7 months prior to screening. • Any medication that could interact with the study drug, according to Investigator's judgement. Prior to screening, the following wash-out periods apply: o Inhaled/nebulized SABA: 6 hours, o Inhaled/nebulized SAMA: 12 hours, o Inhaled/nebulized combination of SABA/SAMA fixed combination: 12 hours, o Inhaled LABA for BID administration: 24 hours, o Inhaled LABA for once daily administration (e.g. indacaterol): 36 hours,

	○ Inhaled ICS/LABA (free or fixed combination) for BID administration: 24 hours, ○ Inhaled ICS/LABA (fixed combination) for once daily administration: 36 hours, ○ Inhaled ICS/LABA+LAMA (free of fixed combination): 4 weeks, ○ ICS: 12 hours, ○ Theophylline and leukotriene modifiers: 72 hours. Prior to each spirometry including serial spirometry, the following wash out periods for concomitant medications must be respected: ○ Inhaled/nebulized SABA: 6h ○ Study treatment: not to be taken in the morning of the visit Prior to each post-treatment visits, the following was-out periods for concomitant medications must be respected: ○ Inhaled/nebulized SABA: 6 hours, ○ Inhaled/nebulized SAMA: 12 hours, ○ Inhaled/nebulized combination of SABA/SAMA fixed combination: 12 hours, ○ Inhaled LABA for BID administration: 24 hours, ○ Inhaled LABA for once daily administration (e.g. indacaterol): 36 hours, ○ Inhaled ICS/LABA (free or fixed combination) for BID administration: 24 hours, ○ Inhaled ICS/LABA (fixed combination) for once daily administration: 36 hours, ○ Inhaled ICS/LABA+LAMA (free of fixed combination): 24 hours, ○ ICS: 12 hours, ○ Theophylline and leukotriene modifiers: 72 hours.
Efficacy variables (and/or pharmacokinetics variables)	**Primary efficacy variable:** • Proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening. **Key-Secondary efficacy variable:** • Change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening. **Secondary efficacy variables** *(evaluated both in the overall study population and in the study sub-population meeting PAL criterion at screening):*

	• Proportion of subjects with an increase ≥ 10% in average 2h FEV_1/FVC ratio over 26 weeks compared to post-BD FEV_1/FVC ratio at screening.
	• Proportion of subjects who consistently exhibit PAL or NPAL status:
	  o Proportion of subjects with PAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).
	  o Proportion of subjects with NPAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).
	• Proportion of subjects with 1, 2, 3, 4 or 5 post-treatment visits (among Week 0, 4, 12, 22, and 26) with PAL and NPAL status.
	• Proportion of subjects with PAL and NPAL status at each post-treatment visit (Week 0, 4, 12, 22, and 26).
	• Proportion of subjects exhibiting on average PAL and NPAL status over 26 weeks of treatment.
	• Change from baseline in 2h post-dose FEV_1 at all clinic visits.
	• Change from baseline in 2h post-dose FEV_1/FVC at all clinic visits and over 26 weeks of treatment.
	• Change from baseline in pre-dose morning FEV_1 at all clinic visits.
	• FEV_1 response (Change from baseline ≥ 100 mL in pre-dose FEV_1) at Week 26.
	• Severe asthma exacerbations rate over 26 weeks of treatment.
	• Moderate or severe asthma exacerbations rate over 26 weeks of treatment.
	• Time to first severe asthma exacerbations rate.
	• Time to first moderate or severe asthma exacerbations rate.
	• Number of days with use of Oral Systemic Corticosteroids (OCS).
	• Change from baseline in pre-dose and 2h post-dose FVC at all clinic visits.
	• Change from baseline in average morning PEF over 26 weeks of treatment and at each inter-visit period.
	• Change from baseline in average evening PEF over 26 weeks of treatment and at each inter-visit period.
	• Change from baseline in Blood Eosinophils at Week 26.
	• Change from baseline in Symptom-Free Days over 26 weeks of treatment and at each inter-visit period.
	• Change from baseline in rescue SABA use over 26 weeks of treatment and at each inter-visit period.
	• Change from baseline in daily (morning and evening) asthma symptoms over 26 weeks of treatment and at each inter-visit period.

	• Change from baseline Asthma control days over 26 weeks of treatment and at each inter-visit period. • Change from baseline in ACQ-5, ACQ-7, AQLQ at Week 12 and Week 26.
Exploratory assessments	• Blood and Urine samples will be collected for biobanking at the randomization visit (V2, Week 0), end of treatment (V6, Week 26) and Early Treatment Discontinuation Visit, to perform post-hoc biomarker analysis. The results of this post- hoc investigation will not be part of the statistical analysis and might not be included in the Clinical Study Report. • Change from baseline in oscillometric parameters at all clinic visits (resistance, reactance). • Change from baseline in FeNO at Week 26. • Average Healthcare resource utilization (HCRU) over the 26 weeks of treatment period for each treatment group. • Change from baseline in home spirometry parameters.
Safety variables	• Adverse Events (AEs), adverse drug reactions (ADRs). • Vital signs (systolic and diastolic blood pressure). • 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS. • Standard haematology and blood chemistry.
Sample size calculation	The sample size has been calculated to demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) over high-dose BDP/FF (200/6 µg, 2 puffs bid) in terms of both primary and key secondary endpoints. A total of 1400 subjects will be randomised according to a 1:1 ratio to either BDP/FF/GB 100/6/12.5 pMDI or BDP/FF 200/6 pMDI (i.e. 700 subjects per group). Considering that subjects meeting PAL criterion at screening will constitute 65% of the total randomised population, approximately 910 subjects (i.e. 455 per group) included in this study sub-population will be randomised, and approximately 822 of them (i.e. 411 per group) will continue the study treatment till Week 26 (considering an early treatment discontinuation rate of approximately 10% at Week 26). This sample size will provide: • Approximately 95% of power to detect a difference of 0.11 in favour of BDP/FF/GB 100/6/12.5 pMDI over BDP/FF 200/6 pMDI in the proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening. The lower limit of 95% confidence interval of the odds ratio derived from a logistic model being aims to be > 1. Two-sided significance level of 0.05 is considered, assuming a proportion of

	subjects exhibiting on average NPAL status over 26 weeks of 0.31 and 0.20 for BDP/FF/GB 100/6/12.5 pMDI and BDP/FF 200/6 pMDI, respectively. • Approximately 84% of power to detect a mean difference of 70 ml in favour of BDP/FF/GB 100/6/12.5 over BDP/FF 200/6 pMDI in terms of change from baseline in pre-dose FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 339 ml. Jointly considering the two endpoints, an overall study power of at least 80% will be ensured.
Statistical methods	**Analysis sets** The following analysis sets will be considered: • **Safety set**: all randomised subjects who receive at least one dose of the study drug (analysed as treated). • **ITT set**: all randomised subjects who receive at least one dose of the study drug (analysed as randomized). **Primary efficacy variable** <u>Main estimand</u> *Population*: Subjects with asthma meeting PAL criterion at screening. *Treatment:* Randomised treatment (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) including rescue medication and any other asthma treatments that may be administered during the study. *Variable:* Proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment. *Population-level summary:* Adjusted odds ratio comparing BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI. *Strategy for intercurrent events and events leading to missing data:* • *Early discontinuation from study treatment:* Missing FEV1/FVC values (both on-treatment and off-treatment) will be imputed considering "Missing at Random" (MAR) assumption (i.e. targeting a hypothetical strategy). • *Use of not allowed medication and other important protocol deviations:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy). • *Wrong study drug intake*: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).

	Sensitivity analyses – strategy for intercurrent events and events leading to missing data: • *Early discontinuation from study treatment*: Missing FEV_1/FVC values (both on-treatment and off-treatment) will be imputed considering "Missing not at Random" (MNAR) assumption: o Copy Reference (CR) imputation based on BDP/FF 200/6 pMDI arm if reason for treatment discontinuation is likely to be related to study treatment. o CR imputation based on the relevant treatment arm if reason for treatment discontinuation is not likely to be related to study treatment. <u>Alternative estimand</u> The attributes of the alternative estimand in terms of population, treatments, variable and population-level summary are consistent with those for main estimand provided above. *Strategy for intercurrent events and events leading to missing data:* • *Early discontinuation from study treatment:* FEV1/FVC values collected after the treatment discontinuation will be included in the analysis (i.e. targeting a treatment policy strategy). • *Early discontinuation from study:* The collected off-treatment FEV1/FVC observed on all patients will be considered for the imputation of missing FEV1/FVC after the study discontinuation of both treatment groups (i.e. targeting a hypothetical strategy). In case of few off-treatment FEV1/FVC values collected, a CR imputation based on BDP/FF 200/6 pMDI arm will be considered for all the treatment arms. • *Use of not allowed medication and other important protocol deviations:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy). • *Wrong study drug intake:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy). *Sensitivity analyses – strategy for intercurrent events and events leading to missing data:* • No sensitivity analysis is planned for this alternative estimand. <u>Analysis</u> The proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening will be analysed on the ITT set using a logistic regression model including treatment and region as factors and baseline FEV_1/FVC value (i.e. Week 0, pre-dose) as covariate. The odds ratio for the treatment effect (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) with its 95% Wald CI and corresponding p-value will be estimated by the model. Superiority of BDP/FF/GB 100/6/12.5 pMDI will be demonstrated by a statistically significant difference between treatments (defined as $p<0.05$)

	favouring BDP/FF/GB 100/6/12.5 pMDI. A subject will be considered as having on average a NPAL status over 26 weeks of treatment if the mean of the 2h post-dose FEV_1/FVC values is ≥ 0.7
	
	Key-secondary efficacy variable
	
	Main estimand
	
	Population: Subjects with asthma meeting PAL criterion at screening.
	
	Treatment: Randomised treatment (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) including rescue medication and any other asthma treatments that may be administered during the study.
	
	Variable: Change from baseline in pre-dose FEV_1 at Week 26.
	
	Population-level summary: Adjusted between treatment difference comparing BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI.
	
	Strategy for intercurrent events and events leading to missing data:
	• *Early discontinuation from study treatment:* Missing FEV1 values (both on-treatment and off-treatment) will be managed by the mixed model for repeated measures, which relies on MAR assumption for missing data (i.e. targeting a hypothetical strategy).
	• *Use of not allowed medication and other important protocol deviations:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	• *Wrong study drug intake:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	
	Sensitivity analyses – strategy for intercurrent events and events leading to missing data:
	• *Early discontinuation from study treatment:* Missing FEV1 values (both on-treatment and off-treatment) will be imputed considering MNAR assumption:
	  ○ CR imputation based on BDP/FF 200/6 pMDI arm if reason for treatment discontinuation is likely to be related to study treatment.
	  ○ CR imputation based on the relevant treatment arm if reason for treatment discontinuation is not likely to be related to study treatment.
	
	Alternative estimand
	
	The attributes of the alternative estimand in terms of population, treatments, variable and population-level summary are consistent with those for main estimand provided above.
	
	Strategy for intercurrent events and events leading to missing data:

	• *Early discontinuation from study treatment:* FEV1 values collected after the treatment discontinuation will be included in the analysis (i.e. targeting a treatment policy strategy).
	• *Early discontinuation from study:* The collected off-treatment FEV1 observed on all patients will be considered for the imputation of missing FEV1 after the study discontinuation of both treatment groups (i.e. targeting a hypothetical strategy). In case of few off-treatment FEV1 values collected, a CR imputation based on BDP/FF 200/6 pMDI arm will be considered for all the treatment arms.
	• *Use of not allowed medication and other important protocol deviations:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	• *Wrong study drug intake:* Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	
	Sensitivity analyses – strategy for intercurrent events and events leading to missing data:
	• No sensitivity analysis is planned for this alternative estimand.
	
	<u>Analysis</u>
	
	Change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening will be analysed on the ITT set using using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction and region as fixed effects, and baseline value (i.e. Week 0, pre-dose) 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% CIs at Week 26 will be estimated by the model. Superiority of BDP/FF/GB 100/6/12.5 pMDI will be demonstrated by a statistically significant difference between treatments at Week 26 (defined as $p<0.05$, in case the primary variable analysis is successful) favouring BDP/FF/GB 100/6/12.5 pMDI.
	
	Control Type 1 error
	
	• The primary and key-secondary efficacy endpoints will be tested for statistical significance following a hierarchical strategy to control the familywise type I error rate using the main estimand. Each test will be considered confirmatory only if the tests at all the previous steps are successful. The hierarchy for the primary and key secondary endpoints is as follows:
	  ○ Step 1: Primary endpoint using the main estimand
	  ○ Step 2: Key-secondary endpoint using the main estimand
	• The alternative estimand described above for the primary and key-secondary endpoints is considered for exploratory purpose and it is not included in the hierarchical strategy to control the familywise type I error rate.

	Secondary efficacy and safety variables • Analyses of secondary efficacy variables are planned to target the same main estimand as described for the primary and key-secondary variables, i.e. excluding off-treatment data for subjects who discontinue the study treatment prior to the planned treatment completion (i.e. 26 weeks of treatment). • Safety analysis will be based on Safety set. For subjects who discontinue the study treatment but accept to remain in the study, assessments conducted following 1 week after the last dose of study drug will not be considered in analysis or presentation of safety data. Details for secondary efficacy and safety variables are defined in the section 12 of protocol.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AOS	Airwave Oscillometry System
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
ATC	Therapeutic Chemical classification
ATS	American Thoracic Society
BD	Bronchodilator
BDP	Beclometasone Dipropionate
BID	Bis in die (twice a day)
BMI	Body Mass Index
BP	Blood Pressure
BTPS	Body Temperature and Pressure Saturated
BUN	Blood Urea Nitrogen
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Copy Reference
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
DALYs	Disability Adjusted Life Years
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	Eosinophil
ERS	European Respiratory Society
ETD	Early Treatment Discontinuation
EVC	Expiratory Volume Capacity
FDC	Fixed Dose Combination
$FEF_{25\%-75\%}$	Forced Expiratory Flow 25-75%
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FF	Formoterol Fumarate
FOT	Forced Oscillation Technique
FSFV	First Subject First Visit
FSH	Follicle-stimulating Hormone
FU	Follow up
FVC	Forced Vital Capacity
γ-GT	Gamma-glutamyl Transpeptidase
GB	Glycopyrronium Bromide
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease

GINA	Global Initiative For Asthma
GMP	Good Manufacturing Practices
Hb	Hemoglobin
HCRU	Healthcare Resource Utilization
Hct	Hematocrit
HFA	Hydrofluoroalkane
HR	Heart Rate
HS	High Strength
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IMP	Investigation Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-release System
LABA	Long-acting β2-agonist
LAMA	Long-acting Muscarinic Antagonist
LLN	Lower Limit of Normal
LSLV	Last Subject Last Visit
MAOI	Monoamine Oxidase Inhibitors
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at Random
MS	Medium Strength
NPAL	No Persistent Airflow Limitation
OCS	Oral Systemic Corticosteroids
PAL	Persistent Airflow Limitation
PEF	Peak Expiratory Flow
PLT	Platelet
pMDI	Pressured Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval Between the P and R wave in the ECG
QRS	Time Interval Between the Q and R and S wave in the ECG
QTc	Time interval between the Q and T waves in the ECG (corrected for HR)
QTcF	QT interval corrected using Fridericia's formulas
RBC	Red Blood Cells
RV	Residual Volume
SABA	Short-acting β2-agonist
SAMA	Short-acting Muscarinic Antagonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood pPessure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event

TIA	Transient Ischemic Attack
TLC	Total Lung Capacity
VC	Volume Capacity
WBC	White Blood Cells
WOCBP	Women of Childbearing Potential
WONCBP	Women of Non-Childbearing Potential

CONTENT

1. INTRODUCTION

1.1 Background information

Asthma is a serious, sometimes fatal disease affecting people of all ages, characterized by chronic airway inflammation, respiratory symptoms (e.g. wheeze, shortness of breath, cough, chest tightness), and variable expiratory flow limitation, that is completely or partially reversible with treatment [1].

Asthma not only impacts the daily life of the affected individuals, but also the life of their families. The number of disability adjusted life years (DALYs) lost due to asthma amounts to 26.2 million representing about 1% of DALYs lost by any disease and are similar to diabetes or Alzheimer's disease [2]. Recent estimates suggest that about 350 million people suffer from asthma worldwide, of which more than 30 million in Europe, with 0.4 million annual deaths [3, 4].

The goal of asthma management is to achieve and maintain disease control for prolonged periods with regard to good symptom control and prevention of future risk of exacerbations, persistent airflow limitation, asthma-related mortality, and side-effects of treatment [1]. A 5-step approach to the pharmacological treatment of asthma has been established by the Global Initiative for Asthma (GINA) and is widely accepted. Treatment with regular daily dose inhaled corticosteroids (ICS) is highly effective in asthma management, and for many patients the addition of a long-acting β2-agonist (LABA) to ICS has been shown to improve symptom control, lung function and quality of life. A long-term, daily treatment with ICS in combination with LABA is the preferred controller option recommended in GINA for mild to severe asthma. However, for a substantial proportion of patients, asthma remains uncontrolled even with ICS/LABA, and this is a crucial point, as poorly controlled asthma increases the risk of severe asthma exacerbations [5]. With the 2021 revision GINA guideline recommends added treatment "tracks" complementing the 5-step approach to start the therapy. The Track 1 suggests using ICS/Formoterol combinations either as maintenance and as reliver therapy at all steps. The Track 2 allows to use SABA as a reliver complementing appropriate strength of ICS/LABA maintenance treatment. However, GINA recognise the Track 1 as a preferred reasoning it with additional reduction of exacerbations with ICS/Formoterol as a reliver comparing to SABA and improved adherence.

Starting from the 2015 GINA update, an alternative and effective approach was introduced with the addition of a long-acting muscarinic antagonist (LAMA) on top of ICS/LABA at GINA step 4-5, with a different pathway of action. Cholinergic tone is an independent mechanism resulting in contraction of airway smooth muscle and release of mucus from submucosal glands, and muscarinic receptor blockade (M3-receptors) results in bronchodilation [6].
The use of LAMA in asthma is well known, and their efficacy and safety have been supported by several controlled clinical studies [7-15]. They produce a rapid onset of sustained bronchodilation, reduce airways hyperresponsiveness and severe/moderate exacerbations, and increase the time to first severe exacerbation in patients with inadequately controlled asthma [16, 7-8, 17, 18].
Inhaled glycopyrronium bromide (GB) has been found to be an effective LAMA in chronic obstructive pulmonary disease (COPD) [19,20] and has been shown to induce prolonged bronchodilation in patients with asthma and improve asthma control [17, 21-23].

Trimbow is an extrafine fixed dose combination of the ICS beclometasone dipropionate (BDP), the LABA formoterol fumarate (FF) and the LAMA glycopyrronium bromide (GB), developed by Chiesi. The extrafine ICS/LABA combination with BDP and FF has been approved for asthma, in Europe, since 2006 (Foster medium strength: 100/6 µg), and 2015 (Foster high strength: 200/6 µg). Trimbow has been approved by the European Commission in July 2017 for treatment of COPD, and has proven to be effective and safe also in asthma [14]. It was therefore authorized by the European Commission in January 2021 for maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of LABA and ICS (at medium or high dose, for Trimbow medium or high strength, respectively), and who experienced one or more asthma exacerbations in the previous year [24]. Two strengths of Trimbow are currently registered in Europe for asthma, namely 100/6/12.5 µg (medium strength, MS) and 200/6/12.5 µg (high strength, HS), delivered with a single inhaler, with the advantage of reducing the burden of using multiple inhalers that are often of a different type, with different posology, and therefore may impact patient's adherence to their inhaled medication [25].

1.2 Study rationale

According to GINA 2021 recommendations, asthmatic patients not adequately controlled with medium dose of ICS/LABA have the following treatment options:

1. Increase the dose of ICS;
2. add-on treatment with LAMA;
3. add-on treatment with other controllers (e.g. leukotriene receptor antagonists, azithromycin);
4. administration of oral corticosteroids;
5. administration of biologic therapies, if available and appropriate after phenotyping.

Despite being authorized in several markets since 2014 and recommended by GINA since 2015, the use of tiotropium as add-on LAMA is widely variable, reported to be between 13 to 45% of patients with severe asthma uncontrolled on medium-dose or high-dose ICS/LABA [26-28]. This in part may be due to absent availability of other LAMAs, and the need to use multiple inhalers until the recent approval of fixed-dose triple ICS/LABA/LAMA combinations (Trimbow, Enerzair Breezhaler) in Europe in 2020. More importantly, a barrier to appropriate use of add-on LAMA has been the lack of robust evidence to guide the decision of when to adding a LAMA to medium-dose ICS/LABA is preferred overstepping up from medium-dose to high-dose ICS/LABA.

Indeed, it is known that there are asthmatic patients who are low responders to ICS (e.g. "low-Th2 phenotype") [29-32]. These patients are unlikely to experience better disease control following ICS dose step-up and would be unnecessarily exposed to the risk of adverse effects associated with long-term exposure to high-dose ICS [33, 34].

Two pivotal trials evaluated the efficacy and safety of medium-dose BDP/FF/GB vs medium-dose BDP/FF (TRIMARAN) and high-dose BDP/FF/GB vs high-dose BDP/FF (TRIGGER). As the two study populations differed with regards to their prior asthma control medications (medium dose ICS/LABA in TRIMARAN, high-dose ICS/LABA in TRIGGER) a comparison

of the medium-dose BDP/FF/GB to the high-dose BDP/FF was not possible. Moreover, two recently completed large RCTs (CAPTAIN[13], IRIDIUM[15]) that included both a medium-dose ICS/LABA/LAMA and a high-dose ICS/LABA treatment arms failed to provide a conclusive answer to this question as well. In these two RCTs, 33% and 37% of subjects enrolled, respectively, had uncontrolled asthma on prior high-dose ICS/LABA which meant that they experienced a step-down in their ICS dose when randomized to medium-dose triple therapy (TT). In the IRIDIUM study, an evaluation of the results in the subset uncontrolled on prior medium-dose ICS showed that treatment with medium-dose MF/IND/GB resulted in better pre-dose FEV_1 (41 mL) at week 26 with no difference in the annualized rate of moderate-severe asthma exacerbations compared to high-dose MF/IND (RR 1.03), and a comparison in the overall study population between medium-dose MF/IND/GB and high-dose FP/SLM showed a much a large increase in lung function (+99 mL) and lower rate of mod/severe (-19%) and severe exacerbations (-16%). No breakdown of results by prior treatment is available from the CAPTAIN study which evaluated FluF/VIL/UMEC vs FluF/VIL.
There is evidence suggesting that subgroups with persistent airflow limitation (PAL), defined by a post-salbutamol FEV_1/FVC ratio < 0.7, might respond better to LAMAs [35-37], with data suggesting improvements by adding a LAMA on top of medium dose ICS/LABA, compared to stepping up to high dose of ICS, in lung function, exacerbations, emergency department visits and hospitalizations, and use of reliever therapy [15, 36, 38].

However, according to the latest European Respiratory Society/American Thoracic Society guideline on management of severe asthma [39], further studies are needed to confirm these findings and identify additional phenotypes, treatable traits and associated biomarkers that may have a role in driving the best therapeutic choice.

Recently, the EMA evaluation of these three single-inhaler triple therapies (SITT) resulted in the approval of ENERZAIR® Breezhaler® (MF/IND/GB) only at the high-strength, the rejection of TRELEGY® ELLIPTA® (FluF/VIL/UMEC) based on insufficient proof of efficacy, and the approval of TRIMBOW® (BDP/FF/GB) at both medium and high-strength as maintenance treatment for asthma. Therefore, the market availability of the medium-dose BDP/FF/GB as well as the availability of the high-strength FOSTER (BDP/FF) in the same pMDI device provides a unique opportunity to design this study to evaluate, prospectively, the treatment response of adding a LAMA compared to doubling the dose of ICS in patients whose asthma is uncontrolled on medium-dose ICS/LABA and who show persistent airflow limitation post-salbutamol.

The study will compare the efficacy and safety of the fixed-dose triple ICS/LABA/LAMA combination BDP/FF/GB given at a medium ICS total daily dose (BDP/FF/GB 400/24/50 µg) *versus* the fixed-dose ICS/LABA BDP/FF given at a high ICS total daily dose (800/24 µg) for 26 weeks, in subjects with uncontrolled asthma under medium doses of ICS/LABA.

The primary efficacy endpoint is chosen to be the proportion of subjects who on average no longer exhibit persistent airflow limitation (NPAL) over the 26 weeks of the study treatment, and the key-secondary outcome will be the change from baseline in pre-dose morning FEV_1 at week 26. These will be evaluated primarily in the subgroup of subjects who show PAL at screening which will constitute approximately 65% of the overall enrolled population, closely mimicking its prevalence in prior RCTs [35].

The choice of the primary efficacy outcome is supported considering the positive correlation of PAL status with increased risk of asthma exacerbation and with the increased likelihood that patients with PAL would normalize their airflow following LAMA add-on [40,41].

In this study, we elected to apply the definition of PAL provided in the 2021 GOLD Report [42] which specifies a post-bronchodilator FEV_1/FVC ratio cut-off <0.7. We defined PAL status at V1 (screening) as a $FEV_1/FVC < 0.7$ within 30 min post-salbutamol 400 mcg inhalation; and post-randomization as a $FEV_1/FVC < 0.7$ at 2hr post study treatment dose at V2, V3, V4, V5 and V6 to correspond to peak bronchodilator effect. Secondarily, we will evaluate PAL status using $FEV_1/FVC <$ lower limit of normal (LLN) standard since it is helpful to avoid under-diagnosis of abnormalities in younger, taller individuals and over-diagnosis in those older or shorter. We expect the results between the two methods to be concordant [43].

Furthermore, to mitigate the potential variability in PAL status over time, we will measure this parameter at several time points during the 26 weeks of treatment, and we will consider the average of values obtained at all visits. Secondarily, we will also calculate the proportions of subjects who consistently exhibit PAL status on treatment at every visit and those who don't.

Chiesi believes that this study can shed light on the above-mentioned open questions, in a context where the triple therapy (ICS/LABA/LAMA) is being increasingly deployed to treat moderate to severe asthma, and personalized medicine plays an important role in asthma, as new treatable traits are found to be linked to asthma management.

1.3 Risk/benefit assessment

Participants will be treated either with Trimbow MS or Foster HS. Therefore, the baseline treatment of the study population (medium dose of ICS/LABA) will be either stepped up to high doses of ICS/LABA or added with LAMA, as per GINA recommendations in case of uncontrolled asthma at this step.

Foster® HS was licensed and marketed in 2015, but patients have been using it since 2006 at MS for treatment of moderate to severe asthma. Several studies have shown its favorable efficacy and safety profile [44-46] and it is now widely prescribed around the world. Trimbow has been approved in 2017 for COPD, and in 2021 for the target population of this study (asthmatic adult patients) by the European Commission. Therefore, subjects are not exposed to any foreseen risks related to non-marketed medical products.

The exclusion criteria are defined in order to minimize potential risks for the participants (e.g. subjects with a history of "at risk" asthma, recent exacerbations or respiratory tract infections, contraindications to the investigation medical products, any other concurrent uncontrolled diseases). Participants will have regular assessments including safety at the clinical site during the study. The decision to discontinue the subject from further participation to the study will be at the investigator's discretion if deemed necessary due to any reason.
Participants will be informed about the objective, the potential risks and benefits of the study, as per Good Clinical Practice (GCP).

Enrollment in the study will be restricted to patients with a post-BD $FEV_1/FVC \geq 0.5$ because our *post-hoc* analysis of the TRIMARAN data (which recruited subjects with asthma uncontrolled on medium-dose ICS/LABA) indicated that > 90% of the patients enrolled in that RCT fell above this cut-off value and that no subjects with a ratio below 0.5 normalized their airflow on ICS/LABA or ICS/LABA/LAMA therapy.

Chiesi believes that the above reported background information supports the conduct of the proposed study and that the results of this study may help to elucidate further the role of LAMA add-on in the management of asthma. Considering the safety profile of the IMPs and the measures in place to assure the subjects' safety, the overall risk/benefit assessment is considered acceptable for the proposed trial.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) [47], current ICH E6 Good Clinical Practices [48], and all other applicable laws and regulations.

2. STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) compared to high-dose BDP/FF pMDI (200/6 µg, 2 puffs bid) in terms of the proportion of subjects exhibiting on average No Persistent Airflow Limitation (NPAL) over 26 weeks of treatment in the study sub-population with Persistent Airflow Limitation (PAL) at screening.

- A subject is defined as having PAL at screening if their post-bronchodilator (salbutamol) FEV_1/FVC ratio is < 0.7.

- A subject is defined as having NPAL during the treatment period if the mean of their 2h post-dose FEV_1/FVC ratios collected during the 26-week treatment period (i.e. from Week 0 to Week 26) is ≥ 0.7.

The main estimand associated to the primary objective is defined by the following attributes:

Population	Subjects with asthma meeting PAL criterion at screening. Further details about the population are provided in Section 4
Treatments	Randomised treatment (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) including rescue medication and any other asthma treatments that may be administered during the study
Variable	Proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment
Strategy for intercurrent events / events leading to missing data	*Early discontinuation from study treatment*: Missing FEV_1/FVC values (both on-treatment and off-treatment) will be imputed considering "Missing at Random" (MAR) assumption (i.e. targeting a hypothetical strategy)
	Use of not allowed medication and other important protocol deviations: Data will be used regardless of whether or not the

	intercurrent event occurs (i.e. targeting a treatment policy strategy)
	Wrong study drug intake: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy)
Population-level summary	Adjusted odds ratio comparing BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI

2.2 Key Secondary Objective

To demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) compared to high-dose BDP/FF pMDI (200/6 µg, 2 puffs bid) in terms of change from baseline in pre-dose FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening.

The main estimand associated to the key-secondary objective is defined by the following attributes:

Population	Subjects with asthma meeting PAL criterion at screening. Further details about the population are provided in Section 4
Treatments	Randomised treatment (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) including rescue medication and any other asthma treatments that may be administered during the study
Variable	Change from baseline in pre-dose FEV_1 at Week 26
Strategy for intercurrent events / events leading to missing data	*Early discontinuation from study treatment*: Missing FEV_1 values (both on-treatment and off-treatment) will be managed by the mixed model for repeated measures, which relies on MAR assumption for missing data (i.e. targeting a hypothetical strategy)
	Use of not allowed medication and other important protocol deviations: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy)
	Wrong study drug intake: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy)
Population-level summary	Adjusted treatment difference comparing BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI

2.3 Other Secondary Objectives

- To compare the study treatments on other lung function assessments, clinical outcomes, risk of exacerbations in the study sub-population meeting PAL criterion at screening and in the overall study population.

- To assess the safety and tolerability of the study treatments in the study sub-population meeting PAL criterion at screening and in the overall study population.

3. STUDY DESIGN

This is a phase IV, randomized, double-blind, active-controlled, 2-arm parallel group study. Approximately 1400 subjects will be randomized at approximately 200 sites.

The study entails three periods: a run-in period of 2-week duration, a treatment period of 26 weeks duration, and a post-treatment follow-up period of 1 week (see figure 1).

A total of 7 clinic visits (V0 to V6) and one follow-up call will be performed.

- **A pre-screening visit (V0)** will be carried out in order to fully explain the study to potential subjects and to obtain the written informed consent from the subject and instruct the subject on screening visit procedures (such as medication restrictions).
- **A screening visit (V1)** (within 7 days after V0) will help establishing the subjects' eligibility for inclusion in the study. This visit will be followed by a 2-week open-label run-in period during which the subjects will receive BDP/FF 100/6 µg 2 inhalations BID (daily dose 400/24 µg).
- **A randomization visit (V2),** at which eligible subjects will be randomized to one of the 2 treatment groups. All subjects will receive their 1st study drug treatment.
- **After randomization,** subjects will be assessed after 4, 12, 22 and 26 weeks of treatment (visits **V3 to V6 respectively**) at the clinic/hospital.
- **A follow up (FU) call** will take place 1 week after the last study visit (V6 or ETD visit) of the subject to check safety and the subjects' status.

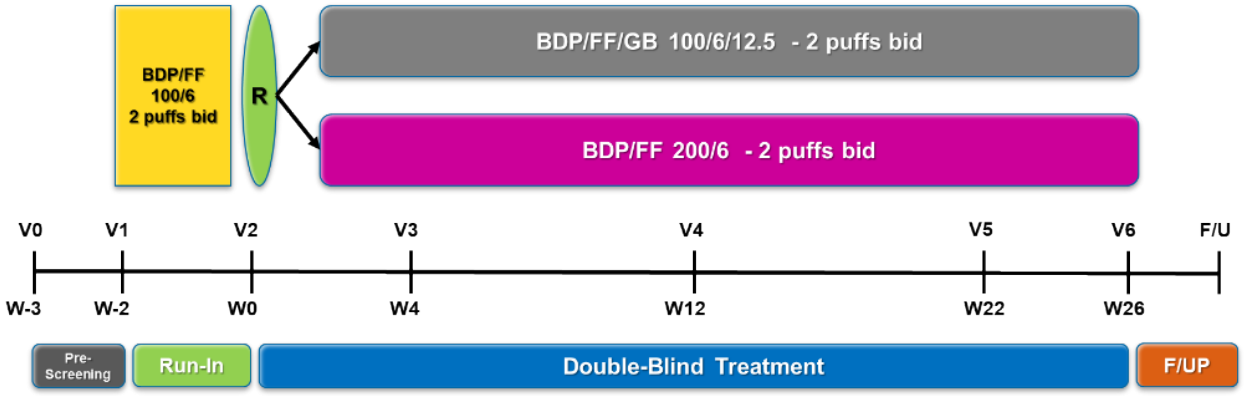


Figure 1: study design

The total study duration (V0 to FU call) is 30 weeks for any subject completing the trial.
The start of the trial is defined as the date of first site initiation visit in the trial.

The end of the study trial is defined as the last contact of the last subject in the trial:
- Last follow-up contact if the last subject in the trial is discontinued from the study;
- Last study visit if the last subject in the trial is discontinued from the treatment and agrees to remain in the study.

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Outpatients attending the hospital clinics/study sites will be recruited.
Approximately 1400 adults (700 subjects per group) (see section 12.1) will be randomised and evaluated for the analysis of primary efficacy endpoint. The end of recruitment will be communicated to study sites by the sponsor (or designee).

If a subject is screen failed, he/she can be reselected at a later stage (at least 4 weeks should elapse from the Screen failure date) providing the medical conditions of the subject are appropriate with the inclusion in the study according to the investigator judgement and after sponsor approval. In case of screen-failure due to exacerbation, 4 weeks should elapse from the end of exacerbation date. In case of rescreening, the subject should sign a new informed consent and will be assigned with a new subject number.

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

4.2 Inclusion Criteria

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

1. **Informed consent:** Subject's written informed consent obtained prior to any study related procedures;

2. **Gender and age:** Male or female subjects aged ≥ 18 and ≤ 75 years;

3. **Diagnosis of asthma:** A documented diagnosis of permanent asthma for at least 1 year according to GINA recommendations (Box 1-2, GINA report 2021) [1], and with diagnosis before the subject's age of 40 years;

4. **Stable asthma therapy:** a stable treatment with medium dose of Inhaled corticosteroids (ICS) (extrafine BDP daily dose > 200 and ≤400 µg or estimated clinically comparable dose, as described in GINA 2021 box 3-6) plus a long-acting ß2-agonist (LABA) (formoterol 24 µg or salmeterol 100 µg or vilanterol 25 µg or other approved dose of LABA as clinically comparable to the others) for at least 4 weeks prior to screening;

Drug*	Medium daily dose (µg)
BDP non extrafine (pMDI, HFA)	> 500-1000 µg
BDP extrafine (pMDI, HFA)	> 200-400 µg
Budesonide (DPI)	> 400-800 µg
Ciclesonide (pMDI, HFA)	> 160-320 µg
Fluticasone furoate (DPI)	100 µg
Fluticasone propionate (DPI)	> 250-500 µg
Fluticasone propionate (pMDI, HFA)	> 250-500 µg
Mometasone furoate (DPI)	200-400 µg
Mometasone furoate (HFA/pMDI)	200-400 µg

*Table adapted from box 3-6 GINA 2021 [1]
BDP = Beclometasone dipropionate; DPI = Dry powder inhaler;
HFA = Hydrofluoroalkane; pMDI = Pressurized metered dose inhaler.

5. **Lung function:** A pre-bronchodilator FEV_1 < 80% of the predicted normal value, after appropriate washout from bronchodilators, at the screening and randomisation visits;

6. **Reversibility of bronchoconstriction:** A demonstrated increase in FEV_1 > 12% *and* > 200 mL over baseline within 30 minutes after inhaling 400 µg of salbutamol pMDI (based on ATS/ERS guidelines);

7. **A Post-bronchodilator FEV_1/FVC ratio ≥ 0.5** within 30 minutes after inhaling 400 µg of salbutamol pMDI at screening (based on ATS/ERS guidelines);

8. **Poor Asthma control:** Evidence of poorly controlled or uncontrolled asthma as based on an Asthma Control Questionnaire© (ACQ-7) score ≥ 1.5 at screening and at randomisation;

9. **History of exacerbations:** A documented history of one or more asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or inpatient hospitalisation in the last 3 years prior to screening;

10. **A cooperative attitude and ability**:
    - to correctly use the pMDI inhalers;
    - to perform all trial related procedures including technically acceptable pulmonary function tests;
    - to correctly use the e-Diary/e-Peak flow meter and home-spirometry device.

11. **Female subjects:**
    a. Woman of Childbearing Potential (WOCBP) fulfilling one of the following criteria:
        i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up call *or*
        ii. WOCBP with non-fertile male partners (contraception is not required in this case).

For the definition of WOCBP and of fertile men and the list of highly effective birth control methods, refer to Appendix 4.

or

b. Female patient of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile, as per definitions given in Appendix 4). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

In case one of the inclusion criteria #5, #6 or #7 (#5: Pre-bronchodilator FEV_1 value, #6: Reversibility threshold, #7: Post-bronchodilator FEV_1/FVC ratio) is not met at screening, they can be repeated together with ACQ-7 (inclusion criterion #8) once, no later than 5 days before randomisation.

Inclusion criteria #5 (Lung function), #8 (Poor Asthma control) and #10 (Co-operative attitude and ability) should be re-checked at the randomisation visit.

4.3 Exclusion Criteria

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

1. **Pregnant or lactating woman** where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive pregnancy test (serum pregnancy test to be performed at screening visit and urine pregnancy test to be performed prior to randomisation);

2. **Run-in compliance** to study drug and e-Diary completion< 50% at randomisation;

3. **History of "at risk" asthma:** 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 subject at undue risk;

4. **Recent exacerbation:** 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;

   Note: Subjects experiencing an exacerbation during the run-in period may be re-screened once, at least 4 weeks after recovery.

5. **Non-permanent asthma:** exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine;

6. Subjects using **systemic corticosteroid** medication in the 4 weeks or slow release corticosteroids in the 12 weeks, prior to screening;

7. **Asthma requiring use of biologics:** Subjects receiving asthma treatment with an injectable biologic drug such as monoclonal antibodies;

8. **Respiratory disorders other than asthma:** Subjects with known respiratory disorders other than asthma. This can include but is not limited to: diagnosis of COPD as defined by the current guidelines (e.g. GOLD Report), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;

9. **Lung cancer or history of lung cancer**: Subjects with an active diagnosis of lung cancer or a history of lung cancer;

10. **Lung resection**: Subjects with a history of lung volume resection;

11. **Respiratory tract infection**: subjects with respiratory tract infection within 4 weeks prior to screening or during the run-in period;

    Note: Subjects experiencing a respiratory tract infection during the run-in period may be re-screened once, at least 4 weeks after recovery.

12. **Smoking status:** Current smokers, or ex-smokers with total cumulative exposure equal or more than 10 pack-years; (pack-years = the number of cigarette packs per day times the number of years). Ex- smokers must have stopped smoking for ≥1 year (≥ 6 months for e-cigarettes).

13. **Cancer or history of cancer (other than lung):** Subjects with active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g. basal cell carcinoma, in situ carcinoma of the cervix adequately treated, …) is acceptable;

14. **Cardiovascular diseases:** Subjects who have clinically significant (CS) cardiovascular condition according to Investigator's judgement, such as but not limited to: congestive heart failure (NYHA class IV), unstable or acute ischaemic heart disease in the last year prior to screening, history of sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months prior to screening (sustained meant lasting more than 30 seconds or ending only with external action, or led to haemodynamic collapse; non-sustained meant > 3 beats < 30 seconds, and or ending spontaneously, and or asymptomatic), high degree impulse conduction blocks (> 2nd degree atrioventricular block type 2), persistent, long standing or paroxysmal atrial fibrillation (AF);

    Note: Subjects with permanent AF (for at least 6 months prior screening) 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 enrolment;

15. **ECG criteria:** Any abnormal and CS 12-lead ECG that in the investigator's opinion would affect efficacy or safety evaluation or place the subjects at risk.

16. **ECG QTcF:** Male subjects with a Fridericia's corrected QT interval (QTcF) >450 msec and female subjects with a QTcF >470 msec at screening are not eligible (not applicable for subjects with permanent atrial fibrillation and for subjects with pacemaker);

17. Subjects 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 subjects who are stable under treatment can be considered for inclusion.

18. **CNS disorders:** Subjects with a history of symptoms or significant neurological disease such as but not limited to transient ischemic attack (TIA), stroke, seizure disorder or behavioural disturbances according to the investigator's opinion;

19. **Other medical conditions**: Subjects with other severe acute or chronic medical or malignancy or psychiatric condition or clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease, that might in the judgment of the Investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study;

20. **Other concurrent diseases:** Subjects with historical or current evidence of uncontrolled concurrent disease such as but not limited to hyperthyroidism, diabetes mellitus or other endocrine disease; haematological disease; autoimmune disorders (e.g. rheumatoid arthritis), gastrointestinal disorders (e..; poorly controlled peptic ulcer, GERD), significant renal and hepatic impairment or other disease or condition that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study;

21. **Liver diseases:** Subjects with severe hepatitis, chronic active hepatitis or evidence of uncontrolled chronic liver disease according to the investigator's opinion;

22. **Vaccination:** Subjects who receive a vaccination within 2 weeks prior to screening or during the run-in;

23. Subjects mentally or legally incapacitated, or subjects accommodated in an establishment as a result of an official or judicial order;

24. **Contra-indications to IMPs**: Contra-indications to IMPs constitute an exclusion criterion. For warnings, eligibility will be judged by the investigator;

25. **Alcohol/drug abuse:** Subjects with a history of alcohol or drug abuse within two years prior to the start of the study;

26. **Hypersensitivity:** Subjects with known intolerance/hypersensitivity or contraindication to treatment with $ß_2$-agonists, ICS, anticholinergics or propellant gases/excipients. For warnings/precaution for use, eligibility will be judged by the investigator;

27. **Surgery:** Subjects with major surgery in the 3 months prior to screening visit or planned surgery during the trial;

28. **Subjects treated** with non-potassium sparing diuretics (unless administered as a fixed dose combination (FDC) with a potassium conserving drug or changed to potassium

sparing before the screening), nonselective beta blocking drugs, quinidine, quinidine like anti-arrhythmics, or any medication with a corrected QT interval (QTc) prolongation potential or a history of QTc prolongation;

29. Subjects treated with **monoamine oxidase inhibitors** (MAOIs) and tricyclic anti-depressants;

30. Subjects receiving any therapy that could interfere with the study drugs according to Investigator's opinion;

31. **Participation to investigational trial:** Subjects who have received an investigational drug within 2 months or six half-lives (whichever is greater) prior to screening visit, or have been previously randomised in this trial, or are currently participating in another clinical trial;

32. Documented **COVID-19 diagnosis or its complication** which has not resolved within 14 days prior to screening.

Exclusion criterion #2 (Run-in compliance) will be checked only at randomisation visit.

Exclusion criteria #1 (Pregnancy/contraception), #4 (Recent exacerbation), #11 (Respiratory tract infection), #19 (Other medical conditions), #21 (Liver diseases), #22 (Vaccination), #27 (Surgery,) #30 (Any therapy) will be re-checked at randomisation visit.

4.4 Discontinuation from study treatment

Subject who discontinues study treatment **should not be considered automatically withdrawn from the study** (except if the reason is consent withdrawal or lost to follow up). The investigator and study staff must discuss with the subject who will be asked to continue attending the remaining study visits while off investigational treatment.

Protocol Defined Criteria for Discontinuation from Study Treatment:
Occurrence or initiation of an adverse event, concomitant medication, or other event at the investigator's discretion, for which remaining on study drug would create a **safety risk** for the subject. Any of the criteria listed in protocol section 4.5 may lead to discontinuation from study treatment.

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 treatment, all efforts will be made to complete and report the observations as thoroughly as possible.

An **asthma exacerbation is not a reason to withdraw the subject from the study treatment**.
It will be the Investigator judgement to withdraw or not the subject from the study treatment if he/she deems it will place the subject at undue risk by continuing their participation.

Actions following Permanent Discontinuation from Study treatment (see Figure 2):

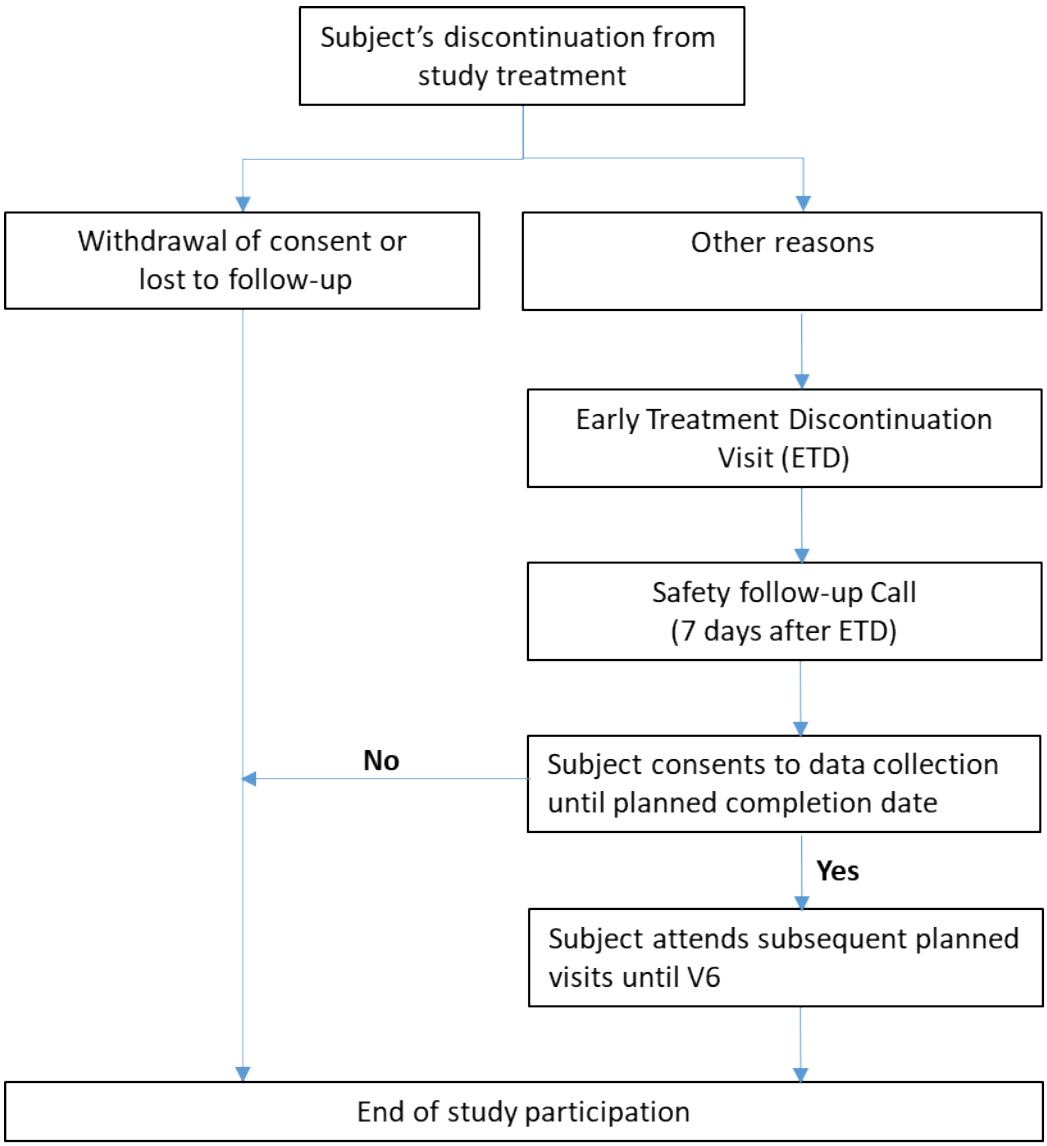


Figure 2: Subject's discontinuation from treatment scheme

The subject should return to the clinic as soon as possible for an Early Treatment Discontinuation Visit (ETD).
The investigator is responsible for the optimal individual treatment prescription after the study treatment discontinuation. The post treatment asthma medications should be recorded in the eCRF.

The investigator must contact the IRT to register the subject's **Early Treatment Discontinuation**. The Investigator must report in the eCRF the main reason for Early treatment discontinuation.

The safety follow-up call must be done one week after the Early Treatment Discontinuation Visit, except for the subject who withdraws consent or is lost to follow-up.

Subject who consent to data collection till the planned V6 will continue attending study visits according to the study visit schedule. Before each post-treatment visits the wash-out periods for concomitant medications detailed in section 5.2 must be respected. The following assessments will be performed:

- Spirometry (pre- and post- the intake of subject's maintenance inhaled therapy for asthma);
- FeNo;
- oscillometry measurements (pre- and post- the intake of subject's maintenance inhaled therapy for asthma);
- The subject should continue to complete e-diary data / home-PEF / home spirometry;
- The investigator (or designee) will check the concomitant medications, surgeries, procedures, adverse events and asthma exacerbations that occurred since last visit;
- Urine pregnancy tests in all women of childbearing potential;
- Health economic information collection;
- Questionnaires.

For safety purposes, it must be emphasized that after a subject withdraws from the trial, the investigator is still responsible for reporting Serious Adverse Events, if he/she becomes aware of them.

4.5 Discontinuation from study

Subject must be discontinued from the study for any of the following reasons:

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

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. Every effort will be made to retain the subject in the study.

An **asthma exacerbation is not a reason to withdraw the subject from the study**. It will be up to the Investigator's judgement to withdraw or not the subject from the study if he/she deems it will place the subject at undue risk by continuing their participation.

Subjects who wish to withdraw from further participation in the study should return to the clinic as soon as possible to perform pre-dose assessments planned at the completion visit (sections 7.1.7 and 7.1.8). If a subject is lost to follow-up or after the subject withdraws consent, no further information will be collected.
The safety follow-up call must be done one week after the Early Treatment Discontinuation Visit.
The investigator must document the reason (if specified by the subject) for withdrawal of consent in the eCRF.

The investigator must register the subject's status in IRT and must also fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal.

The investigator is responsible for the optimal individual treatment prescription after the study discontinuation. The post treatment asthma medications should be recorded in the eCRF.
If a subject is withdrawn/dropped-out of the study, the subject number should not be reassigned to another subject.
For safety purposes, it must be emphasized that after a subject withdraws from the trial, the investigator is still responsible for reporting Serious Adverse Events, if he/she becomes aware of them.

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

- 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 subject needs rescue medication within this time window, the visit must be postponed.

- Short courses (≤ 14 days each) of systemic corticosteroid and/or brief uses of nebulized treatment containing β2-agonists and/or corticosteroids, and/or antibiotics therapy for asthma exacerbation.

- Antihistamines (oral, ocular, intranasal) and intranasal corticosteroids for the treatment of allergy or rhinoconjunctivitis symptoms.

- Allergen immunotherapy for the treatment of respiratory allergy, if already started before the study

- Appropriate treatment for concomitant diseases, seasonal influenza and SARS-CoV-2 vaccination (1 week should elapse from vaccination and the post-randomisation study visits) 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 concomitant medications".

5.2 Non-permitted concomitant Medications

- Inhaled corticosteroids other than the study drugs.
- Inhaled LABA other than the study drugs.
- Inhaled fixed or free combinations ICS/LABAs (e.g. Seretide®, Symbicort®) or ICS/LABA/LAMA other than the study drugs.
- Inhaled Short-Acting Muscarinic Antagonists (SAMAs).
- Any other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers).
- Theophylline.
- Systemic anticholinergics.
- Systemic corticosteroids (see exception above)
- Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs).
- Non-selective ß-blocking drugs (including eye drops).
- Quinidine and Quinidine-like anti arrhythmics.
- Monoclonal antibodies (e.g. anti-IgE or anti-IgG antibodies) or biological drugs used for the treatment of respiratory conditions, and for any other condition if impact on respiratory outcomes cannot be excluded, for more than 7 months prior to screening.
- 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	6h
Inhaled/nebulized SAMA	12h
Inhaled/nebulized of SABA/SAMA (fixed combination)	12h
Inhaled LABA for BID administration	24h
Inhaled LABA for once daily administration (e.g. indacaterol)	36h

Inhaled ICS/LABA (free or fixed combination) for BID administration	24h
Inhaled ICS/LABA (fixed combination) for once daily administration	36h
Inhaled ICS/LABA+LAMA (free or fixed combination)	4 weeks
ICS	12h
Theophylline and leukotriene Receptor Antagonist	72h

Prior to each spirometry including serial spirometry, the following wash out periods for concomitant medications must be respected:

Inhaled/nebulized SABA	6h
Study treatment	Not to be taken the morning of the visit

Prior to each post-treatment visit, the following wash-out periods for concomitant medications must be respected:

Inhaled/nebulized SABA	6h
Inhaled/nebulized SAMA	12h
Inhaled/nebulized of SABA/SAMA (fixed combination)	12h
Inhaled LABA for BID administration	24h
Inhaled LABA for once daily administration (e.g. indacaterol)	36h
Inhaled ICS/LABA (free or fixed combination) for BID administration	24h
Inhaled ICS/LABA (fixed combination) for once daily administration	36h
Inhaled ICS/LABA+LAMA (free or fixed combination)	24h
ICS	12h
Theophylline and leukotriene Receptor Antagonist	72h

6. TREATMENT(S)

The study medications (randomized treatment, training medication and run-in 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.
The Sponsor will also provide spacer devices (AeroChamber Plus Flow Vu Antistatic™).

6.1 Appearance and Content

Both Test Treatment and Reference Treatment are administered via double-blinded pMDIs while Training and Run-in are administered via open label pMDIs.

- ***CHF 5993 pMDI 100/6/12.5 µg (Test Treatment A)***

  Active ingredients: *Beclometasone dipropionate/Formoterol fumarate/ Glycopyrronium bromide 100/6/12.5 µg per metered dose*

Excipients: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
Presentation: Each canister contains 120 doses
Appearance: Aluminum canister + grey dose counter actuator

- ***CHF 1535 pMDI 200/6 µg (Reference Treatment B)***

Active ingredients *Beclometasone dipropionate/Formoterol fumarate 200/6 µg per metered dose*
Excipients: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
Presentation: Each canister contains 120 doses
Appearance: Aluminum canister + grey dose counter actuator

- ***CHF 1535 pMDI 100/6 µg (Run-in)***

Active ingredients *Beclometasone dipropionate/Formoterol fumarate 100/6 µg per metered dose*
Excipients: HFA-134a propellant, ethanol anhydrous, hydrochloric acid
Presentation: Each canister contains 120 doses
Appearance: Aluminum canister + pink dose counter actuator

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

Active ingredients: None
Excipients: HFA-134a propellant, ethanol anhydrous
Presentation: Each canister contains 120 doses
Appearance: Aluminum canister + grey dose counter actuator

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

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

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

The selection of the dose for CHF 5993 100/6/12.5 µg and CHF 1535 200/6 µg is based on the marketed dose of Trimbow® (BDP/FF/GB 100/6/12.5 µg) and Foster® (BDP/FF 200/6 µg) pMDI for asthma. Treatment will be used according to their Summary of Product Characteristics.

6.2.2 Dosage

6.2.2.1 Run-in period

- **CHF 1535 pMDI 100/6 µg:** 2 inhalations BID (daily dose 400 /24 µg)

6.2.2.2 Randomised Treatment period

According to the allocation based on the randomization list, eligible subjects will self-administer one of the following study drugs for a treatment period of 26 weeks:

- **Treatment A: CHF 5993 100/6/12.5µg:** 2 inhalations bid: 4 inhalations; total daily dose of BDP/FF/GB: 400/24/50µg

- **Treatment B: CHF 1535 200/6µg:** 2 inhalations bid: 4 inhalations; total daily dose of BDP/FF: 800/24µg

6.2.3 Administration

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

6.2.3.1 Priming of the pMDI inhalers and inhalation

Before using the pMDI inhaler for the first time, one inhalation must be released into the air after removing the protection cap.
Subjects will be instructed to perform priming of inhalers as reported in the packaging instruction leaflet. Additional information regarding instructions for use of the study drug and inhalers will be provided to sites/subjects in the packaging instruction leaflet.

6.2.3.2 Run-in kits

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

At screening visit (V1), the Investigator/designee, will contact the Interactive Response Technology (IRT) system to dispense to each subject 1 run-in kit of CHF 1535 100/6 µg, **to be taken with 2 inhalations BID,** in replacement of the subject's current asthma therapy**.**
Note: the first dose of run-in medication must be administered at clinic at the end of Visit 1 (the run-in kit should be dispensed at V1 even if the reversibility test needs to be re-performed before the randomisation).

The run-in drug will be administered BID (in the morning and in the evening) from the same inhaler:

- **Morning administration (preferably between 6 am and 10 am):**
  - 2 inhalations from pMDI inhaler

- **Evening administration (preferably between 6 pm and 10 pm):**
  - 2 inhalations from pMDI inhaler

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

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

On the morning of the randomization visit (V2), eligible subjects will be instructed to refrain from taking the Run-in medication.

6.2.3.3 Study treatment kits

At randomization visit (V2) after the confirmation of eligibility, the subject will be randomized to one of the double-blind study drugs. The investigator or designee will use the IRT system to allocate the treatment kit which will cover the period between each visit.

From Visit 2 to Visit 5 each subject will receive:

- One box containing 3 pMDI inhalers (3 CHF 5993 pMDI or 3 CHF 1535 pMDI)

Each canister will be numbered (canister number 1, canister number 2, canister number 3). Subject will be instructed to take the medication starting with the inhaler labelled number 1 and to use the inhaler labelled number 2 when the dose counter of inhaler 1 shows the number 0 as reported in the package instruction leaflet. At the same way the subject will be instructed to use the inhaler labelled number 3 (if needed) when the dose counter of inhaler 2 shows the number 0.

The study drug will be administered BID (in the morning and in the evening) from the same inhaler:

- **Morning administration (preferably between 6 am and 10 am):**
  - 2 inhalations from pMDI inhaler
- **Evening administration (preferably between 6 pm and 10 pm):**
  - 2 inhalations from pMDI inhaler

To the extent possible, the time of dosing must remain constant for each subject for the whole duration of the study.
The first morning dose from inhaler 1 of each newly assigned kit of study drug will take place at clinical site under the supervision of the Investigator/designee.
Note: At the time of drug intake at site, the study drug, stored between 2°C and 8°C, should be removed from the refrigerator and the canister should be taken out of the mouthpiece and warmed with the hands for few minutes before administration to the subject. The canister should never be warmed by artificial means. **The subject should never inhale a cold medication (**see section 6.8 for storage conditions).

The priming of the inhaler number "1" will be performed at clinical site by Investigator/designee while for inhaler number "2" and "3" and the subjects will be instructed to perform the priming at home prior to start the administration with the new inhaler.

On study visit days, study drug should not be taken before coming to the clinical site.
Administration will be done according to the package instruction leaflets in local languages included with the study drug.

6.2.3.4 Use of AeroChamber Plus™

Subjects used to inhale their pMDI medications with a spacer device and subjects who require a spacer device to properly use the pMDI, will be issued a spacer to use with the study drug during both the run-in and randomized treatment periods.
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 subjects, **each inhalation** (for the run-in and randomisation periods) **must be performed via AeroChamber Plus™. For each puff, the subject must inhale slowly and deeply and** hold his breath as long as possible.
One spacer will be assigned to the subject by the Investigator/designee at screening (V1), and at randomisation (V2).

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

From Visit 1, the spacer must be washed every week until the end of the study, including the night before V2 after the evening dose.
For more details concerning the use of the spacer, please refer to the packaging instruction leaflet.

6.2.3.5 Rescue Medication

The rescue medication (salbutamol 100 µg/puff) must be used only for the relief of breakthrough asthma symptoms. **The maximum dose allowed is 8 puffs per day. In case the** subjects**' 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 (V1), the Investigator/designee will contact the IRT system to allocate a training kit to each subject.
At screening (V1) and at randomization visit (V2), the correct use of the pMDI inhalers (according to the product leaflets provided by Chiesi) will be explained to the subjects and they will be trained by using training inhalers identical to the devices used for the administration of the study drug containing placebo. The investigator/designee should make sure the subject is properly using their study drug inhaler at each clinic visit. Additional re-training should be done if needed.

The training kit will be kept at the site by the investigator (will not be dispensed to the subjects) and they will be used again if needed in order to check again the proper use of the inhaler.

Subjects used to inhale their pMDI medications with a spacer device and subjects who require a spacer device to properly use the pMDI,will be trained on the use of pMDI with the Aerochamber Plus™ spacer.

At screening visit (V1) and at randomization visits (V2), the subject will be trained with the same Aerochamber Plus™ dispensed at V1.
For more details concerning the use of the pMDI with spacer and the Aerochamber Plus™, please refer to the corresponding subject leaflets.

6.3 Packaging

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

6.3.1 Treatment Kit

One box will contain 3 pMDI inhalers of CHF 5993 100/6/12.5 µg pMDI **or** CHF 1535 200/6 µg pMDI. The 3 inhalers will be labeled respectively with a "1" sticker, a "2" sticker and a "3" sticker identifying the sequence for use.

- *Primary packaging:* 3 labelled canisters (with study label in English only) and 1 labelled dose counter actuator (with study multi language label). The tree inhalers will be numbered 1, 2 and 3.

- *Secondary packaging:* 1 carton box labelled (with study multi language label) with a tear/peel off portion plus instruction for use (multi language)

6.3.2 Training Kit

One box will contain 1 CHF 5993 placebo pMDI.

- *Primary packaging*: 1 labelled canister (with a study label in English only) plus 1 labelled dose counter actuator (with a study label in English only)

- *Secondary packaging:* 1 carton box (with a study label in English only) with a tear/peel off portion.

6.3.3 Run-in Kit

One box will contain 1 CHF 1535 100/6 µg pMDI.

- *Primary packaging*: 1 labelled canister (with a study label in English only) canister plus 1 labelled dose counter actuator (with a study multilanguage label)

- *Secondary packaging:* 1 carton box labelled (with a study multi language label) with a tear/peel off portion plus instruction for use (multi language)

6.3.4 AeroChamber Plus™ Spacer

- *Primary packaging:* Spacer AeroChamber Plus™ Flow-Vu antistatic VHC.

- *Secondary packaging:* 1 box containing 1 spacer AeroChamber Plus™ Flow-Vu antistatic VHC with a tear/peel off portion plus instruction for use (multi language)

6.4 Labeling

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

For all the labels, the subject 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.

6.5 Treatment allocation

A balanced block stratified randomisation scheme will be prepared via a computerized system. Randomisation list will be stratified by region (i.e. *"Eastern Europe"*, *"Western Europe"*), persistent airflow limitation status at screening post-salbutamol (i.e. *"PAL"* including 65% of the randomized patients, *"NPAL"* including 35% of the randomized patients) and age group (i.e. *"<50"*, *"≥50"*)

The region *"Eastern Europe"* will include the following countries: Bulgaria, Finland, Greece, Latvia, Poland, Sweden.
The region *"Western Europe"* will include the following countries: Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Slovakia, Spain, UK.
Subject will be centrally assigned to one of the two treatment arms with a 1:1 ratio.
An Interactive Response Technology (IRT) system will be used at each visit (from pre-screening to follow-up call) to record subject status.

After the treatment allocation, for each stratum defined by the randomisation list, a subset of 50% of the patients will be randomly selected to be part of the group for which home spirometry will be additionally QC'ed using automatic algorithms.

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

Subject numbers will consist of a 9 digit-number:

- the 6 first digits correspond to the centre number (first 3 digits for the country number corresponding to the ISO country codes and 3 last progressives 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 subjects and assign treatment kits according to the sequence described in the randomisation list. The IRT will track also subject screen failures and discontinuations from the treatment and 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 subject 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 labeling 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, where he/she considers essential to know what treatment the subject was taking, unblinding of the treatment code will be done through IRT and the treatment group will be disclosed. 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, including unblinding. The IRT will also promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.
Users from Chiesi Global Pharmacovigilance will have their own credentials to unblind subjects 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 on the e-Diary as well as the information recorded in the eCRF during the treatment visits.

The evaluation of compliance will be done using the following formula:

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

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each subject. A range of 65-135 % will be taken into account for a satisfactory level of compliance, while a level of compliance equal or superior to 50 % will be considered as satisfactory for the run-in medication.

To optimize subjects' compliance to study medication, a compliance check using metrics will be periodically reviewed.

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.
Handling of the study drugs must be according to the package instruction leaflets. A package leaflet will be included in each kit in local languages.

- **Run-in and randomized treatments kits (*CHF 5993 pMDI and CHF 1535 pMDI)***

Treatment kits must be stored between 2˚C (36˚F) and 8˚C (46˚F) by pharmacist/investigator at the Hospital Pharmacy or clinical site.
At the clinic visit, the kit to be dispensed must be removed from the refrigerator before priming and administration.
Once dispensed, the subjects will be instructed to keep the box at ambient temperature not above 25°C (77 ˚F).
At this temperature condition the residual shelf life of the pMDI kits will be three months (**90 days**).
Therefore, **the pharmacist/investigator must write the use-by-date on the labels of each pMDI** once the kit is removed from the refrigerator, before assigning it to the subject.
The **use-by-date corresponds to the dispensing date plus three months (90 days).** Please note that the use-by-date must not exceed the total shelf life of the product.

- **Training Kits (*CHF 5993 pMDI placebo)***

Training kits must be kept on site and **not** dispensed to the subjects. Training kits must be stored between 2˚C (36 ˚F) and 8˚C (46 ˚F) by pharmacist/investigator at the Hospital and they must be removed from the refrigerator before priming and administration.
Once used, the training pMDI must be kept at the site at ambient temperature not above 25°C (77 ˚F), and outside the refrigerator.
At this temperature condition the residual shelf life of the training pMDI will be four months (**120 days**).
Therefore, **the pharmacist/investigator at the Hospital or study site must write the use-by-date on the kit labels** once the pMDI is removed from the refrigerator, before using it. The **use-by-date corresponds to the dispensing date plus 4 months.**
Please note that the use-by-date must not exceed the total shelf life of the product. Subjects will use the same training kit at screening (V1) and randomization visits (V2).

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

The site must check the Min/Max temperatures once daily for adequate storage of refrigerated and ambient kits. Automated recorders may allow skipping daily records during weekends of bank holidays for no longer than 3 consecutive days. The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation from the requirement for storage will be promptly reported and Chiesi shall assess if the affected study drug can still be used.

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 the designated distributor center to be destroyed centrally. Return and destruction of kits will be done only after full investigational product reconciliation and accountability are completed and after Chiesi's approval.

6.10 Provision of additional care

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

7. STUDY PLAN

7.1 Study Schedule

The study entails four periods: a 1-week pre-screening phase, a 2 weeks run-in period, a 26-weeks treatment period, and a 1-week follow-up period.

A total of 7 visits (V0 to V6 at clinic, plus a follow-up phone call) will be performed during the study.

The visits shall be performed with appropriate wash-out of medications as described in section 5.2. In case the wash-out of medications is not respected:

- At Visit 1, 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 subjects will be screen failed;
- At 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 subjects will be screen failed;
- From Visit 3 to Visit 6, the visit will be rescheduled within 2 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 if needed. The relevant information will be collected in the eCRF.
- At Visit 1, in case the pre salbutamol FEV_1 is $\geq$ 80% or the reversibility test is negative or the FEV1/FVC ratio is < 0.5, or the pre/post salbutamol spirometry tests have not acceptable blows/quality, the test can be repeated once before randomisation visit (no less than 5 days before the visit), after an appropriate wash-out from rescue medication and run-in medication, together with the ACQ-7. The relevant information will be collected in the eCRF.

The study plan and scheduled tests are summarised in the following flow-chart (table 1):

	Pre-screening	Screening	Treatment Period					FU
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6/ETD***	
Time (Wks)	**-3**	**-2**	**0**	**4**	**12**	**22**	**26**	**27**
Windows (Days)			**+ 2d**	**+ 3d**	**+ 3d**	**+ 3d**	**+ 3d**	
Informed consent procedures	**X**							
Demographic data collection	**X**							
Inclusion/Exclusion criteria		**X**	**X**					
Medical history/Previous medications/smoking history		**X**						
Concomitant medications/procedures		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events/Asthma exacerbation assessments		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination		**X**					**X**	
Weight and Height		**X**						
ACQ-7 questionnaire		**X**	**X**		**X**		**X**	
AQLQ			**X**		**X**		**X**	
Health Economics information			**X**	**X**	**X**	**X**	**X**	
Vital signs (BP) pre-salbutamol/ pre-dose [1]		**X**					**X**	
12-lead ECG (single) pre-salbutamol/pre-dose [2]		**X**						
FeNO pre-dose			**X**				**X**	
Oscillometry pre-dose/post-dose[3]			**X**	**X**	**X**	**X**	**X**	
Pre-salbutamol/dose spirometry [4]		**X**	**X**	**X**	**X**	**X**	**X**	
Reversibility testing [5]		**X**						
Post-dose spirometry (2 hours) [6]			**X**	**X**	**X**	**X**	**X**	
Haematology and blood chemistry		**X**	**X** [7]				**X** [7]	
Total serum IgE			**X**					
Biobanking			**X**				**X**	
Serum and urinary pregnancy test [8]		**X**	**X**	**X**	**X**	**X**	**X**	
Home Spirometry pre-dose /2 hours post-dose		**X (once weekly in the morning)**						
Home PEF (pre-dose)		**X (daily am/pm)**						
e-Diary completion (asthma symptoms, treatment compliance, rescue intake)		**X (daily am/pm)**						
e-Diary review [9]			**X**	**X**	**X**	**X**	**X**	
Training [10] -to the use of inhaler device/e-Diary/e-peak flow/home spirometry -on recognition of a developing asthma exacerbation		**X**	**X**					
IRT	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Run-in dispensation (D) /Collection (C)		**D**	**C**					
Study treatment dispensation (D) /Collection (C)			**D**	**D/C**	**D/C**	**D/C**	**C**	
Spacer dispensation (D) /Collection (C) [11]		**D**	**D**				**C**	

Table 1: flow chart of the study

*ETD = Early treatment discontinuation

1. SBP and DBP after 10 minutes rest in sitting position.
2. Single 12-lead ECG (local ECG) after 10 minutes rest in sitting position.
3. Oscillometry to be performed at the following timepoints: pre-dose (before spirometry) and 2 hours post-dose (before spirometry).
4. Lung function tests: pre-salbutamol at V1, pre-dose at -45 minutes and -15 minutes at the other visits.

5. Reversibility within 30 minutes after 4x100 µg of inhaled salbutamol at V1.
6. Lung function tests: 2hrs post-dose from V2 to V6.
7. Only WBC differential for EOS evaluation will be collected at V2 and V6.
8. Serum pregnancy test at V1. Urinary pregnancy test from V1 to V6/ETD (or monthly if required by local regulations)
9. e-Diary review: by the Investigator and/or designee at each visit and in case of e-Diary alert. Phone call(s) to the subject to be done in case of bad compliance and/or asthma control worsening.
10. Training for pMDI (and for spacer in the subjects who used it). Re-training could be done during the study if needed.
11. Spacer (AeroChamber Plus Flow Vu Antistatic™) only dispensed for subject who currently are using a spacer or who require a spacer for proper pMDI use.

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 subjects.

Informed Consent Form (ICF): The investigator or his/her designee will explain the study to the subject and written informed consent will be obtained from the subject. 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.

The following procedures will take place:

- **Demographic data:** Recording of demographic data including gender, race (for spirometry purpose), date of birth (real or dummy depending on country privacy restrictions) and childbearing potential status (for female only).

- Instructions will be given to the subject 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 subject 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 8 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 subject number. This number will be sequentially assigned.

- **An appointment for Visit 1** will be made within 1 week (maximum) in the morning.

Before discharge:

- **A subject card** with the Investigator's contact details will be handed out to the subject.

- **Subjects will be instructed:**
  - To fast overnight (at least 8 hours) before the next visit in order to perform blood sampling (only water is allowed);
  - To respect the wash-out period of non-permitted medications prior to the screening visit as mentioned in section 5.2.

7.1.2 Visit 1 – Screening visit

A screening visit will be carried out in order to identify eligible consenting subjects for the study.

If any of the wash-out for asthma medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 2 days. Only one re-schedule is allowed. If wash-out is still not respected in the morning of the re-scheduled visit, the subjects will be recorded in the IRT as screening failure.

The following procedure will take place:

- **Medical History:** The medical history including asthma history.
- **Smoking history:** smoking status with all the data needed to calculate the pack year will be recorded in eCRF.
- **Previous and concomitant medication:** all medications taken by the subjects in the last 3 months will be recorded in the eCRF. Intake of non-permitted medication constitutes non-eligibility criterion for enrolment in the study.
- **Adverse Events (AEs):** The occurrence of any AE between informed consent signature and screening visit will be checked. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the subjects' medical history in the eCRF, unless its onset 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 AE in the eCRF.
- **Asthma Exacerbation history**: The subjects' history of asthma exacerbations will be assessed (see section 7.2.13), the stop date of the last exacerbation recorded.

  The subjects are eligible if there is documentation in subjects' records of at least one exacerbation in the last 3 years prior to screening (inclusion criterion #9). Eligible subjects should remain free of exacerbation requiring systemic steroids within 4 weeks prior to screening.

  Subjects experiencing an exacerbation during the screening visit should be screened failed as such exacerbation constitutes an exclusion criterion (exclusion criteria #4).
  The screening failure shall be recorded in the IRT system. The subjects may be re-screened once, 4 weeks after exacerbation recovery.
- **ACQ-7:** subjects will complete the ACQ-7 questionnaire (see section 7.2.1).
  Eligible subjects must have a score ≥1.5 (inclusion criterion #8).
- A full **physical examination** including body weight, height and body temperature assessments will be performed.
- **Vital Signs:** Pre-bronchodilator vital signs will be recorded (pulse rate, systolic [SBP] and diastolic [DBP] blood pressure, after 10 minutes of rest, in sitting position) (section 7.2.4).

- **12-Lead ECG:** Single pre-bronchodilator 12-lead ECG will be recorded after at least 10 minutes of rest (section 7.2.5).

  Eligible subjects must have a mean QTcF ≤450 msec (males) and ≤470 msec (female). (criterion not applicable for subjects with pacemaker or permanent atrial fibrillation) (exclusion criterion #14).

- **Blood samples:** A blood sample will be collected before salbutamol administration and after an overnight fasting for the assessments of
  - 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 central laboratory will analyse the samples and provide the subjects' reports to the site. In case of non-interpretable data, another determination must be performed as soon as possible and prior to Visit 2 (randomisation visit).

- A **urine pregnancy test** will be performed in women of childbearing potential. This test will allow confirmation that the woman tested is not pregnant before the serum pregnancy test results are made available by the central laboratory.

- **Pre-bronchodilator spirometry** will be carried out: the subjects will have to perform a SVC manoeuvre to assess pre-dose inspiratory capacity (IC) followed by a FVC manoeuvre for other pre-dose parameters (FEV_1, FVC and FEV_1/FVC) (section 7.2.9).

- **Salbutamol intake:** Subjects will inhale 4 puffs (4 × 100 µg) of salbutamol. Time will be recorded in eCRF.

- **Post-bronchodilator spirometry** (FVC manoeuvre) will be carried out from **10-15 min** up to 30 minutes after the inhalation of 400 µg of salbutamol to assess FEV_1, FVC and confirm eligibility.

  To be eligible, subjects must have:

  - *A prebronchodilator FEV_1 < 80% of the predicted normal value (inclusion criterion #5) (section 7.2.9);*
  - *a positive reversibility response defined as ΔFEV_1>12% and >200mL over baseline after inhaling 400 µg of salbutamol (inclusion criterion #6) (section 7.2.9);*
  - *and a post-bronchodilator FEV_1/FVC ratio ≥ 0.5 after inhaling 400 µg of salbutamol (inclusion criterion #7 (section 7.2.9).*

  In case the thresholds are not met at screening, the test can be performed once more no later than 5 days before the planned randomisation visit.

- If the subject is **not eligible**, the investigator will assess IRT to record the subject as screening failure.

- If the subject is potentially **eligible**, an electronic diary (e-Diary) and a peak flow meter (PEF) will be handed out to the subject with a training on how to perform pre-dose home-PEF measurement and record daily symptoms, standard of care/study medication/rescue

medication intakes. The subject will also receive a device to perform spirometry at home once a week and will be trained on how to perform this assessment.

- Subjects will be also trained on how to recognize worsening of their asthma condition and report asthma exacerbations to investigator (or designee).

- If the training is successful, the investigator will access IRT in order to confirm the subjects as "screening" and to obtain the run-in medication (CHF 1535 100/6 µg) to be taken during the run-in period.

- **The morning dose of run-in medication** (first administration) will be administered at the clinic visit (before 10.00 am) under medical supervision. Subject will be instructed to inhale 2 puffs from the run-in inhaler.

  Note: For the subject using a spacer, the run-in medication will be taken via the AeroChamber PlusTM.

- Once the report of central laboratory is available at site, the investigator (or designee) will check parameters' values and confirm if abnormalities are relevant and compatible with subjects' safety and Inclusion/Exclusion criteria. If subject is confirmed to be eligible, the investigator will access IRT in order to confirm the subject as "screened".

- An **appointment** for Visit 2 will be scheduled in 14 ± 2 days in the morning.

Before discharge:

- One kit of **Run-in Medication** (CHF 1535 100/6 µg) 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.

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

- **Subjects will be instructed:**
  - To inhale 2 puffs in the morning and 2 puffs in the evening. In addition, subject will be also instructed to take salbutamol as rescue if necessary (see sections 6.2.2 and 6.2.3).
  - To answer twice daily, questions on symptoms, medication intake (run-in and rescue).
  - To perform home-PEF measurement twice daily (am/pm).
  - To perform once a week (preferably on the same morning day each week) the home-spirometry assessment.
  - Not to take the morning dose of run-in medication before coming to the clinical visit. Not to take rescue medication in the 6 hours preceding the next visit.
  - To bring back the run-in medication/AeroChamber Plus™ (in their boxes), the e-Diary/home-PEF device and the home spirometry device with them at the next visit.

7.1.3 Visit 2 – Randomisation (Week 0)

The subjects will visit the clinical site for the randomisation visit (2 weeks ± 2 days after Visit 1) in the morning, approximately between 7.00-9.00 am.
If the wash-out of the medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 2 days. Only one re-schedule is allowed. If wash-out is still not respected in the morning of the re-scheduled visit, the subjects will be recorded as screen failure in the IRT.

The following procedures will take place:

- Run-in Medication (CHF 1535 100/6 µg) taken during the run-in period will be collected.

- **E-Diary & Peak Flow Meter:** The investigator (or designee) will check in the electronic diary (e-Diary)/Peak Flow Meter portal whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF (am/pm).

  In case of **inconsistencies**, the investigator (or designee) will retrain the subjects on how to complete the e-Diary, perform home-PEF manoeuvres and on the medication intake (rescue and study medications). While retraining the subjects, the investigator (or designee) will verify subjects' co-operative attitude and ability to correctly use the electronic e-Diary/peak flow meter. If the subjects are not co-operative and do not meet inclusion criteria #10, they will be recorded as screen failure in the IRT system.

- **Home spirometry device:** The investigator (or designee) will check in the portal whether subject has completed the expected weekly assessments.

- **Adverse Events (AEs):** The occurrence of any AE since the last visit will be recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable.

- The **asthma exacerbation assessment** will be done (see section 7.2.13))

  Note: Subjects experiencing an asthma exacerbation during the run-in period should be screened failed as such exacerbation constitutes an exclusion criterion (exclusion criteria #3).
  The screening failure shall be recorded in the IRT system. The subjects may be re-screened once, at least 4 weeks after exacerbation recovery.

- **Concomitant Medications:** The investigator (or designee) will check that the subjects did not take any of the non-permitted medications since the screening visit. Any change of medications shall be recorded in the eCRF.

- **Surgical and medical procedures:** the occurrence of any procedure from the ICF signature will be checked and recorded in the eCRF.

- **Questionnaires:** Subjects will complete the **ACQ-7** questionnaire (see section 7.2.1). Eligible subjects must have a score ≥1.5 confirmed at the randomisation visit. Subjects will complete the **AQLQ** (see section 7.2.2)**. Health economic information** will be collected (see section 7.2.3).

- Pre-dose FeNO will be assessed according to section 7.2.6.

- Pre-dose oscillometry will be carried out to assess lung function according to section 7.2.7.

- **Pre-dose spirometry** will be carried out: the subjects will have to perform a **SVC manoeuvre** to assess pre-dose inspiratory capacity (IC) at 45 minutes prior to first dosing, followed by a **FVC manoeuvre** for other pre-dose parameters (FEV1, FVC) at 45 minutes and 15 minutes prior to first dosing. This measurement will constitute the pre-dose baseline values (see section 7.2.9).

- **Blood sample**s will be collected before dose administration for the assessments of:
  - Total IgE and EOS count;
  - Biobanking samples (blood and urine).

  The blood samples must be collected **after FeNO and oscillometry assessments.**

  Once the report is received at site, the investigator (or designee) will verify any abnormalities. New clinically relevant findings shall be recorded in the eCRF as adverse events.

- **A urine pregnancy test** will be performed in women of childbearing potential. This test will allow confirmation that the woman tested is still not pregnant at randomisation visit.

If **eligibility criteria are confirmed**:

- The investigator (or designee) will randomise **the subjects** in the IRT system and dispense the study medication kit allocated by the IRT system.

- **The morning dose of study medication (first administration)** will be administered at the clinic visit (before 10.00 am) under medical supervision (the time of first inhalation corresponds to Time 0 of spirometry). Subjects will be instructed to inhale 2 puff from the inhaler n°1.

- A 2 hours post-dose oscillometry will be carried out.

- A **2 hours post-dose** spirometry will be carried out: the subjects will have to perform a **SVC manoeuver** to assess post-dose inspiratory capacity (IC) at 2 hours post-dose, followed by a **FVC manoeuvre** for other post-dose parameters (FEV_1, FVC) at 2 hours post dose.

- An **appointment** for Visit 3 will be scheduled in 4 weeks ± 3 days in the morning approximately between 7.00-9.00 am.

Before discharge:

- **Study medication** (1 kit) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study medication.

  Note: For the subject using a spacer, a new AeroChamber PlusTM will be dispensed to the subject.

- **Subjects will be instructed:**
  - To inhale from the first inhaler (n°1) 2 puffs in the morning and 2 puffs in the evening (i.e. 2 puffs BID). The evening dose will be administered at home. Subject will be also instructed to take salbutamol as rescue if necessary (see section 6.2.2).
  - To answer twice daily: questions on symptoms, medication intake (randomised treatment and rescue) in the e-Diary.
  - To perform home-PEF measurement twice daily (am/pm).
  - To perform once a week the home-spirometry assessment (preferably on the same morning day each week).
  - Not to take the morning dose of the study medication before coming to the next visit. Not to take rescue medication in the 6 hours preceeding the next visit.
  - To bring back the study medication/AeroChamber Plus™ (in their boxes), the e-Diary/home-PEF device and the home spirometry device with them at the next visit.

7.1.4 Visit 3 – Week 4

The subjects will visit the clinical site for the visit 3 (4 weeks ± 3 days after Visit 2) in the morning, approximately between 7.00-9.00 am.
If the wash-out of the medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 3 days.

The following procedures will take place:

- Study Medication will be collected.

- **E-Diary & Peak Flow Meter:** The investigator (or designee) will check in the electronic diary (e-Diary)/Peak flow Meter portal whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF (am/pm).

  In case of **inconsistencies**, the investigator (or designee) will retrain the subjects on how to complete the e-Diary, perform home-PEF manoeuvres and on the medication intake (rescue and study medications).

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

- **Home spirometry device:** The investigator (or designee) will check in the portal whether subject has completed the expected weekly assessments.

- **Adverse Events (AEs):** The occurrence of any AE since the last visit will be recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable.

- The **asthma exacerbation assessment** will be done (see section 7.2.13)

- **Concomitant Medications:** The investigator (or designee) will check that the subjects did not take any of the non-permitted medications since the screening visit. Any change of medications shall be recorded in the eCRF.

- **Surgical and medical procedures:** the occurrence of any procedure from previous visit will be checked and recorded in the eCRF.

- **Questionnaires: Health economic information** will be collected (see section 7.2.3).

- **A urine pregnancy test** will be performed in women of childbearing potential. This test will allow confirmation that the woman tested is still not pregnant at randomisation visit.

- Pre-dose Oscillometry will be carried out to assess lung function according to section 7.2.7.

- **Pre-dose spirometry** will be carried out: the subjects will have to perform a **SVC manoeuver** to assess pre-dose inspiratory capacity (IC) at 45 minutes prior to first dosing, followed by a **FVC manoeuvre** for other pre-dose parameters (FEV1, FVC) at 45 minutes and 15 minutes prior to first dosing (see section 7.2.9).

- **Study medication dosing:** The investigator (or designee) will access IRT to enter the subject status and to obtain the appropriate study medication kit number. This **study medication kit will be dispensed** at and will cover the period until the next visit. **The morning dose of study medication will be administered** at the clinic visit (before 10.00 am) under medical supervision. Subjects will be instructed to inhale 2 puffs.

  Note: For the subject using a spacer, the study medication will be taken via the AeroChamber Plus™.

- The Investigator will access the IRT to register the status the subject.

- A 2 hours post-dose oscillometry will be carried out.

- A **2 hours post-dose** spirometry will be carried out: the subjects will have to perform a **SVC manoeuver** to assess post-dose inspiratory capacity (IC) at 2 hours post-dose, followed by a **FVC manoeuvre** for other post-dose parameters (FEV1, FVC) at 2 hours post dose.

- An **appointment** for Visit 4 will be scheduled in 8 weeks ± 3 days in the morning approximately between 7.00-9.00 am.

Before discharge:

- **Study medication** (1 kit) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study medication.

- **Subjects will be instructed:**
  - To inhale from the first inhaler (n°1) 2 puffs in the morning and 2 puffs in the evening (i.e. 2 puffs BID). The evening dose will be administered at home. Subject will be also instructed to take salbutamol as rescue if necessary (see sections 6.2.2 and 6.2.3).
  - To answer twice daily: questions on symptoms, medication intake (randomised treatment and rescue) in the e-Diary.
  - To perform home-PEF measurement twice daily (am/pm).

- To perform once a week the home-spirometry assessment (preferably on the same morning day each week).
- Not to take the morning dose of the study medication before coming to the next visit. Not to take rescue medication in the 6 hours preceding the next visit.
- To bring back the study medication/AeroChamber Plus™ (in their boxes), the e-Diary/home-PEF device and the home spirometry device with them at the next visit.

7.1.5 Visit 4 – Week 12

The subjects will visit the clinical site for the visit 4 (12 weeks ± 3 days after Visit 2) in the morning, approximately between 7.00-9.00 am.
If the wash-out of the medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 3 days.

The following procedures will take place:

- Study Medication will be collected.
- **E-Diary & Peak Flow Mater:** The investigator (or designee) will check in the electronic diary (e-Diary)/Peak Flow Meter portal whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF (am/pm).

  In case of **inconsistencies**, the investigator (or designee) will retrain the subjects on how to complete the e-Diary, perform home-PEF manoeuvres and on the medication intake (rescue and study medications).

  Note: the investigator (or designee) should check regularly the subject's compliance/PEF/asthma symptoms through a dedicated portal.
- **Home spirometry device:** The investigator (or designee) will check in the portal whether subject has completed the expected weekly assessments.
- **Adverse Events (AEs):** The occurrence of any AE since the last visit will be recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable.
- The **asthma exacerbation assessment** will be done (see section 7.2.13).
- **Concomitant Medications:** The investigator (or designee) will check that the subjects did not take any of the non-permitted medications since the screening visit. Any change of medications shall be recorded in the eCRF.
- **Surgical and medical procedures:** the occurrence of any procedure from previous visit will be checked and recorded in the eCRF.
- **Questionnaires:** Subjects will complete the **ACQ-7** questionnaire (see section 7.2.1), the **AQLQ** (see section 7.2.2)**.). Health economic information** will be collected (see section 7.2.3)

- **A urine pregnancy test** will be performed in women of childbearing potential. This test will allow confirmation that the woman tested is still not pregnant at randomisation visit.

- Pre-dose Oscillometry will be carried out to assess lung function according to section 7.2.7.

- **Pre-dose spirometry** will be carried out: the subjects will have to perform a **SVC manoeuver** to assess pre-dose inspiratory capacity (IC) at 45 minutes prior to first dosing, followed by a **FVC manoeuvre** for other pre-dose parameters (FEV1, FVC) at 45 minutes and 15 minutes prior to first dosing (see section 7.2.9).

- **Study medication dosing:** The investigator (or designee) will access IRT to enter the subject status and to obtain the appropriate study medication kit number. This **study medication kit will be dispensed** at and will cover the period until the next visit. **The morning dose of study medication** will be administered at the clinic visit (before 10.00 am) under medical supervision. Subjects will be instructed to inhale 2 puffs.

  Note: For the subject using a spacer, the study medication will be taken via the AeroChamber Plus™.

- The Investigator will access the IRT to register the status the subject.

- A 2 hours post-dose oscillometry will be carried out.

- A **2 hours post-dose** spirometry will be carried out: the subjects will have to perform a **SVC manoeuver** to assess post-dose inspiratory capacity (IC) at 2 hours post-dose, followed by a **FVC manoeuvre** for other post-dose parameters (FEV1, FVC) at 2 hours post dose.

- An **appointment** for Visit 5 will be scheduled in 10 weeks ± 3 days in the morning approximately between 7.00-9.00 am.

Before discharge:

- **Study medication** (1 kit) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study medication.

- **Subjects will be instructed:**
  - To inhale from the first inhaler (n°1) 2 puffs in the morning and 2 puffs in the evening (i.e. 2 puffs BID). The evening dose will be administered at home. Subject will be also instructed to take salbutamol as rescue if necessary (see sections 6.2.2 and 6.2.3).
  - To answer twice daily: questions on symptoms, medication intake (randomised treatment and rescue) in the e-Diary.
  - To perform home-PEF measurement twice daily (am/pm).
  - To perform once a week the home-spirometry assessment (preferably on the same morning day each week).
  - Not to take the morning dose of the study medication before coming to the next visit. Not to take rescue medication in the 6 hours preceding the next visit.
  - To bring back the study medication/AeroChamber Plus™ (in their boxes), the e-Diary/home-PEF device and the home spirometry device with them at the next visit.

7.1.6 Visit 5 – Week 22

The subjects will visit the clinical site for the visit 5 (22 weeks ± 3 days after Visit 2) in the morning, approximately between 7.00-9.00 am.
If the wash-out of the medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 3 days.

The following procedures will take place: See assessments of visit 3.

Before discharge:

- **Study medication** (1 kit) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study medication.

- **Subjects will be instructed:**
  - To inhale from the first inhaler (n°1) 2 puffs in the morning and 2 puffs in the evening (i.e. 2 puffs BID). The evening dose will be administered at home. Subject will be also instructed to take salbutamol as rescue if necessary (see sections 6.2.2 and 6.2.3).
  - To answer twice daily: questions on symptoms, medication intake (randomised treatment and rescue) in the e-Diary.
  - To perform home-PEF measurement twice daily (am/pm).
  - To perform once a week the home-spirometry assessment (preferably on the same morning day each week).
  - Not to take the morning dose of the study medication before coming to the next visit. Not to take rescue medication in the 6 hours preceding the next visit.
  - To bring back the study medication/AeroChamber Plus™ (in their boxes), the e-Diary/home-PEF device and the home spirometry device with them at the next visit.

7.1.7 Visit 6 – completion Visit (week 26)

The subjects will visit the clinical site for the visit 6 (26 weeks ± 3 days after Visit 2) in the morning, approximately between 7.00-9.00 am.
If the wash-out of the medications has not been respected (see section 5.2), the visit needs to be re-scheduled within 3 days.

The following procedures will take place:

- Study Medication will be collected.

- **E-Diary & Peak Flow Meter:** The investigator (or designee) will check in the electronic diary (e-Diary)/Peak Flow Meter portal whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF (am/pm).

- **Home spirometry device:** The investigator (or designee) will check in the portal whether subject has completed the expected weekly assessments.

- **Adverse Events (AEs):** The occurrence of any AE since the last visit will be recorded in the eCRF. The status of ongoing AEs will be checked and updated in the eCRF when applicable. In case of any new clinically significant abnormality revealed during the physical examination or procedures, it will be recorded as an adverse event.

- The **asthma exacerbation assessment** will be done (see section 7.2.13))

- **Concomitant Medications:** The investigator (or designee) will check that the subjects did not take any of the non-permitted medications since the screening visit. Any change of medications shall be recorded in the eCRF.

- **Surgical and medical procedures:** the occurrence of any procedure from the ICF signature will be checked and recorded in the eCRF.

- A full **physical examination** will be performed.

- **Questionnaires:** Subjects will complete the **ACQ-7** questionnaire (see section 7.2.1), the **AQLQ** (see section 7.2.2)**.). Health economic information** will be collected (see section 7.2.3)

- **Vital Signs:** Pre-bronchodilator vital signs will be recorded (pulse rate, systolic [SBP] and diastolic [DBP] blood pressure, after 10 minutes of rest, in sitting position) (section 7.2.4).

- Pre-dose FeNO will be assessed according to section 7.2.6.

- Pre-dose Oscillometry will be carried out to assess lung function according to section 7.2.7.

- **Pre-dose spirometry** will be carried out: the subjects will have to perform a **SVC manoeuver** to assess pre-dose inspiratory capacity (IC) at 45 minutes prior to first dosing, followed by a **FVC manoeuvre** for other pre-dose parameters (FEV1, FVC) at 45 minutes and 15 minutes prior to first dosing (see section 7.2.9).

- **Study medication dosing:** The investigator (or designee) will access IRT to enter the subject status. **The morning dose of study medication will be administered from the latest kit dispensed at the clinic visit** (before 10.00 am) under medical supervision. Subjects will be instructed to inhale 2 puffs.
  Note: For the subject using a spacer, the study medication will be taken via the AeroChamber Plus™.

- **Blood samples:** will be collected before dose administration for the assessments of:
  - EOS count;
  - Biobanking samples (blood and urine).

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

- A **urine pregnancy test** will be performed in women of childbearing potential.

- A 2 hours post-dose oscillometry will be carried out.

- A **2 hours post-dose** spirometry will be carried out: the subjects will have to perform a **SVC manoeuver** to assess post-dose inspiratory capacity (IC) at 2 hours post-dose, followed by a **FVC manoeuvre** for other post-dose parameters (FEV1, FVC) at 2 hours post-dose.

- The Investigator will access the IRT to register the visit completion.

Before discharge:

- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer to the General Practitioner.

- An appointment will be made in **1-week time** for the follow-up phone call.

7.1.8 Early treatment discontinuation visit

If a subject is withdrawn before the end of treatment period, a final evaluation will be done.
All the pre-dose assessments foreseen at Visit 6, should be done at early treatment discontinuation to the extent possible, providing there is **no safety issue for the subject.**

In case of early termination for withdrawal of consent, no further assessments will be done except the check of AEs/SAEs status up to the date of withdrawal of consent.

Subjects who discontinue study treatment **should not be considered automatically withdrawn from the study** (except if the reason is consent withdrawal or lost to follow up). The investigator and study staff must discuss with the subjects who will be asked to continue attending the remaining study visits while off investigational treatment (see section 4.4).

Depending on the subjects' decision to continue or not attending the remaining study visits while off investigational treatment, the investigator (or designee) will access IRT to register the subjects' **Early Treatment Discontinuation or End of Study Participation**.

Before discharge:

- The investigator will prescribe the most appropriate treatment or refer to the General Practitioner.

- An appointment will be made in **1-week time** for the follow-up phone call.

7.1.9 Follow-up call

A safety follow-up call will be done 1 week after Visit 6 or Early Treatment Discontinuation (except if the subjects withdraw the consent or is lost to follow up). The subjects will be contacted to check any unresolved AE/SAEs at these visits and any AEs/SAEs that have occurred after these visits, as well as the concomitant medications taken for asthma and AEs/SAEs.

The investigator will access IRT to record the follow-up completion.

If the follow up is done after the Early Treatment Discontinuation Visit and the subjects are not willing to perform the remaining clinical visits, the subjects must be informed that they cannot participate in another clinical study for 2 weeks after this contact and the subjects are exited from the study.

7.2 Investigations

The following rules should be followed:

- The pre-dose vital signs and 12-lead ECG recording must be performed before the blood sampling;
- Any FeNO measurement must be always performed before Oscillometry;
- Oscillometry measurements must be performed before spirometry and blood sampling;
- Spirometry SVC measurements must be performed before Spirometry FVC measurements.

7.2.1 Asthma control Questionnaire (ACQ-7)

Only uncontrolled asthmatic subjects 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, i.e. at randomisation)**.**

Asthma control will be evaluated by the completion of the Asthma Control Questionnaire© (ACQ-7) [49, 50]. The ACQ-7 is able to identify the adequacy of asthma control in individual subjects. 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-7 is administered at Visit 1, Visit 2, Visit 4 and Visit 6.

*Note: In case the pre-bronchodilator FEV_1 value (inclusion criterion #5) or the reversibility threshold (inclusion criterion #6) or the post-bronchodilator FEV_1/FVC ratio (inclusion criterion #7) is not met at screening, the **ACQ-7 questionnaire** will have to be completed again at the same time of the repeated spirometry tests, once no later than 5 days before randomisation.*

Subjects 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-7 will be completed by subjects on an electronic diary (e-diary) in a quiet place before the pulmonary function testing, only question 7 will be completed after the testing.

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

The appropriate language version of the questionnaire should be used in each participating country. The same language version should be used by a particular subject throughout the study.

Missing data should be avoided; therefore, the investigator (or designated site-personnel) will check the questionnaire for completeness before the subjects leave the clinic and if necessary, encourage the subjects to complete any missing responses. Anyway, the response to each item should not be questioned.

7.2.2 AQLQ Questionnaire

The Asthma Quality of Life Questionnaire (AQLQ) [49, 51] was validated as a disease-specific tool in asthma to measure quality of life, investigating the functional problems (physical, emotional, social and occupational) that are most troublesome to adults with asthma.

The questionnaire comprises a total of 32 individual questions that span a total of 4 domains: symptoms, activity limitation, emotional function and environmental stimuli.

Subjects are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7= not impaired at all, 1= severely impaired).

The AQLQ will be self-administered at the clinic; it takes about 5 minutes.
The questionnaire will be completed by subjects on an electronic diary (e-diary) at randomisation (Visit 2), Visit 4 and Visit 6, in a quiet place, and before the pulmonary function testing.

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

The appropriate language version of the questionnaire should be used in each participating country. The same language version should be used by a particular subject throughout the study.

Missing data should be avoided; therefore, the investigator (or designated site-personnel) will check the questionnaire for completeness before the subjects leave the clinic and if necessary, encourage the subjects to complete any missing responses. Anyway, the response to each item should not be questioned.

The questionnaire will be then transmitted to vendor (eResearch Technology) central database.

7.2.3 Health Economic information

Information on the total use of healthcare resources and absence from work associated with the subjects' condition will be collected during the trial.

Professional status will be collected at Visit 2.
Health Economic information will be collected electronically by the Investigator based on medical records and subjects' interviews at each visit from Visit 3 until end of treatment (Visit 6).

The questionnaire will be then transmitted to vendor (eResearch Technology**)** central database.

7.2.4 Vital signs

Pulse rate, systolic and diastolic blood pressure (SBP, DBP) will be measured after 10 min rest in sitting position:
-pre-salbutamol at V1;
-pre-dose at V6.

The vital signs should be assessed **before the blood sampling, and before the pulmonary function testing**.

7.2.5 12-lead ECG

Single pre-salbutamol/dose 12-lead ECG will be performed locally at the site at screening for eligibility check (all subjects). The evaluation will be done by the site.

Before recording, subjects should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and 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/3√RR). It will be calculated automatically by the eCRF system. Heart rate (HR), PR and QRS values will be also evaluated from ECG.

ECGs with computerized protocol interpretation are considered normal if:
- 45≤ Heart rate ≤110 bpm,
- 120 ms ≤ PR ≤210 ms,
- QRS ≤120 ms.

In case of clinically significant ECG abnormalities (as reported by the investigator) not set as exclusion criteria, the inclusion of the subjects will be judged by the investigator. ECG abnormalities in eligible subjects may be investigated at all time by the medical monitors and Sponsor. In any case, the trace must have **QTcF values ≤ 450 (males) and ≤ 470 ms (females) at screening and randomisation**. The final decision for enrolment would be documented in the Medical File of the subjects.

Clinically significant abnormalities evaluated by the investigator 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.

7.2.6 FeNO measurement

All sites will be provided with the same FeNO device in order to standardize data collected: NIOX VERO® from Circassia®. The specific procedures for FeNO measurement will be provided to the investigator by eResearch Technology.
Subjects will have to refrain from eating, drinking (even water) and/or smoking for at least 1 hour prior to the FeNO measurement. Training on the use of the device to perform FeNO measurements will be conducted by the site study staff according to the guidelines in the user manual. Subjects will be instructed to deep inhale and then exhale into the device for 10 seconds [52, 53].

The device rejects all non-validated measurements; the value of the first accepted measurement must be recorded and transferred in the eResearch Technology database.
FeNO measurements will be performed at V2 and V6/ETD before the intake of any medications, and always **before oscillometry, spirometry and blood sampling.**

7.2.7 Oscillometry – Forced Oscillation Technique (FOT)

All sites will be provided with the same device: Tremoflo® C-100 Airwave Oscillometry System (AOS) from Thorasys®. Centralised oscillometry (with central reading done by eResearch Technology) will be used. The specific procedures for centralised oscillometry will be provided to the investigator by the eResearch Technology.

Any oscillometric measurement **must be always performed before spirometry manoeuvres.**

All oscillometry assessments will be done according to the ERS Task Force guidance [54].
At Visit 2, Visit 3, Visit 4, Visit 5 and Visit 6 oscillometric parameters will be collected before the administration of the study drug intake.
At the same visits, oscillometric parameters profile will be collected at 2h hours post study drug administration (± 15 min).
The following parameters for each measurement and for each timepoint will be collected: AX, X5, R5, R19 and RF.

7.2.8 Blood Collections

7.2.8.1 Haematology and Chemistry

Blood samples for a total of about 15-20 mL will be collected at visit 1 in the morning, after an overnight fasting (only water is allowed during the night). WBC differential for EOS evaluation will be collected at V2 and V6. The blood withdrawal should be performed **after vital signs, 12-lead ECG recording, FeNO and oscillometry assessments.**

An additional blood sample will be collected for serum pregnancy test in women of childbearing potential at Visit 1. In addition, a urine pregnancy test will be performed from Visits 1 to Visit 6/ETD (and monthly when required by country regulations).

The following evaluation will be performed at Visit 1**:**

- 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) or urea, 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 pregnancy tests (β-HCG) at V1.

Moreover, at randomization (Visit 2), sample will be collected to undergo a total IgE level and WBC differential for eosinophils (EOS) count evaluation.
At V6, sample will be collected to undergo a repeated WBC differential for EOS count evaluation.
No fasting conditions are needed before assessment of EOS count.

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

7.2.8.2 Urine and serum biobanking

Urine and whole blood (for serum generation) will be collected at the randomization visit (V2, Week 0) and at end of treatment (V6, Week 26 or Early Treatment Discontinuation Visit) before study drug administration. Two aliquots of urine and two aliquots of serum will be prepared in appropriate tubes.
No fasting conditions are needed before collection of biobanking samples.

These samples could be used for post-hoc biomarker investigations and will be stored for a maximum of 20 years by **the central laboratory**. These post-hoc investigations might not be part of the statistical analysis and results might not be included in the Clinical Study Report.

All the instructions regarding collection, processing and handling will be provided and detailed in the laboratory manual.

7.2.9 Spirometry

Lung function measurements will be done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society [55]. All sites will be provided with the same spirometer. Centralised spirometry (with central reading done by eResearch Technology) will be used. The specific procedures for centralised spirometry will be provided to the investigator by the eResearch Technology.

Lung function measurements will be done with subjects either standing or sitting (for each subject, this should be consistent throughout the study) with the nose clipped after appropriate rest.

Throughout the study, the clinic visits and the lung function measurements will start in the morning (no later than 11.00 am for pre- salbutamol/dose spirometry assessment), approximately at the same time of the day for each subject.

The following parameters will be collected and transferred to sponsor. It includes at least the following:

- Inspiratory Capacity (IC, L) and Volume Capacity (VC)
- ERV (L)
- Forced Expiratory Volume in the 1st second (FEV_1, L and % of predicted)
- Forced Vital Capacity (FVC, L and % of predicted)
- FEV_1/FVC ratio
- FEF_{25-75}
- LLN for FEV_1/FVC
- Reversibility (ml and %)

Note: some additional standard parameters (for instance PEF) will be assessed by the spirometer during the visit only to inform the investigator.
Predicted values of FEV_1 will be calculated according to formulas reported by Quanjer et al [56, 57].

At screening, the post-bronchodilator FEV_1, FVC and FEV_1/FVC ratio (within 30 min after administration of salbutamol 4x100 mcg) will be considered for eligibility [55, 58].

Note: In case one of the following inclusion criteria (#5 - pre-bronchodilator FEV_1 value, #6 - reversibility threshold, #7 - post-bronchodilator FEV_1/FVC ratio) is not met at screening, they can be repeated together with ACQ-7 (inclusion criterion #8) once, no later than 5 days before randomisation.

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, will be recorded at each clinic visit from a slow vital capacity manoeuvre.
The **average** of at least 3 acceptable slow vital capacity (SVC) manoeuvres will be recorded for **IC**.
VC is the volume change between total lung capacity (TLC) and residual volume (RV), and it will be measured as expiratory VC (EVC: the volume of gas slowly expired from TLC to RV). These manoeuvres are unforced, except at the point of reaching RV or TLC, respectively, when extra effort is required.
For VC, the **largest value** from at least three acceptable manoeuvres will be reported.
IC and **VC** will be assessed at 45 min pre-salbutamol at Visit 1, and at 45 minutes pre-dose and 2h post-dose from Visit 2 to Visit 6.
These SVC manoeuvres must be performed before the forced vital capacity (FVC) manoeuvres used to assess other lung function parameters 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. The ratio **FEV_1/FVC** will be derived from these **highest values** of each parameter.

Note: The following time tolerances from theoretical spirometry times will **be allowed**:

-Pre-dose:	Ideally 45 min and 15 min before drug intake but acceptable up to 11.00 am
-V1 post salbutamol:	From 10 min up to 30 min after salbutamol
-V2 to V6 2 hours post-dose	2 hours ± 15 min after study drug intake

Predicted values will be calculated according to formulas reported by Quanjer et al [55].

Each spirometry manoeuvre and overall session will be reviewed centrally by a Central Over-Reader.
The Over-Reader can recommend changes to the site's original decision on selected spirometry tests and judge the overall quality of the session.

The Principal Investigator or Sub-Investigator must review and sign all the Over-Read Reports, even if the Over-Reader has accepted the overall spirometry session and no changes are recommended to individual spirometry manoeuvres.
If changes are proposed, the investigator can agree or disagree.
The final spirometry values will be the one confirmed by the investigator, while the Over-Reader overall session judgment will not vary.

The rescue medication must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit. If the subjects require rescue medication within this timeframe, the visit should be rescheduled once within the 2 next days.

The run-in and randomised treatment medication should not be taken before coming to the visit according to section 5.2. If taken, the measurements should be deferred (i.e. the visit needs to be re-scheduled to take place within 2 days).

7.2.10 Home Spirometry

Lung function measurements pre-dose and 2 hours post-dose will be done by subjects at home using a portable spirometer device in the morning. The home spirometry should be performed by the subjects once a week, possibly on the same day of the week throughout the whole study period. Each subject is allowed to select the most proper day of the week to perform the home spirometry.

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

The following parameters will be collected and transferred to sponsor. It includes at least the following:

- FEV_1 (L and %pred)
- FVC (L and %pred)
- FEV_1/FVC ratio
- FEF_{25-75} (if available in the home-spirometer)

FEV_1 and **FVC** will be recorded from a forced vital capacity manoeuvre. Predicted values will be calculated according to formulas reported by Quanjer et al [57].

Note: The following time tolerances from theoretical spirometry times will **be allowed**:

-Pre-dose:	Ideally 45 min and 15 min before drug intake
-V2 to V6 Post-dose	2 hours ± 15 min after drug intake

Data from the spirometry device will be automatically transmitted from subjects' home to eResearch Technology database.
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 subjects' compliance. **In case of bad compliance and/or worsening in lung function measurements during the study, phone call(s) to the subjects will be done by the site and instructions will be given again to the subjects if appropriate.**

The home spirometry will be additionally checked for quality using automatic algorithm according to ATS/ERS guidelines; the sites will be provided with the QC feedback on a subset of subjects in order to conduct post hoc analysis on the performance of the algorithm. In case of poor quality, the Investigator will evaluate subject's retraining.
These post-hoc investigations will not be part of the statistical analysis and results will not be included in the Clinical Study Report. The methodology for the home spirometry QC and the sites alerting approach will be detailed in a specific document.

7.2.11 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 V6) by subjects at home using a portable electronic peak flow meter.

This will be done before the intake of the study medication.
Specific question will be included in the e-Diary to ask if PEF measurements have been performed before the intake of study medication.

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

During each measurement session (morning or evening before the intake of the study medication) the subjects 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 subjects to perform measurements.

Data from the electronic peak flow meter will be automatically transmitted from subjects' home to eResearch Technology central 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 subjects' compliance. **In case of bad compliance and/or worsening of asthma control during the study, phone call(s) to the subjects will be done by the site and instructions will be given again to the subjects if appropriate.**

7.2.12 Asthma symptoms, use of randomised treatment and rescue medication

During the run-in and randomization period (from V1 to V6), the subjects will answer twice daily in the morning and in the evening and before the PEF measurements the following questions in the electronic diary:
- the asthma symptom scores;
- the nocturnal awakening occurrence due to asthma requiring rescue medication;
- the use of study medication (rescue and study treatment).

In case of Early Treatment Discontinuation, the subjects will answer twice a day in the morning and in the evening and before the PEF measurements the following questions in the electronic diary:
- the asthma symptom scores;
- the nocturnal awakening occurrence due to asthma requiring rescue medication;
- the use of rescue medication.

The data will be automatically transmitted from home to theeResearch Technology central 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

- **Nocturnal awakening occurrence due to asthma requiring rescue medication**
  The subjects will confirm, answering once a day simple question whether nocturnal awakening occurred due to asthma requiring rescue medication.

- **Randomised medication**
  The intake of randomised treatment medication will be recorded twice daily as follows: the number of puffs taken in the morning and in the evening.

- **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, 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.

7.2.13 Asthma exacerbation

Asthma exacerbations (as per ATS/ERS guidelines and Virchow paper [59, 60]) are defined as follows:

A **moderate asthma exacerbation** is defined as ≥ 1 of criteria fulfilled and leading to a change in treatment*:

a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights 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 (min. 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 ER/trial site for asthma treatment not requiring systemic corticosteroids

** A sustained increase of at least 1 puff of SABA for 2 consecutive days is considered as a change in treatment. Asthma worsenings requiring the initiation of treatment with systemic corticosteroids for < 3 days are considered as moderate exacerbations.*

A Severe Asthma Exacerbation is defined as 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. Asthma worsenings treated with depot costicosteroids (for sustained systemic effect of at least 3 days) are considered as severe exacerbations.

To be eligible at screening (Visit 1), the subject should have experienced at least one asthma exacerbation in the last 3 years preceding screening (according to inclusion criterion n°9). However, eligible subjects should remain free of exacerbation requiring hospitalisation, emergency room admission or use of systemic corticosteroids within 4 weeks prior to screening and during the run-in period (according to exclusion criterion n°4).

During the run-in period, if the subject experiences any asthma exacerbation the subject will not be randomised in the study.
In this case, the subject could be re-selected at a later stage (one month minimum after recovering) with a new subject number (the subject should sign a new informed consent), providing the medical conditions of the subject is appropriate with the inclusion in the study according to the investigator.

After the randomisation, if the subject experiences a 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 subject's stabilization. In addition, a minimum timeframe of 2 weeks between the end 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 subject**, it is up to the investigator to decide to withdraw from the study treatment or not the subject.**

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

The investigator should detect any asthma worsening during the study and decide whether to ask the subjects to come to the clinic for an unscheduled visit and whether the subjects are experiencing a moderate or severe exacerbation as per protocol definitions.

The investigator is supported in the detection of asthma worsening by the e-Diary data and spirometry alerts generated.

Asthma worsening alerts are generated by the e-Diary in case of:

a. *Decreases in morning PEF ≥20% from AM PEF baseline on two or more consecutive mornings*
b. *Decreases in evening PEF ≥20% from PM PEF baseline on two or more consecutive evenings*
c. *Decrease in FEV_1 at clinic visits ≥20% from baseline*
d. *Increase in rescue medication usage: increase from baseline of at least 4 puffs in daily rescue medication use on two or more consecutive days*
e. *Increase from baseline of at least 0.75 in daily symptoms score on two or more consecutive days*
f. *Nocturnal awakenings due to asthma requiring SABA for two or more consecutive nights*

For each moderate exacerbation recorded in the eCRF, the investigator should specify how the asthma worsening was detected (by e-Diary data or other way e.g. subject contact/subject visit…).
Asthma day-to-day symptoms variations that do not satisfy the moderate and severe definitions should be reported in the eCRF only as symptoms in the Adverse Event form, if considered clinically significant events.

Subject will be also trained on recognition of signs and symptoms signalling a developing asthma exacerbation and to call the investigator in this case.

In case of asthma exacerbations during the study, the subjects will be allowed to receive **short courses (≤ 14 days)** of systemic corticosteroids (see section 5.1).

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 subjects 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 subjects' clinical conditions.

In the recovery period during exacerbation episode, if the condition of the subjects 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 subjects according to the protocol as early as possible.

An asthma exacerbation is not a reason to withdraw the subject from the study treatment, 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.

8 EFFICACY ASSESSMENTS

Primary efficacy variable:

- Proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening.

Key-Secondary efficacy variable:

- Change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening.

Secondary efficacy variables:
(evaluated both in the overall study population and in the study sub-population meeting PAL criterion at screening)

- Proportion of subjects with an increase ≥ 10% in average 2h FEV1/FVC ratio over 26 weeks compared to post-BD FEV_1/FVC ratio at screening.
- Proportion of subjects who consistently exhibit PAL or NPAL status:
  - Proportion of subjects with PAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).
  - Proportion of subjects with NPAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).
- Proportion of subjects with 1, 2, 3, 4 or 5 post-treatment visits (among Week 0, 4, 12, 22, and 26) with PAL and NPAL status.
- Proportion of subjects with PAL and NPAL status at each post-treatment visit (Week 0, 4, 12, 22, and 26).
- Proportion of subjects exhibiting on average PAL and NPAL status over 26 weeks of treatment.
- Change from baseline in 2h post-dose FEV_1 at all clinic visits.
- Change from baseline in 2h post-dose FEV_1/FVC at all clinic visits and over 26 weeks of treatment.
- Change from baseline in pre-dose morning FEV_1 at all clinic visits.
- FEV_1 response (Change from baseline ≥ 100 mL in pre-dose FEV_1) at Week 26.
- Severe asthma exacerbations rate over 26 weeks of treatment.
- Moderate or severe asthma exacerbations rate over 26 weeks of treatment.
- Time to first severe asthma exacerbations rate.
- Time to first moderate or severe asthma exacerbations rate.
- Number of days with use of Oral Systemic Corticosteroids (OCS).
- Change from baseline in pre-dose and 2h post-dose FVC at all clinic visits.
- Change from baseline in average morning PEF over 26 weeks of treatment and at each inter-visit period.
- Change from baseline in average evening PEF over 26 weeks of treatment and at each inter-visit period.
- Change from baseline in Blood Eosinophils at Week 26.
- Change from baseline in Symptom-Free Days over 26 weeks of treatment and at each inter-visit period.
- Change from baseline in rescue SABA use over 26 weeks of treatment and at each inter-visit period.
- Change from baseline in daily (morning and evening) asthma symptoms over 26 weeks of treatment and at each inter-visit period.
- Change from baseline Asthma control days over 26 weeks of treatment and at each inter-visit period.
- Change from baseline in ACQ-7 at Week 12 and Week 26.
- Change from baseline in ACQ-5 at Week 12 and Week 26.
- Change from baseline in AQLQ at Week 12 and Week 26.

Exploratory variables:

- Blood and Urine samples will be collected at the randomization visit (V2, Week 0), end of treatment (V6, Week 26) and Early Treatment Discontinuation Visit for biobanking, to perform post-hoc biomarker analysis. The results of this post- hoc investigation will not be part of the statistical analysis and might not be included in the Clinical Study Report.
- Change from baseline in oscillometric parameters at all clinic visits (resistance, reactance).
- Change from baseline in FeNO at Week 26.
- Average Healthcare resource utilization (HCRU) over the 26 weeks of treatment period for each treatment group.
- Change from baseline in home spirometry parameters.

9 SAFETY ASSESSMENTS

9.1 Safety variables

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

9.2 Emergency situation

In case of health emergency, including COVID-19, the investigator/site staff must take all necessary precautions to minimise and avoid the risk of transmission and exposure to study subjects and site staff, according to local guidelines.
In that particular case:

- a time window for study visits could be allowed when subjects are not able to arrive to the site or to attend the visit;
- Onsite study visits could be cancelled or replaced by phone calls, some assessments could be missed
- Home-delivery of clinical trial supplies including study treatment, and home-based assessment of disease outcomes (e.g. telehealth, digital tools, self-administered testing, etc.) could be considered when appropriate as a contingency.

Appropriate guidance will be provided to sites.

Special case of COVID-19 outbreak:

Every effort should be made by the site to confirm all suspected incidences of COVID-19 in accordance with local diagnostic guidelines. Documentation of testing and results obtained outside the clinical site, should be collected within 14 days of confirmed diagnosis (or whenever possible) and recorded in the eCRF.

All incidences of COVID-19 as well as the impact on study visits and subject completion must be captured in the eCRF.

Occurrence of SARS-CoV-2 infection and/or COVID-19 disease during the study does not automatically lead to withdrawal of the subject or discontinuation of study treatment. It will be up to the investigator's judgement to withdraw the subject from the study if he/she deems that remaining in the study will place the subject and/or the clinical site at undue risk by continuing their participation. All efforts should be made to keep the subject on study treatment, if possible.

In case study visits or procedures are modified or missed due to COVID-19, the relevant information will be recorded in the eCRF.

As of the date of this protocol version, there is no specific treatment for COVID-19 and several vaccine therapies have been developed and approved by health authorities with vaccination campaigning being initiated worldwide. For all confirmed cases of COVID-19/SARS-CoV-2 the investigator must follow the standard of care in accordance with local treatment guidelines. All concomitant treatments must be recorded in the eCRF.

In case of COVID-19 suspect**,** investigators are encouraged to **perform diagnostic testing locally** or obtain results of tests from hospital where the event was diagnosed and/or managed, and every effort should be made to complete the assessments required by the current local guidelines for COVID-19 management (e.g. SARS-CoV-2 test, chest imaging), and to guarantee the appropriate management.

The investigators will use their clinical assessment to report COVID-19 as AE based on the definition and assessment of event.

10 ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".
An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

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

- **Results in death**

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

- **Is life-threatening**

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

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

Hospitalization refers to a situation whereby an AE is associated with unplanned formal overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as 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 (included in the Summary of Product Characteristics (SmPC) for Trimbow® 100/6/12.5 µg pMDI and for Foster® 200/6 µg pMDI), 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 reference safety information 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.

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" assessments will be considered 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 to onset between first administration of study drug to onset of adverse event/adverse event
- 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 permanently withdrawn
- Drug temporarily interrupted
- Unknown
- Not applicable

10.6 Other actions taken

- Specific therapy/Medication
- Concomitant Procedure

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 electronic Serious Adverse Event Form must also be completed.

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

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

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

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

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

10.9 Reporting Serious Adverse Events to Chiesi

The Investigator must report all Serious Adverse Events to the Labcorp Safety Contact listed below within 24 hours of awareness. The information must be sent by providing the electronic Serious Adverse Event form. The Labcorp Safety Contact, upon notification, 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
Labcorp Safety Contact	+ 44 1628 548171 +1 888-724-4908	+44 1628 540028 +1-888-887-8097	SAEIntake@covance.com
Chiesi Safety Contact Benedetta Borella GPO specialist	+39 0521 1689271	+39 0521 1885003	b.borella@chiesi.com CT_CDS@chiesi.com

- 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 Labcorp Safety Contact. New serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committees

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 according to local UK regulations and according to EU Directive 2001/20/EC [Directive 2001/20/EC of the European parliament and of the council of 4/April/2001] 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]. 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 fulfill 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 Labcorp Safety Contact together with the Serious Adverse Event form, retaining a copy on site.

- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Labcorp Safety Contact as soon as available, retaining a copy on site.

- All documents provided by the Investigator or site staff to the Labcorp Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.

- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and till the age of one year of the child to detect any congenital anomaly or birth defect. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail to the Labcorp Safety Contact using the paper Pregnancy Report Form. The Labcorp 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 Labcorp 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, but the subject participating to the study should not be discontinued from the study.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in/rescue medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.

- Any Adverse Drug Reaction (ADR) occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority according to the applicable laws. The Investigator is also recommended to report all adverse drug reactions to the relevant Marketing Authorisation Holders of the involved medicinal products. Additionally, also conditions of use outside the marketing authorisation of the medicinal products (i.e. off-label, overdose, misuse, abuse and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy should be reported.

11 DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her representative designee.
All subjects who sign the informed consent will be databased. For subjects who are screened but not randomized a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, 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 level 5th.

External data (spirometry, FeNo, oscillometry, eDiaries/PEF, laboratory samples, IRT) will be processed centrally, sent to the designated CRO and reconciled with the corresponding information recorded in the CRF.

Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

After the completion of data collection and cleaning, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened, and the planned statistical analysis will be performed. If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by Chiesi.

At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The investigators will receive copies of the subject data for retention at the investigational sites.

12 STATISTICAL METHODS

12.1 Sample Size

The sample size has been calculated to demonstrate the superiority of medium doseBDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) over high-dose BDP/FF pMDI (200/6 µg, 2 puffs bid) in terms of both primary and key secondary endpoints.

A total of 1400 subjects will be randomised according to a 1:1 ratio to either BDP/FF/GB 100/6/12.5 pMDI or BDP/FF 200/6 pMDI (i.e. 700 subjects per group).

Considering that subjects meeting PAL criterion at screening will constitute 65% of the total randomised population, approximately 910 subjects (i.e. 455 per group) included in this study sub-population will be randomised, and approximately 822 of them (i.e. 411 per group) will continue the study treatment till Week 26 (considering an early treatment discontinuation rate of approximately 10% at Week 26).

This sample size will provide:

- Approximately 95% of power to detect a difference of 0.11 in favour of BDP/FF/GB 100/6/12.5 pMDI over BDP/FF 200/6 pMDI in the proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening. The lower limit of 95% confidence interval of the odds ratio derived from a logistic model being aims to be > 1. Two-sided significance level of 0.05 is considered, assuming a proportion of subjects exhibiting on average NPAL status over 26 weeks of 0.31 and 0.20 for BDP/FF/GB 100/6/12.5 pMDI and BDP/FF 200/6 pMDI, respectively.
- Approximately 84% of power to detect a mean difference of 70 ml in favour of BDP/FF/GB 100/6/12.5 over BDP/FF 200/6 pMDI in terms of change from baseline in pre-dose FEV1 at Week 26 in the study sub-population meeting PAL criterion at screening at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 339 ml.

Jointly considering the two endpoints, an overall study power of at least 80% will be ensured.

The primary and key secondary efficacy endpoints will be tested for statistical significance following a hierarchical strategy to control the familywise type I error rate using the main estimand. Each test will be considered confirmatory only if the tests at all the previous steps are successful. The hierarchy for the primary and key secondary endpoints is as follows:

- Step 1: Primary endpoint using the main estimand - Tested at a 2-sided 5% significance level
- Step 2: Key-secondary endpoint using the main estimand - Tested at a 2-sided 5% significance level

Of note, the alternative estimand for the primary and key secondary efficacy endpoints is defined for exploratory purpose and it is not included in the hierarchical strategy to control the familywise type I error rate.
See sections 12.3.4 and 12.3.5 for the details on the main and alternative estimand for the primary and key-secondary efficacy endpoints.

12.2 Populations for analysis

- ***Safety set***: all randomised subjects who receive at least one dose of the study drug (analysed as treated).
- ***ITT set***: all randomised subjects who receive at least one dose of the study drug (analysed as randomised).

12.3 Statistical analysis

A detailed statistical analysis plan will be described in the Statistical Analysis Plan (SAP). The plan might be reviewed and updated as a result of the blind review of the data and will be finalized before breaking the blind.

12.3.1 Descriptive Statistics

General descriptive statistics for numeric variables will include the n (number of observed values), the mean, the standard deviation, the median, the minimum, and the maximum values. For categorical variables, the number and percent of subjects with a specific level of the variable will be presented.

12.3.2 Missing data

- If one of the lung function measurements at 45min and 15min pre-dose is not available, then the non-missing measurement will be taken as the pre-dose value. If no measurement is available, then the pre-dose value will be considered as missing.

- A minimum of 7 days with available measurements will be required in each inter-visit period (including run-in period) and in the entire treatment period to consider the following variables as non-missing: morning and evening PEF, use of rescue medication, daily asthma symptoms, percentage of asthma control days.

- For ACQ-7 questionnaire, the total score will be calculated only if all the scores derived from all the seven items are recorded.

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

12.3.3 Subject demographics and baseline characteristics

Demographics and baseline variables will be summarized by treatment arm using descriptive statistics for the ITT population.

12.3.4 Primary efficacy variables

Main estimand

The attributes of the main estimand in terms of population, treatments, variable and population-level summary are provided in Section 2.1. The strategy for intercurrent events and events leading to missing data for the primary analyses and the sensitivity analyses targeting this estimand is summarized below.

Intercurrent event / event leading to missing data	Strategy	Strategy for sensitivity analyses
Early discontinuation from study treatment	*Hypothetical*: Missing FEV_1/FVC values (both on-treatment and off-treatment) will be imputed will be imputed considering MAR assumption in all treatment groups. This approach targets the treatment effect that would have been observed if all subjects had continued the study treatment for the whole study duration.	*Sensitivity 1*: Missing FEV_1/FVC values (both on-treatment and off-treatment) will be imputed considering MNAR assumption: - CR imputation based on BDP/FF 200/6 pMDI arm if reason for treatment discontinuation is likely to be related to study treatment (i.e. adverse event, lack of efficacy, death). - CR imputation based on the relevant treatment arm if reason for treatment discontinuation is not likely to be related to study treatment (i.e. lost to follow-up, consent withdrawal, occurrence of pregnancy, protocol violation, other)

Use of not allowed medication and other important protocol deviations	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.
Wrong study drug intake	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.

Alternative estimand

The attributes of the alternative estimand in terms of population, treatments, variable and population-level summary are the same as the ones provided in Section 2.1 for the main estimand. The strategy for intercurrent events and events leading to missing data for the primary analyses and the sensitivity analyses targeting this estimand is summarized below.

Intercurrent event / event leading to missing data	**Strategy**	**Strategy for sensitivity analyses**
Early discontinuation from study treatment	*Treatment policy*: FEV_1/FVC values collected after the treatment discontinuation will be included in the analysis.	No sensitivity analysis is planned for the alternative estimand
Early discontinuation from study	*Hypothetical*: The collected off-treatment FEV_1/FVC observed on all patients will be considered for the imputation of missing FEV_1/FVC after the study discontinuation of both treatment groups. This approach targets the off-treatment effect that would have been observed if all subjects discontinued from study treatment had consented to continue the study. In case of few collected off-treatment FEV_1/FVC values, the imputation based on the collected off-treatment data could be not appropriate. In this case, a CR imputation based on BDP/FF 200/6 pMDI arm will be considered for all the treatment arms	
Use of not allowed medication and other important protocol deviations	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	

Wrong study drug intake	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	

Analysis

The proportion of subjects exhibiting on average NPAL status over 26 weeks of treatment in the study sub-population meeting PAL criterion at screening will be analysed on the ITT set using a logistic regression model including treatment and region as factors and baseline FEV_1/FVC value (i.e. Week 0, pre-dose) as covariate. The odds ratio for the treatment effect (BDP/FF/GB 100/6/12.5 pMDI vs. BDP/FF 200/6 pMDI) with its 95% Wald CI and corresponding p-value will be estimated by the model. Superiority of BDP/FF/GB 100/6/12.5 pMDI will be demonstrated by a statistically significant difference between treatments (defined as $p<0.05$) favouring BDP/FF/GB 100/6/12.5 pMDI. A subject will be considering exhibiting on average the NPAL status over 26 weeks of treatment if the mean of the 2h post-dose FEV_1/FVC ratios is > 0.7.

Subgroups analyses

For the primary efficacy analysis using the main estimand, subgroups analyses will be performed considering various factors (e.g. Th2 phenotype, sex, BMI and other factors). These subgroups analyses will be pre-planned in the SAP.

12.3.5 Key-Secondary efficacy variables

Main estimand

The attributes of the main estimand in terms of population, treatments, variable and population-level summary are provided in Section 2.2. The strategy for intercurrent events and events leading to missing data for the primary analyses and the sensitivity analyses targeting this estimand is summarized below.

Intercurrent event / event leading to missing data	Strategy	Strategy for sensitivity analyses
Early discontinuation from study treatment	*Hypothetical*: All available data up to study treatment discontinuation (i.e. on-treatment data only) will be included in the analysis. No imputation will be performed for data after study treatment discontinuation. Missing FEV_1 values (both on-treatment and off-treatment) will be managed by the mixed model for repeated measures. This approach implies a MAR assumption on missing data in all	*Sensitivity 1*: Missing FEV_1 values (both on-treatment and off-treatment) will be imputed considering MNAR assumption: - CR imputation based on BDP/FF 200/6 pMDI arm if reason for treatment discontinuation is likely to be related to study treatment (i.e. adverse event, lack of efficacy or death). - CR imputation based on the relevant treatment arm if

	treatment groups, targeting the treatment effect that would have been observed if all subjects had continued the study treatment for the whole study duration.	reason for treatment discontinuation is not likely to be related to study treatment (i.e. lost to follow-up, consent withdrawal, occurrence of pregnancy, protocol violation, other) This sensitivity analysis will be conducted on the imputed complete dataset using an ANCOVA model including treatment and region as fixed effects, and baseline value (i.e. Week 0, pre-dose) as covariates
Use of not allowed medication and other important protocol deviations	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.
Wrong study drug intake	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.

Alternative estimand

The attributes of the alternative estimand in terms of population, treatments, variable and population-level summary are the same as the ones provided in Section 2.2 for the main estimand. The strategy for intercurrent events and events leading to missing data for the primary analyses and the sensitivity analyses targeting this estimand is summarized below.

Intercurrent event / event leading to missing data	**Strategy**	**Strategy for sensitivity analyses**
Early discontinuation from study treatment	*Treatment policy*: FEV_1 values collected after the treatment discontinuation will be included in the analysis.	No sensitivity analysis is planned for the alternative estimand

Early discontinuation from study	*Hypothetical*: The collected off-treatment FEV_1 observed on all patients will be considered for the imputation of missing FEV_1 after the study discontinuation of both treatment groups. This approach targets the off-treatment effect that would have been observed if all subjects discontinued from study treatment had continued the study. In case of few collected off-treatment FEV_1 values, the imputation based on the collected off-treatment data could be not appropriate. In this case, a CR imputation based on BDP/FF 200/6 pMDI arm will be considered for all the treatment arms	
Use of not allowed medication and other important protocol deviations	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	
Wrong study drug intake	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	

Analysis

Change from baseline in pre-dose morning FEV_1 at Week 26 in the study sub-population meeting PAL criterion at screening will be analysed on the ITT set using using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction and region as fixed effects, and baseline value (i.e. Week 0, pre-dose) 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% CIs at Week 26 will be estimated by the model. Superiority of BDP/FF/GB 100/6/12.5 pMDI will be demonstrated by a statistically significant difference between treatments at Week 26 (defined as $p<0.05$, in case the primary variable analysis is successful) favouring BDP/FF/GB 100/6/12.5 pMDI.

Subgroups analyses

For the key-secondary efficacy analysis using the main estimand, subgroups analyses will be performed considering various factors (e.g. Th2 phenotype, sex, BMI and other factors). These subgroups analyses will be pre-planned in the SAP.

12.3.6 Secondary efficacy variables

The secondary efficacy variables will be analyses in the ITT set both in the overall study population and in the study sub-population meeting PAL criterion at screening.

Analyses of secondary efficacy variables are planned to target the same main estimand as described for the primary and key-secondary variables, i.e. excluding off-treatment data for subjects who discontinue the study treatment prior to the planned treatment completion (i.e. 26 weeks of treatment) with:

- *Discontinuation from study treatment* managed with a hypothetical strategy with missing values imputed considering MAR assumption or managed by the statistical model according to the endpoint (in line with the approaches described in sections 12.3.4 and 12.3.5 for the primary and the key-secondary variables).
- *Use of not allowed medication and other important protocol deviations* managed with a treatment policy strategy
- *Wrong study drug intake* managed with a treatment policy strategy

For some secondary efficacy analysis, subgroups analyses might be performed considering various factors (e.g. Th2 phenotype, sex, BMI and other factors). These subgroups analyses will be pre-planned in the SAP.
For the secondary efficacy analyses to be performed in the overall study population, the PAL status at screening (i.e. PAL, NPAL) will be included in the models.

- Proportion of subjects with an increase ≥ 10% in average 2h FEV_1/FVC ratio over 26 weeks compared to post-BD FEV_1/FVC ratio at screening will be analysed with a logistic regression model as described for the analysis of primary efficacy variable.

- Proportion of subjects who consistently exhibit PAL status will be analysed with a logistic regression model as described for the analysis of primary efficacy variable:
  - Proportion of subjects with PAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).
  - Proportion of subjects with NPAL status at screening and at each post-treatment visit (Week 0, 4, 12, 22, and 26).

- Proportion of subjects with 1, 2, 3, 4 or 5 post-treatment visits (among Week 0, 4, 12, 22, and 26) with PAL and NPAL status will be analysed with a logistic regression model as described for the analysis of primary efficacy variable.

- Proportion of subjects with PAL and NPAL status at each post-treatment visit (Week 0, 4, 12, 22, and 26) will be analysed with a logistic regression model as described for the analysis of primary efficacy variable.

- Proportion of subjects exhibiting on average PAL and NPAL status over 26 weeks of treatment will be analysed with a logistic regression model as described for the analysis of primary efficacy variable.

- Change from baseline in 2h post-dose FEV_1 at all clinic visits will be analysed with a linear mixed model for repeated measures as described for the analysis of the key-secondary efficacy variable.

- Change from baseline in 2h post-dose FEV_1/FVC at all clinic visits and over 26 weeks of treatment will be analysed with a linear mixed model for repeated measures as described for the analysis of the key-secondary efficacy variable.

- Change from baseline in pre-dose morning FEV_1 at all clinic visits will be analysed with a linear mixed model for repeated measures as described for the analysis of the key-secondary efficacy variable.

- FEV_1 response (Change from baseline ≥ 100 mL in pre-dose FEV_1) at Week 26 will be analysed with a logistic regression model as described for the analysis of the primary efficacy variable, including baseline FEV_1 (i.e. Week 0, pre-dose) as covariate.

- Severe asthma exacerbations rate over 26 weeks of treatment will be analysed using a negative binomial model including treatment, region, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset.

- Moderate or severe asthma exacerbations rate over 26 weeks of treatment will be analysed using a negative binomial model including treatment, region, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset.

- Time to first severe asthma exacerbations rate will be analysed using a Cox proportional hazards model including treatment, region, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.

- Time to first moderate or severe asthma exacerbations rate will be analysed using a Cox proportional hazards model including treatment, region, number of exacerbations in the previous year (1 or >1) as factors. A Kaplan-Meier plot will also be presented.

- Number of days with use of Oral Systemic Corticosteroids (OCS) will be analysed using a negative binomial model including treatment, region, and number of exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset.

- Change from baseline in pre-dose and 2h post-dose FVC at all clinic visits will be analysed with a linear mixed model for repeated measures as described for the key-secondary efficacy analysis, including baseline FVC (i.e. Week 0, pre-dose) as covariate.

- Change from baseline in average morning PEF over 26 weeks of treatment and at each inter-visit period will be analysed using a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction and region as fixed effects, and baseline value and baseline by period interaction as covariates.

- Change from baseline in average evening PEF over 26 weeks of treatment and at each inter-visit period will be analysed using a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction and region as fixed effects, and baseline value and baseline by period interaction as covariates.

- Change from baseline in Blood Eosinophils at Week 26 will be analysed by descriptive statistics.

- Change from baseline in Symptom-Free Days over 26 weeks of treatment and at each inter-visit period will be analysed with a linear mixed model for repeated measures as described for the PEF.

- Change from baseline in rescue SABA use over 26 weeks of treatment and at each inter-visit period will be analysed with a linear mixed model for repeated measures as described for the PEF.

- Change from baseline in daily (morning and evening) asthma symptoms over 26 weeks of treatment and at each inter-visit period will be analysed with a linear mixed model for repeated measures as described for the PEF.

- Change from baseline Asthma control days over 26 weeks of treatment and at each inter-visit period will be analysed with a linear mixed model for repeated measures as described for the PEF.

- Change from baseline in ACQ-7, ACQ-5 and AQLQ at Week 12 and Week 26 will be analysed with a linear mixed model for repeated measures as described for the analysis of the key-secondary variable, including baseline ACQ-7, ACQ-5 or AQLQ (i.e. Week 0) as covariate.

12.3.7 Exploratory variables

- Average Healthcare resource utilization (HCRU) over the 26 weeks of treatment period for each treatment group will be analysed by descriptive statistics.

- Change from baseline in oscillometric parameters at all clinic visits (resistance, reactance) will be analysed with a linear mixed model for repeated measures as described for the analysis of the key-secondary variable, including baseline value of the oscillometric parameter (i.e. Week 0) as covariate.

- Change from baseline in FeNO at Week 26 will be analysed by descriptive statistics.

- Details on change from baseline in home spirometry parameters will be specified in the SAP.

12.3.8 Safety variables

Safety analysis will be based on Safety set. For subjects who discontinue study drug but remain in the study, assessments conducted following 1 week after the last dose of study drug will not be considered in analysis or presentation of safety data.

Adverse Events
All adverse events starting on or after the time of first study treatment intake and up to 1 week after the last dose of study treatment intake will be classified as treatment emergent adverse even (TEAE).
Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse events.
Any adverse events started later than 1 week after the last dose of study drug will be considered as post-treatment adverse events.

The number of subjects who experienced at least one TEAE, drug-related TEAE, serious TEAE, non-serious TEAEs, serious related TEAE, TEAE leading to study discontinuation, and TEAE leading to death will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events) and by System Organ Class and Preferred Term (number and percentage of subjects having at least one occurrence of that event). All adverse events will be listed. Pre-treatment adverse event will be listed only.

ECG
ECG parameters will be summarised for each treatment group and visit by descriptive statistics.

Vital signs
Vital signs will be summarised for each treatment group and visit by descriptive statistics.

Laboratory data
The laboratory values will be summarised for each treatment group and visit by descriptive statistics.

12.3.9 Interim analysis

No interim analysis is planned.

13 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

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

The EC 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 will be provided to the Sponsor.

The Investigator should provide written reports to the EC 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 has been obtained and the study notified to Health Authorities (or authorized by).

15 INFORMED CONSENT

Informed consent must be written in a language understandable to the subjects. It is the responsibility of the Investigator to obtain written consent from each subject prior to any study related procedures taking place, by using the latest EC/IRB approved version of the document.

Adequate time shall be given to the subject to enquiry the PI about any clarification needed and to consider his or her decision to participate to the trial.
If the subject is unable to read, they are not eligible to enter the study. According to the inclusion criteria #10, subject has to be able to read and answer questionnaires and use the e-Diary device all along the study.

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.
In case of rescreening, the subject should sign a new informed consent and will be assigned with a new subject number; a link to prior subject number will be recorded in the eCRF.

Female subjects becoming pregnant during the study and partner of a subject participating to the study becoming pregnant will have to sign a specific informed consent form to provide permission to Chiesi to collect information about the pregnancy, its outcome and the birth and health of the newborn child.
In case of pregnancy during the study, if the subject partner and his/her legal representative are unable to read, the specific informed consent for pregnancy follow-up will be obtained in the presence of an impartial witness, eg., a person independent of the study who will read the informed consent form and the written information for the subject partner.

16 SOURCE DOCUMENTS/DATA

16.1 Recording of source data

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

16.2 Direct access to source document/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 Labcorp) 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, provided that subject confidentiality is respected. Whenever needed (e.g in case of emergency or sanitary situations), the monitoring CRO and sponsor may agree to convert planned physical visits into phone or video visits, to postpone or completely cancel planned visits.

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 eCRF 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 MANAGEMENT AND ASSURANCE

The sponsor will implement processes to manage quality and oversight throughout all stages and activities of the trial based on data and processes identified as critical for the subjects' rights and safety as well as data reliability and robustness.
Quality management will include tools, and procedures for data collection and processing, as well as the collection of information essential to decision making.
The quality management system will use a risk-based approach as described in ICH E6 with:

- Critical Process and Data Identification
- Risk Identification/Evaluation/Control/Communication and Review
- Risk Reporting

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 current ICH E6 Good Clinical Practices [48] and the protocol.

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. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21 PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.

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

22 CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to Co-ordinating Investigator's 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 the 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 and, if they fall under the Chiesi commitments on Clinical Trial Transparency, to make them available on www.chiesi.com website.
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 according to the relevant regulatory requirements.

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APPENDIX 1 - Approval of the protocol by clinical investigator(s)

A 26 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN SUBJECTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS (**MiSTIC**)

Product: CHF 5993

Pharmaceutical Form: Pressurized metered dose inhaler

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 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 Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

International Coordinating Investigator's Name: _____, MD

Centre No.: _____

_____ _____
Signature Date

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

APPENDIX 2 - Approval of the protocol by clinical investigator(s)

A 26 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN SUBJECTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS (**MiSTIC**)

Product: CHF 5993

Pharmaceutical Form: Pressurized metered dose inhaler

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 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 Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Country-Specific Coordinating Investigator's Name: _____, MD

Centre No.: _____

_____ _____
Signature Date

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

APPENDIX 3 - Approval of the protocol by clinical investigator(s)

A 26 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 2-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 100/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE FORMULATION OF BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) IN SUBJECTS WITH ASTHMA UNCONTROLLED ON MEDIUM DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS (**MiSTIC**)

Product: CHF 5993

Pharmaceutical Form: Pressurized metered dose inhaler

Approval of Clinical Study Protocol by the Principal Investigator:

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

I understand that this trial will not be initiated without Ethics Committee 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 Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Principal Investigator's Name: _____ , MD

Centre No.: _____

_____ _____
Signature Date

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

APPENDIX 4 – Recommendations related to contraception and pregnancy testing in clinical trials

Birth control methods, which may be considered as highly effective

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable [3]
- intrauterine device (IUD) [3]
- intrauterine hormone-releasing system (IUS) [3]
- bilateral tubal occlusion [3]
- vasectomised partner [1, 3]
- sexual abstinence [2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[3] Methods with low user dependency

Definition of women of childbearing potential and of fertile men

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Reference: Recommendations related to contraception and pregnancy testing in clinical trials (Clinical Trial Facilitation Group. Final version 1.1 dd. 21/09/2020).