NCT03453112

# CCD-01535BA0-01

## CLINICAL STUDY PROTOCOL

## IND No: 2015L06250

**A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma**

Version No.:7.0
Date: 31 August 2020



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

# GENERAL INFORMATION

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| **SPONSOR**: | Chiesi Farmaceutici S.p.A.*<br>Via Palermo 26/A<br>43122 Parma - Italy<br>+ 39 0521 2791<br><br>*also reported as Chiesi throughout the text |
| **CLINICAL STUDY MANAGER:** | PPD |
| **SPONSOR MEDICAL EXPERT (Clinical Research Physician)** | PPD<br>Chiesi Farmaceutici S.p.A.<br>via Palermo 26/A<br>I-43122 Parma, Italy<br>PPD<br>Readily available in case of medical questions |
| **INVESTIGATOR Coordinating Investigator)** | ***Pr Zheng Jinping 郑劲平***<br>National Clinical Research Center of Respiratory Disease,<br>Guangzhou Institute of Respiratory Disease<br>First Affiliated Hospital of Guangzhou Medical University<br>151 Yanjiang Rd. Guangzhou 510120, China<br>PPD<br>PPD |
| **MONITORING CRO** | PPD |
| **CENTRAL TECHNICAL LABORATORY OF SPIROMETRY** | PPD |

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| Clinical Study Code: CCD-01535BA0-01 | Version No.:7.0 |
| IND No.: 2015L06250 | Date: 31/08/2020 |

## VERSION HISTORY

| Version No. | Version date | Description of changes |
|---|---|---|
| 4.0 | 16 November 2017 | - Change of Principal Investigator and Chiesi Clinical Research Physician<br>- Clinical visit revised time slot: between 7:00 and 9:00 a.m. ***(+/- 2 hours)*** |
| 5.0 | 12 June 2018 | - Inclusion criteria N° 2: Diagnosis of asthma must be confirmed through a documented positive response in the last ***twenty-four months*** to ***either*** a reversibility test or ***Bronchial challenge test***.<br>***In case the patient does not have any documented reversibility test or challenge test, Salbutamol Reversibility Test will be performed at Visit 1.***<br>Reference to ***GINA 2018***<br>- Inclusion criteria N° 3: $FEV_1$ threshold: ***If this criterion is not met at Visit 1: the test can be repeated once before Visit 2 or at Visit 2.***<br>- Inclusion criteria N°5: Previous regular treatment at stable dose for at least ***1*** month prior to Visit 1. Dosage of previous therapy is enlarged: Either ***medium*** or high daily dose of ICS monotherapy OR ***low*** or medium daily dose of ICS / LABA free/fixed combination.<br>- Visit 1 (screening visit) description is updated according the revisions of inclusion criteria N° 2 (asthma diagnosis) and inclusion criteria N° 2 ($FEV_1$ threshold)<br>- Change of Chiesi Global Pharmacovigilance Operations Specialist<br>- Appendices numbering is updated as Protocol approbation is appendix I according to the new template. |
| V6.0 | 15 July 2018 | - Further clarification on inclusion criteria N°2<br>- A spacer will be provided to every patient who will need such a device for pMDI intake<br>- Update Safety contacts |
| V7.0 | 31 August 2020 | - Update of the number of sites<br>- Update of screened patients number and Screening Failure rate<br>- Update of Most relevant forbidden concomitant treatments section: Addition of "Selective Serotonin Re-uptake Inhibitors".<br>- Update of Global Pharmacovigilance Operations Specialist details. |

# PROTOCOL OUTLINE

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| **Study title** | A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler® , 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma |
| **Sponsor** | Chiesi Farmaceutici S.p.A.<br>Via Palermo 26/A<br>43122 Parma - Italy |
| **Name of the Product** | Foster® 100/6µg NEXThaler® (fixed combination of beclomethasone dipropionate 100µg/formoterol 6µg) |
| **Centres** | About 50 sites in China |
| **Indication** | Asthma |
| **Study design** | Multicentre, randomized, double-blind, double-dummy, 2-arm parallel group, non-inferiority clinical trial design preceded by a 4-week run-in period and 12-week treatment period. |
| **Study phase** | Phase III |
| **Objectives** | **Primary objective**<br>To demonstrate the non-inferiority of Foster®100/6µg NEXThaler® versus Foster® 100/6µg pMDI in terms of pulmonary function (change from baseline to the entire treatment period in average pre-dose morning PEF) in asthmatic patients.<br><br>**Secondary objectives**<br>To evaluate the effect of the test treatments in terms of additional lung function parameters and clinical outcome measures and to assess the safety and tolerability. |
| **Treatment duration** | 4-week run-in period followed by a 12-week randomized treatment period. During the 4-week run-in period, asthma patients will receive Foster® 100/6µg pMDI (two puffs b.i.d.) in a pressurised solution for inhalation. |
| **Test product dose/route/regimen** | Foster® 100/6µg NEXThaler® (Group A) fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation as inhalation powder with a new dry powder inhaler (NEXThaler®).<br>In Group A, Foster® 100/6µg NEXThaler® will be administered as two inhalations b.i.d. (total daily dose 400/24 µg). |

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| **Reference product dose/route/regimen** | Foster® 100/6µg pMDI (Group B) fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation as pMDI with HFA-134a propellant.<br>In Group B, Foster® 100/6µg pMDI will be administered as two puffs b.i.d. (total daily dose 400/24 µg). |
| **Number of subjects** | 220 evaluable patients per treatment group will be required. Estimating a non-evaluable rate of 10%, a total of about 490 patients (245 per treatment group) will be randomized. Anticipating a screening failure rate of 50%, a total number of about 1000 patients will be screened. |
| **Study population** | Male or female patients aged ≥ 18 years with asthma |
| **Inclusion/exclusion criteria** | **Inclusion criteria**<br>1. Male or female outpatients, Chinese ethnicity aged ≥ 18, who have signed an Informed Consent form prior to initiation of any study-related procedure.<br>2. Clinical diagnosis of asthma for a minimum of 6 months prior to Visit 1 confirmed by a chest physician according to international guidelines updated 2018 (GINA). The evidence of asthma must be confirmed through a documented positive response (in the last twenty-four months) either to a bronchial provocation test/challenge test or a reversibility test.<br>3. In case the patient does not have any documented reversibility test or provocation/challenge test, Salbutamol Reversibility Test will be performed at Visit 1 within 10 to 30 min after administration of 400 µg of salbutamol pMDI (ATS/ERS taskforce 2005). Positive test if $\Delta FEV_1 \geq 12\%$ and ≥ 200 mL over baseline.<br>4. Note: In case the reversibility threshold is not met at Visit 1, the test can be repeated once before Visit 2 or at Visit 2.<br>5. $FEV_1$>80% of the predicted normal value after appropriate washout from bronchodilators (to be checked at Visit 1 and at randomization visit (Visit 3).<br>Note: If this criterion is not met:<br>• At Visit 1: the test can be repeated once before Visit 2 or at Visit 2.<br>• At randomization visit: the test can be repeated once within 2 days after this visit.<br>6. ACQ-6 (simplified version of the Asthma Control Questionnaire) score < 0.75 (to be checked at Visit 1and at randomization visits).<br>7. Patients on previous regular treatment at a stable dose for at least 1 month prior to Visit 1 with either medium daily dose of ICS monotherapy (e.g., BDP-CFC > 500 – 1000 µg/day or equivalent dose) or high daily dose of ICS monotherapy (e.g., BDP-CFC > 1000 µg/day or equivalent dose) OR low daily dose of ICS (e.g., BDP-CFC≥200 – 500 µg/day or equivalent dose)/ LABA free/fixed combination or medium daily dose of ICS (e.g., BDP- |

CFC > 500 – 1000 µg/day or equivalent dose)/ LABA free/fixed combination.

8. A cooperative attitude and ability to be trained to the proper use of DPI and pMDI devices and electronic peak flow meter (to be checked at Visit 1and at randomization visits).
9. At least 7 valid pre-dose morning PEF measurements in the last 14 days of the run-in period are necessary (to be checked at randomization visit).

**Exclusion criteria**

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are using one or more of the following highly effective contraceptive measures:
   - Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
   - Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
   - Bilateral tubal occlusion
   - Vasectomised partner
   - Sexual abstinence

   Reliable contraception should be maintained throughout the study.

   Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study.
2. Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at Visit 1 and end of treatment (V9), urine pregnancy test will be performed at all visits except V0 and V9.
3. Intermittent asthma or asthma occurring only during episodic exposure to an allergen or a chemical sensitizer.
4. History of near fatal asthma (e.g., brittle asthma, hospitalization for asthma exacerbation in an Intensive Care Unit).
5. Diagnosis of COPD as defined by the current GOLD guidelines updated 2016.
6. Current smokers, or ex-smokers with total cumulative exposure equal or more than 10 pack-years, or having stopped smoking one year or less prior to Visit 1.
7. Severe asthma exacerbation leading to intake of systemic corticosteroids (≥10 days) within 1 month prior to inclusion or

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| | moderate/severe asthma exacerbation [according to international guidelines updated 2018 (GINA) and Reddel et al. definition [13] during the run-in period (to be checked at Visit 1 and at Visit V3 (randomization).<br>8. Lower respiratory tract infections (e.g. pneumonia) affecting the patient's asthma within 1 month prior to inclusion.<br>9. History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease.<br>10. Diagnosis of restrictive lung disease.<br>11. Patients treated with oral or parenteral corticosteroids in the previous 2 months before Visit 1 (3 months for parenteral depot corticosteroids).<br>12. Intolerance or contra-indication to treatment with β2-agonists and/or inhaled corticosteroids or allergy to any component of the study treatments.<br>13. Having received an investigational medication within 2 months before Visit 1.<br>14. Patients who have a clinical or functional uncontrolled respiratory, haematological, immunologic, renal, neurologic, hepatic, endocrinal or other disease, or any condition (e.g. major surgery) that might, in the judgment of the investigator, represent for the patients an undue risk or that could compromise the results or interpretation of the study.<br>15. History or current evidence of uncontrolled heart failure, clinically relevant coronary artery disease, recent myocardial infarction, severe hypertension, uncontrolled cardiac arrhythmias.<br>16. Clinically relevant laboratory abnormalities such as (but not limited to) hypokalemia (< 3.5 mEq/l), that might compromise patient's safety or compliance, interfere with evaluation, or preclude completion of the study, in the judgment of the investigator. Patients with uncontrolled diabetes including patients with a history of serum glucose levels consistently out of the normal range (> 140 mg/dl) or HbA1C >8.0%.<br>17. Patients who have an abnormal 12-lead ECG parameter (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female) or 12-lead ECG evaluated as abnormal clinical significant by the investigator, at Visit 1.<br>18. Patients who have a concomitant disease of poor prognosis (e.g., cancer).<br>19. Patients treated with monoclonal antibodies (e.s anti-IgE antibodies).<br>20. Patients treated with non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication), non-selective β-blocking medications, |

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| | quinidine, quinidine-like antiarrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation.<br>21. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, unless already taken at stable doses in the month before the Visit 1 and without any safety concern.<br>22. Patients who are receiving therapy that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin).<br>23. Inability to comply with study procedures or with study treatment intake. |
| **Study plan** | Throughout the study, various assessments and tests will be performed according to the Study Flow Diagram and Time and Events Chart.<br>A total of ten clinic visits will be performed during the study:<br>- *Visit 0 (**V0**)*: Pre-screening visit (at week -5 before the randomization visit);<br>- *Visit 1 (**V1**)*: Screening visit, start of 4-week run-in period;<br>- *Visit 2 (**V2**)*: after 2 weeks of run-in period;<br>- *Visit 3 (**V3**)*: randomization visit;<br>- *Visit 4 (**V4**)*: after 2 weeks of treatment;<br>- *Visit 5 (**V5**)*: after 4 weeks of treatment;<br>- *Visit 6 (**V6**)*: after 6 weeks of treatment;<br>- *Visit 7 (**V7**)*: after 8 weeks of treatment;<br>- *Visit 8 (**V8**)*: after 10 weeks of treatment;<br>- *Visit 9 (**V9**)*: after 12 weeks of treatment.<br>- *Follow-up phone contact*: after 7-10 days of last study medication intake.<br>During treatment period a "window" of ±3 days is allowed. |
| **Most relevant allowed concomitant treatments** | **<u>Permitted concomitant Medications (run-in and randomized treatment periods)</u>**<br>1. Inhaled salbutamol administered as rescue medication during the study period. A minimum period of 6 hours should elapse between the use of rescue salbutamol and the lung function measurements.<br>2. Other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers, theophylline) if already taken at stable doses during 3 months prior to Visit 1 and to be maintained at a constant dose during the study.<br>3. Nasal corticosteroids and antihistamines if already taken at stable doses for 2 months prior to Visit 1 (the dose must remain constant during the study).<br>4. Treatment for desensitisation at the "maintenance" phase if already taken at stable doses for at least 1 month prior to Visit 1 (the dose must remain constant for the whole study period). Sublingual |

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| | immunotherapy started before the study can be continued at a stable dose.<br>5. Short courses (each course of maximum 10 days for a maximum of three times) of antihistamines or nasal corticosteroids for the treatment of hay-fever.<br>6. Short courses (< 10 days) of systemic corticosteroid and brief use of nebuliser (containing β2-agonists, anticholinergics and steroids), and antibiotics therapy for asthma exacerbation during the study (*a 3-day washout period since last systemic steroid intake must be respected before each clinic visit*).<br>In case of other concomitant diseases, any appropriate treatment that, according to the investigator, does not interfere with the study evaluation parameters is allowed. |
| **Most relevant forbidden concomitant treatments** | **<u>Non-permitted concomitant Medications (run-in and randomized treatment period)</u>**<br>The following medications are not permitted during the total study period starting from Visit 1 (run-in and treatment period). Intake of these medications during run-in constitutes a noneligibility criterion and the patient will not be randomised into the study. **If any of these medications is taken during the randomised treatment period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest.**<br>1. Inhaled corticosteroids (in the 12 hours preceding screening Visit 1 and during the study period).<br>2. Inhaled short acting β2-agonists (other than nebulised and "rescue" salbutamol) throughout the study period. The use of "rescue" salbutamol should be avoided in the 6 hours preceding all the clinic visits.<br>3. Inhaled long acting β2-agonists in the 24 hours preceding Visit 1 and during the study period.<br>4. Inhaled fixed combinations of corticosteroids and long acting β2-agonists (other than study treatments) (e.g. formoterol plus budesonide) in the 24 hours preceding Visit 1 and during the study period.<br>5. Chronic treatment with systemic corticosteroids.<br>6. Systemic corticosteroids (≥ 10 days) in the month prior to Visit 1 and during the study.<br>7. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), unless already taken at stable doses in the month before Visit 1 and without any safety concern.<br>8. Antihistamines and nasal corticosteroids (exceptions listed under "Permitted Concomitant" medication). |

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| | 9. Short-acting and long-acting anticholinergics (apart from those listed in permitted medication - a washout of 12 hours for short acting and 72 hours for long acting before visit 1 is required).<br>10. Non-selective β-blocking medications (including eye drops).<br>11. Non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication).<br>12. Quinidine and quinidine-like antiarrhythmics.<br>13. Any medication with a QTc prolongation potential.<br>14. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit.<br>15. Any medication that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin).<br>16. Monoclonal antibodies (e.g. anti-IgE antibodies.)<br>17. Traditional Chinese medicines that can interfere with study drugs and/or affect the study outcomes according to investigator's opinion to be stopped before Visit 2 |
| **Efficacy variables** | **<u>Primary efficacy variable</u>**<br>Change from baseline to the entire treatment period in average pre-dose morning PEF.<br><br>**<u>Secondary efficacy variables</u>**<br>– Changes from baseline to each inter-visit treatment period in:<br>• *average pre-dose morning PEF;*<br>– Changes from baseline to each inter-visit treatment period and to the entire treatment period in:<br>• *average pre-dose evening PEF;*<br>• *daily PEF variability;*<br>• *average use of rescue medication (number of puffs/day);*<br>• *percentage of rescue-use free days;*<br>• *average total morning asthma symptom scores;*<br>• *average total evening asthma symptom scores;*<br>• *percentage of asthma symptoms-free days;*<br>• *percentage of asthma control days.*<br>– Changes from baseline in pre-dose morning $FEV_1$ and FVC at each clinic visit.<br>– Change from baseline to end of treatment in the Asthma Control Questionnaire (ACQ) score. |
| **Safety variables** | – Adverse events and adverse drug reactions.<br>– Vital signs (heart rate, systolic and diastolic blood pressure in sitting position at V1 and pre-dose at each visit from V3.).<br>– Moderate / severe asthma exacerbations.<br>– Abnormalities at 12-lead ECG at V1 and pre-dose at V9. |

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| **Sample size calculation** | Two hundred and twenty evaluable patients per group will provide approximately 85% power to test the non-inferiority hypothesis of Foster® 100/6µg NEXThaler® vs. Foster® 100/6µg pMDI, in terms of change from baseline to the entire treatment period in average pre-dose morning PEF. The following conditions and assumptions have been imposed: non-inferiority margin of -15 l/min; a one-sided significance level of 0.025; an expected mean difference of 0 l/min between treatments; a standard deviation of 52 l/min.<br>Estimating a non-evaluable rate of 10% a total number of about 490 patients will be randomized.<br>Anticipating a screening failure rate of 50%, a total number of about 1000 patients will be screened. |
| **Statistical methods** | **Primary efficacy variable**<br>Change from baseline to the entire treatment period in average pre-dose morning PEF will be analysed using an ANCOVA model including treatment, center and sex as factors and baseline as a covariate. Non-inferiority will be demonstrated if the lower limit of the 95% confidence interval (CI) of the adjusted mean difference between Foster® 100/6µg NEXThaler® and Foster® 100/6µg pMDI will be ≥ -15 l/min.<br><br>**Secondary efficacy variables**<br>– All the variables measured repeatedly during the randomized treatment period will be analysed using a linear mixed model for repeated measures (MMRM) including change from baseline at each inter-visit period as dependent variable, treatment, visit/period, treatment × visit/period interaction, center and sex as fixed effect, baseline and baseline × visit/period interaction as fixed covariates.<br>– Change from baseline at each clinic visit in pre-dose morning FEV1 and FVC will be analysed using a linear mixed model for repeated measures (MMRM) including change from baseline at each visit as dependent variable, treatment, visit/period, treatment × visit/period interaction, center and sex as fixed effect, baseline and baseline × visit/period interaction as fixed covariates.<br>– All the variables calculated over the entire treatment period and change from baseline to end of treatment in the ACQ score will be analysed using the same ANCOVA model as for the primary efficacy variable.<br>– For all the variables, analyses within treatment groups will be presented. The mean changes from baseline and their 95% confidence intervals (CIs) will be calculated.<br>For primary and secondary efficacy variables, baselines will be based on the last two weeks of the run in period.<br><br>**Safety variables**<br>– The number and the percentage of patients experiencing adverse events, adverse drug reactions, serious adverse events and adverse events leading to study withdrawal will be summarized by |

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| | treatment group. Adverse events will also be summarized by System Organ Class and Preferred Term using the MedDRA dictionary.<br>– Vital signs (heart rate, systolic and diastolic blood pressure) will be summarized by treatment group using descriptive statistics, and changes from baseline with their 95% CIs will be presented.<br>– ECG parameters (HR, PR, QRS and QTcF) will be summarized at Visit 1 and Visit 9 by treatment group using descriptive statistics. Change from baseline (V9 vs V1) with their 95% CIs will also be presented.<br>– The number and percentage of subjects with an abnormal ECG (i.e.: QRS > 120 msec, PR > 210 msec, HR< 45 bpm or HR > 110 bpm, QTcF > 450 ms for males or QTcF > 470 ms for female,) will be summarised by treatment group at Visit 1 and Visit 9.<br>– The number of moderate/severe asthma exacerbations and the number and the percentage of patients experiencing moderate/severe asthma exacerbations will be summarized by treatment group. |

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
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| **ACQ** | Asthma Control Questionnaire® |
| **ADR** | Adverse Drug Reaction |
| **AE** | Adverse Event |
| **ANCOVA** | Analysis of Covariance |
| **AST** | Aspartate Aminotransferase |
| **BAM** | Breath-actuated mechanism |
| **BDP** | Beclomethasone Dipropionate |
| **b.i.d** | *Bis in die*, Twice a Day |
| **BTPS** | Barometry, Temperature and Pressure Saturation |
| **BP** | Blood pressure |
| **CI** | Confidence Interval |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CRA** | Clinical Research Associate |
| **CRO** | Clinical Research Organization |
| **DBP** | Diastolic Blood Pressure |
| **DPI** | Dry Powder Inhaler |
| **EC** | Ethics Committee |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic Case Report Form |
| **e.g.** | *Exempli gratia,* For Example |
| **$FEV_1$** | Forced Expiratory Volume within the 1st second |
| **FF** | Formoterol Fumarate |
| **FPFV** | First Patient First Visit |
| **FSH** | Follicle Stimulating Hormone |
| **FVC** | Forced Vital Capacity |
| **GCP** | Good Clinical Practice |
| **γ GT** | Gamma Glutamyl Transferase |
| **GINA** | Global Initiative for Asthma |
| **GMP** | Good Manufacturing Practice |
| **GOLD** | Global Initiative for Chronic Obstructive Lung Disease |
| **H** | Hour |
| **HB** | Haemoglobin |
| **β-HCG** | Human Chorionic Gonadotrophin |
| **Hct** | Hematocrit |
| **ICH** | International Conference on Harmonization |
| **ICS** | Inhaled Corticosteroids |
| **i.e.** | *Id est*, Meaning |
| **IgE** | Immunoglobulin E |
| **IRB** | Institutional Review Board |
| **IRT** | Interactive Response Technology |
| **ITT** | Intention to Treat |
| **IU** | International Unit |
| **IUD** | Intra Uterin Device |
| **L** | Litre |
| **LABA** | Long-acting β2-agonist |
| **LPLV** | Last Patient Last Visit |
| **MAOI** | Monoamine Oxidase Inhibitor |
| **max** | Maximum |

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| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **µg** | Micrograms |
| **min** | Minutes |
| **mL** | Millilitre |
| **PEF** | Peak Expiratory Flow |
| **PLT** | Platelets |
| **pMDI** | Pressurized Metered Dose Inhaler |
| **PP** | Per-Protocol |
| **QTc** | Time Interval Between the Q and T wave in the ECG (corrected for heart rate) |
| **QTcB** | Bazett-Corrected QTc |
| **RBC** | Red Blood Cells |
| **SAE** | Serious Adverse Event |
| **SAP** | Statistical Analysis Plan |
| **SBP** | Systolic Blood Pressure |
| **SmPC** | Summary of Product Characteristics |
| **SSRI** | Selective Serotonin Re-uptake Inhibitor |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **V** | Visit |
| **WBC** | White Blood Cells |

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**APPENDICES**

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# 1. BACKGROUNG INFORMATION AND STUDY RATIONALE

## 1.1 Introduction

Asthma is a serious public health problem throughout the world, affecting people of all ages. The disease is characterized by a chronic airway inflammation [1] associated with airway hyperresponsiveness and leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning [1]. These episodes are usually associated with airway narrowing characterized by expiratory airflow limitation [1].

The International Guidelines (GINA 2018) [1] indicate that the goal of asthma treatment is to achieve and to maintain clinical control of the disease. In this respect, inhaled corticosteroids (ICS) and long acting $\beta_2$-agonists (LABA) are classified as controllers. They are medications taken daily on a long-term basis to keep asthma under clinical control [1].
ICS have been shown to reduce asthma symptoms [2], improve quality of life [2] and lung function [2], decrease airway hyperresponsiveness [3], control airway inflammation [3], reduce frequency and severity of exacerbations [4], and asthma mortality [5]. Even though LABA should not be used as monotherapy in asthma as these medications do not appear to influence the airway inflammation in asthma, they are effective when combined with inhaled corticosteroids, and this combination therapy is the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma [6]. Addition of LABA to a daily regimen of inhaled corticosteroids improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of short-acting inhaled $\beta_2$-agonists, reduces the number of exacerbations, and achieves clinical control of asthma in a greater number of patients, more rapidly, and at a lower dose of inhaled corticosteroids than inhaled corticosteroids given alone [7]. Controlled studies have shown that delivering these therapy in a combination inhaler is as effective as giving each medication separately, but fixed combination inhalers are deemed to be more convenient for asthmatic patients, to increase compliance and to ensure that the LABA is always accompanied by ICS [8], [9]. The same GINA Guidelines suggest to titrate the asthma therapy to the minimum dose required to maintain the control of the disease reducing the potential for adverse effects [1].

Foster® pMDI 100/6 µg per actuation (Chiesi Farmaceutici S.p.A.) is a fixed combination of a glucocorticoid, beclomethasone dipropionate (BDP) 100 µg and a long-acting, selective $\beta_2$-adrenergic receptor agonist, formoterol fumarate (FF) 6 µg delivered via a pressurised metered dose inhaler (pMDI) with an "extrafine" particle fraction.

The efficacy and safety of Foster® pMDI (Beclometasone Dipropionate and Formoterol Inhalation Aerosol) 100/6 µg per actuation, were demonstrated in adult patients with moderate or severe persistent asthma at the dose of 1 or 2 inhalations twice daily.

It has been first approved in Germany in 2006 and registered in China on February 3rd, 2013. As of today, the product has been approved in 66 European and non-European countries.

## 1.2 Rationale

In order to expand the therapeutic opportunity to patients and health care providers for asthma control, Chiesi has developed a new formulation of Foster® as inhalation powder with a new dry powder inhaler called NEXThaler®. This formulation maintains the same strength/actuation of the active components (BDP 100 µg / FF 6 µg) as the approved Chiesi pMDI formulation. This new inhaler will provide physicians and patients with an alternative choice of delivery system, expected to improve compliance and potentially avoiding the incomplete availability of the medication to the lungs that

may take place in poorly coordinating patients. The NEXThaler® is a novel, pocket size, reservoir dry powder inhaler, capable of delivering the dose through a breath-actuated mechanism (BAM), which triggers dose delivery with low inspiratory effort. This device has been designed in order to achieve consistency in formulation metering and better ease of use for greater patients' compliance. Clinical trials have already demonstrated the efficacy and safety profile of the formulation Foster®100/6µg delivered via NEXThaler® or pMDI even at high doses.

The aim of the present study is to compare the efficacy and safety of Foster® 100/6µg NEXThaler® (total daily dose 400/24 µg) with the equivalent dose of Foster® 100/6µg pMDI (total daily dose 400/24 µg) in controlled asthmatic patients.

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

## 2. STUDY OBJECTIVES

### 2.1 Primary objective

To demonstrate the non-inferiority of Foster®NEXThaler® 100/6 µg versus Foster®pMDI 100/6 µg in terms of pulmonary function (change from baseline to the entire treatment period in average pre-dose morning PEF) in asthmatic patients.

### 2.2 Secondary Objectives

To evaluate the effect of the test treatments in terms of additional lung function parameters and clinical outcome measures, and to assess the safety and tolerability.

## 3. STUDY DESIGN

It will be a phase III, multicentre, randomized, double-blind, double-dummy, 2-arm parallel group design preceded by a 4-week run-in period, in male or female patients aged ≥ 18 years with asthma.

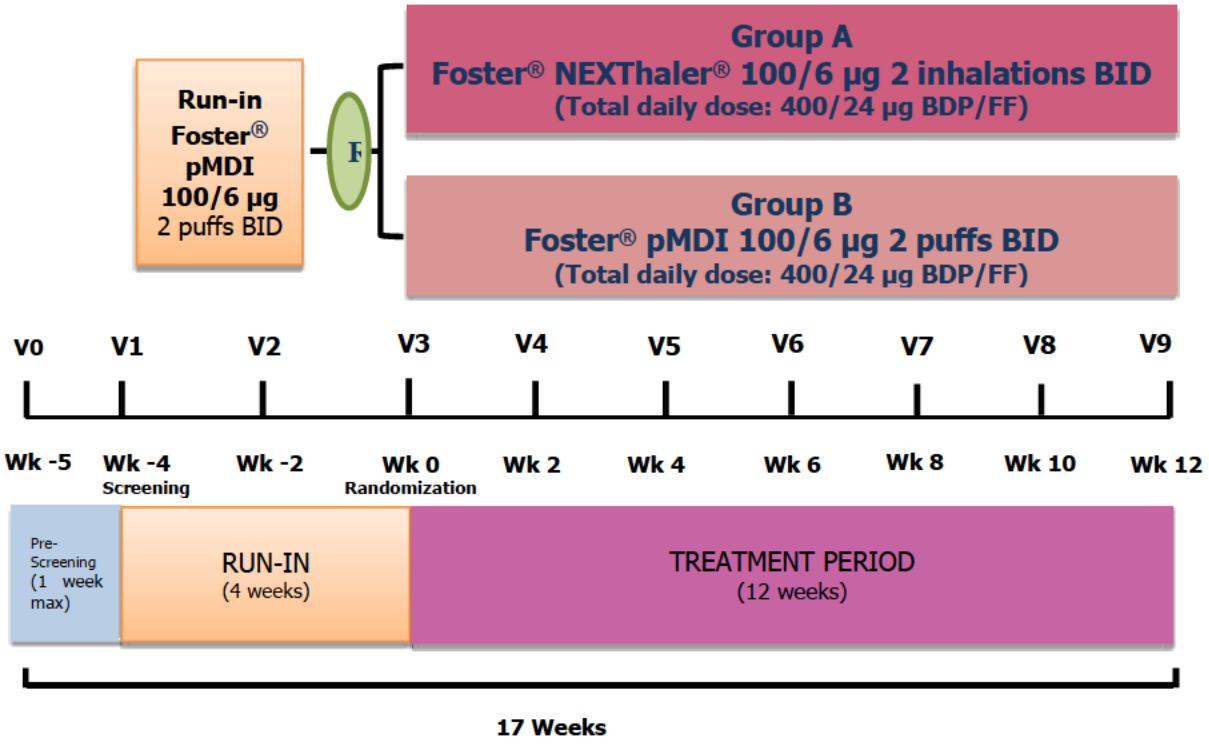
Throughout the study, various assessments and tests will be performed according to the Study Flow Diagram and Time and Events Chart.

A total of ten clinic visits will be performed during the study:

- *Visit 0 (**V0**)*: Pre-screening visit (at week -5 before the randomization visit);
- *Visit 1 (**V1**)*: Screening visit, start of 4-week run-in period;
- *Visit 2 (**V2**)*: after 2 weeks of run-in period;
- *Visit 3 (**V3**)*: randomization visit;
- *Visit 4 (**V4**)*: after 2 weeks of treatment;
- *Visit 5 (**V5**)*: after 4 weeks of treatment;
- *Visit 6 (**V6**)*: after 6 weeks of treatment;
- *Visit 7 (**V7**)*: after 8 weeks of treatment;
- *Visit 8 (**V8**)*: after 10 weeks of treatment;
- *Visit 9 (**V9**)*: after 12 weeks of treatment.
- *Follow-up phone contact for completed and discontinued patients*: after 7-10 days of last study medication intake or the Early Termination visit in order to check the status of any unresolved adverse event at the last visit.

During treatment period a "window" of ±3 days is allowed.

**Figure 1. Study Design**




## 4. SUBJECT SELECTION CRITERIA

### 4.1 Subject Recruitment

Patients attending the hospital clinics/study centres will be recruited. Adults asthmatic patients (Chinese ethnicity, males and females), aged ≥ 18 years will be selected. About **50** sites will be involved.

Anticipating a screening failure rate of 50%, a total number of about 1000 patients will be screened, and a total of about 490 patients will be randomised according to a 1:1 ratio to Foster® 100/6µg NEXThaler® (245 patients), Foster® 100/6µg pMDI (245 patients).

The assumptions for screening failure rate (about 50%) and drop-out rate (about 10% at Week 12) may be refined during the study.

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

### 4.2 Inclusion Criteria

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

1. Male or female outpatients, Chinese ethnicity aged ≥ 18, who have signed an Informed Consent form prior to initiation of any study-related procedure.
2. Clinical diagnosis of asthma for a minimum of 6 months prior to Visit 1 confirmed by a chest physician according to international guidelines updated 2018 (GINA). The evidence of asthma must be confirmed through a documented positive response (in the last twenty-four months) either to a bronchial provocation test/challenge test or a reversibility test
   In case the patient does not have any documented reversibility test or provocation/challenge test, Salbutamol Reversibility Test will be performed at Visit 1 within 10 to 30 min after administration of 400 µg of salbutamol pMDI (ATS/ERS taskforce 2005). Positive test if $\Delta FEV_1 \geq 12\%$ and ≥ 200 mL over baseline.
   Note: In case the reversibility threshold is not met at Visit 1, the test can be repeated once before Visit 2 or at Visit 2.
3. $FEV_1 > 80\%$ of the predicted normal value after appropriate washout from bronchodilators (to be checked at Visit 1and at randomization visit (Visit 3)).
   Note: If this criterion is not met:
   - At Visit 1 the test can be repeated once before Visit 2 or at Visit 2.
   - At randomization visit the test can be repeated once within 2 days after this visit.
4. ACQ-6 (simplified version of the Asthma Control Questionnaire) score < 0.75 (to be checked at Visit 1 and at randomization visits).
5. Patients on previous regular treatment at a stable dose for at least 1 month prior to Visit 1 with either medium daily dose of ICS monotherapy (e.g., BDP-CFC > 500 – 1000 µg/day or equivalent dose) or high daily dose of ICS monotherapy (e.g., BDP-CFC > 1000 µg/day or equivalent dose) OR low daily dose of ICS (e.g., BDP-CFC≥200 – 500 µg/day or equivalent dose) or medium daily dose of ICS (e.g., BDP-CFC > 500 – 1000 µg/day or equivalent dose )/ LABA free/fixed combination.
6. A cooperative attitude and ability to be trained to the proper use of DPI and pMDI inhalers and electronic peak flow meter (to be checked at Visit 1and at randomization visits).
7. At least 7 valid pre-dose morning PEF measurements in the last 14 days of the run-in period are necessary (to be checked at randomization visit).

At Visit 1, all inclusion criteria except 7, will be checked.

At the randomization visit (Visit 3), the following criteria will be re-checked: 3, 4, 6, 7.

### 4.3 Exclusion Criteria

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

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are using one or more of the following highly effective contraceptive measures:
   - Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
   - Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
   - Bilateral tubal occlusion
   - Vasectomised partner
   - Sexual abstinence.

   Reliable contraception should be maintained throughout the study.

Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study.

Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at Visit 1 and end of treatment (V9), urine pregnancy test will be performed at all visits except V0 and V9.

2. Intermittent asthma or asthma occurring only during episodic exposure to an allergen or a chemical sensitizer.
3. History of near fatal asthma (e.g., brittle asthma, hospitalization for asthma exacerbation in an Intensive Care Unit).
4. Diagnosis of COPD as defined by the current GOLD guidelines updated 2016.
5. Current smokers or ex-smokers with total cumulative exposure equal or more than 10 pack-years or having stopped smoking one year or less prior toVisit 1.
6. Severe asthma exacerbation leading to intake of systemic corticosteroids (≥ 10 days) within 1 month prior to inclusion or moderate/severe asthma exacerbation [according to international guidelines updated 2018 (GINA)] during the run-in period (to be checked at Visit 1and at randomization visits).
7. Lower respiratory tract infections (e.g. pneumonia) affecting the patient's asthma within 1 month prior to inclusion.
8. History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease.
9. Diagnosis of restrictive lung disease.
10. Patients treated with oral or parenteral corticosteroids in the previous 2 months before the Visit 1 (3 months for parenteral depot corticosteroids).
11. Intolerance or contra-indication to treatment with β2-agonists and/or inhaled corticosteroids or allergy to any component of the study treatments.
12. Having received an investigational medication within 2 months before the Visit 1.
13. Patients who have a clinical or functional uncontrolled respiratory, haematological, immunologic, renal, neurologic, hepatic, endocrinal or other disease, or any condition (e.g. major surgery) that might, in the judgment of the investigator, represent for the patients an undue risk or that could compromise the results or interpretation of the study.
14. History or current evidence of uncontrolled heart failure, clinically relevant coronary artery disease, recent myocardial infarction, severe hypertension, uncontrolled cardiac arrhythmias.
15. Clinically relevant laboratory abnormalities such as (but not limited to) hypokalemia (< 3.5 mEq/l), that might compromise patient's safety or compliance, interfere with evaluation, or preclude completion of the study, in the judgment of the investigator. Patients with uncontrolled diabetes including patients with a history of fasting plasma glucose levels consistently out of the normal range (> 140 mg/dl) or HbA1C > 8%.
16. Patients who have an abnormal 12-lead ECG parameter (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female) or 12-lead ECG evaluated as abnormal clinical significant by the investigator, atVisit 1.
17. Patients who have a concomitant disease of poor prognosis (e.g., cancer).
18. Patients treated with monoclonal antibodies (e.s anti-IgE antibodies).
19. Patients treated with non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication), non-selective β1-blocking medications, quinidine, quinidine-like antiarrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation.

20. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, unless already taken at stable doses in the month before the Visit 1visit and without any safety concern.
21. Patients who are receiving therapy that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin).
22. Inability to comply with study procedures or with study treatment intake.

At Visit 1, all exclusion criteria will be checked.
At the randomization visit (Visit 3), the following criteria will be re-checked: 1, 3, 6, 7, 13, 14 and 22.

### 4.4 Subject Withdrawals

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

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

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

The Investigator is responsible for the optimal individual treatment for the subject.
It must be emphasised that after a patient withdraws from a trial, the investigator is still responsible for reporting serious adverse events he/she considers causally-related to the study drug. In addition, the investigator needs to assure appropriate treatment and follow-up of each adverse event still ongoing at the time of patient's discontinuation. Even in case of premature discontinuation from the study, a follow-up phone contact will be performed within 7-10 days after the Early Termination visit last study visit to check the status of any unresolved AEs.
In case of withdrawal, the Investigator must fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal."

## 5. CONCOMITANT MEDICATIONS

### 5.1 Permitted concomitant Medications

The following medications are allowed during the study:

1. Inhaled salbutamol administered as rescue medication. A minimum period of 6 hours should elapse between the use of rescue salbutamol and the lung function measurements.
2. Other asthma treatments (e.g. cromolyn sodium, nedocromil sodium, leukotriene modifiers, theophylline) if already taken at stable doses during 3 months prior to Visit 1 and to be maintained at a constant dose during the study.
3. Nasal corticosteroid and antihistamines if already taken at stable doses for 2 months prior to Visit 1 (the dose must remain constant during the study).

4. Treatment for desensitisation at the "maintenance" phase if already taken at stable doses for at least 1 month prior to Visit 1(the dose must remain constant for the whole study period). Sublingual immunotherapy started before the study can be continued at a stable dose.
5. Short courses (each course of maximum 10 days for a maximum of three times) of antihistamines or nasal corticosteroids for the treatment of hay-fever.
6. Short courses (< 10 days) of systemic corticosteroid and brief use of nebulizer (containing $\beta_2$-agonists, anticholinergics and steroids), and antibiotics therapy for asthma exacerbation during the study (*a 3-day washout period since last systemic steroid intake must be respected before each clinic visit*).

In case of other concomitant diseases, any appropriate treatment that, according to the investigator, does not interfere with the study evaluation parameters is allowed. All concomitant medications should be noted in the relevant section of the eCRF.

**5.2 Non-permitted concomitant Medications**

The following medications are not permitted during the total study period starting from Visit 1 (run-in and treatment period). Intake of these medications during run-in constitutes a non eligibility criterion and the patient will not be randomised into the study. **If any of these medications is taken during the randomised treatment period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator on the basis of the potential impact on efficacy or safety evaluation and in the best patient's interest.**

1. Inhaled corticosteroids in the 12 hours before the Visit 1visit and during the study period.
2. Inhaled short acting $\beta_2$-agonists (other than nebulized and "rescue" salbutamol) throughout the study period. The use of "rescue" salbutamol should be avoided in the 6 hours preceding all the clinic visits.
3. Inhaled long acting $\beta_2$-agonists in the 24 hours preceding the Visit 1and during the study period.
4. Inhaled fixed combinations of corticosteroids and long acting $\beta_2$-agonists (other than study treatments) (e.g. formoterol plus budesonide) in the 24 hours preceding the Visit 1and during the study period.
5. Chronic treatment with systemic corticosteroids.
6. Systemic corticosteroids (≥ 10 days) in the month prior to Visit 1and during the study.
7. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), unless already taken at stable doses in the month before theVisit 1 and without any safety concern.
8. Antihistamines and nasal corticosteroids (exceptions listed under "Permitted Concomitant" medication).
9. Short-acting and long-acting anticholinergics (apart from those listed in permitted medication - a washout of 12 hours for short acting and 72 hours for long acting before Visit 1is required).
10. Non-selective β-blocking medications (including eye drops).
11. Non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication).
12. Quinidine and quinidine-like antiarrhythmics.
13. Any medication with a QTc prolongation potential.
14. Selective Serotonin Re-uptake Inhibitors (SSRIs), unless already taken at the time of the screening visit.
15. Any medication that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin).
16. Monoclonal antibodies (e.g. anti-IgE antibodies).
17. Traditional Chinese Medicines that can interfere with study drugs and/or affect the study outcomes according to investigator's opiniontо be stopped before Visit 2.

## 6. TREATMENT(S)

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

### 6.1 Appearance and Content

- **Test product (Group A):**

**Foster® 100/6 µg NEXThaler® (Chiesi Farmaceutici S.p.A.):**
Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation.

- *Active ingredient*: Beclomethasone dipropionate 100 µg and formoterol fumarate 6µg per dose
- *Excipients*: lactose monohydrate, preblend (lactose/magnesium stearate comicronised 98:2)
- *Presentation*: each inhaler contains 120 doses.

**Foster® pMDI matched Placebo (Chiesi Farmaceutici S.p.A.)**

- *Excipients:* HFA-134a propellant, ethanol anhydrous, hydrochloric acid
- *Presentation:* each canister contains 120 puffs.

- **Reference Product (Group B):**

**Foster® 100/6µg pMDI (Chiesi Farmaceutici S.p.A.):**
Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg per actuation.

- *Active ingredient:* Beclomethasone dipropionate 100 µg and formoterol fumarate 6 µg per metered dose
- *Excipients:* HFA-134a propellant, ethanol anhydrous, hydrochloric acid
- *Presentation:* each canister contains 120 puffs

**Foster® NEXThaler® matched Placebo (Chiesi Farmaceutici S.p.A.)**

- *Excipients:* lactose monohydrate, preblend (lactose/magnesium stearate comicronised 98:2).
- *Presentation:* each inhaler contains 120 doses

The matched placebos will be identical to the respective active medication except for active principles and will be provided to realise a complete double blind, double dummy design.
The placebo will be used also for training purpose.

***Note*: salbutamol** (Rescue medication) will be purchased locally and provided by Investigator site to patient. Patients will take if necessary the usual rescue prescribed by the Doctor. Rescue medication should be kept of similar type during the study.

## 6.2 Dosage and Administration

### 6.2.1 Selection of doses in the study

The dose used in this study is the one of the Chinese Marketed Authorization in accordance with Foster pMDI SmPC.

### 6.2.2 Dosage

***6.2.2.1 Run-in period:***

- **Foster® 100/6µg pMDI**

**2 puffs** of **Foster® 100/6µg pMDI** in the morning AND **2 puffs** of **Foster® 100/6µg pMDI** in the evening (daily dose of BDP 400 µg plus FF 24 µg).

***6.2.2.2 Randomised Treatment period:***

- **Test Product (Group A):**

**2 inhalations** of **Foster® 100/6µg NEXThaler® plus 2 puffs** of pMDI matched placebo **in the morning** AND **2 inhalations of Foster® 100/6µg NEXThaler® plus 2 puffs** of pMDI matched placebo**, in the evening** (daily dose of BDP 400 µg plus FF 24 µg).

- **Reference Product (Group B):**

**2 puffs** of **Foster® 100/6µg pMDI** ***plus*** **2 inhalations** of **NEXThaler®** matched placebo **in the morning** AND **2 puffs** of **Foster® 100/6µg pMDI plus 2 inhalations** of **NEXThaler®** matched placebo, **in the evening** (daily dose of BDP 400 µg plus FF 24 µg).

- **Morning administration:** One pMDI inhaler and one NEXThaler® inhaler will be used during the morning administration *(inhalers with SUN label)*.
- **Evening administration:** One pMDI inhaler and one NEXThaler® inhaler will be used during the evening administration *(inhalers with MOON label)*.

### 6.2.3 Administration

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

***6.2.3.1 Run in kits***

At Visit 1, each eligible patient will receive the medication to cover the 4-week run-in:

- One run-in box containing containing two inhalers of **Foster® pMDI 100/6 µg**. In case of need, patients will be allowed to inhale their pMDI medications using a spacer device. They shall continue using a spacer (during the randomised period). The spacer device to be used in the study, the **AeroChamber Plus™** Flow-Vu antistatic (referred as AeroChamber Plus™ in the rest of the document), will be assigned to the patient by the Investigator (one spacer at visits V1 and V3). For these patients, **each inhalation** (from the pMDI) **must be performed via AeroChamber Plus™. For each puff, patient must inhale slowly and deeply** and hold his/her breath as long as possible. For more details concerning the use of the **Foster®pMDI** with Aerochamber Plus™, please refer to the corresponding patient leaflets. Instructions will be provided in a separate document.

Salbutamol used as rescue medication will be taken as needed in response to symptoms.

#### *6.2.3.2 Treatments kits*

Each patient will receive two boxes at V3, V5 and V7 to cover the treatment duration between 2 visits with dispensation:

- one kit containing Foster® 100/6µg NEXThaler® or its matched placebo

and

- one kit containing Foster® 100/6µg pMDI or its matched placebo.

In total, each patient will receive three kits with NEXThaler® medication and three kits with pMDI medication.

The treatment kits will consist in:

- **NEXThaler® kit:** 1 box containing two inhalers of Foster® 100/6µg NEXThaler® or its matched placebo. One inhaler is for the morning administration and one inhaler is for the evening administration.

- **pMDI kit:** 1 box containing two inhalers of Foster® 100/6µg pMDI or its matched placebo. One inhaler is for the morning administration and one inhaler is for the evening administration.

**For Groups A and B:**

- **Morning administration:**
  - Two puffs from the pMDI inhaler with SUN label,
  - Two inhalations from the NEXThaler® inhaler with SUN label

- **Evening administration:**
  - Two puffs from the pMDI inhaler with MOON label
  - Two inhalations from the NEXThaler® inhaler with MOON label

In case of need, the patient will be allowed to take a pMDI medication via a spacer, he/she shall use a new AeroChamber Plus™ Flow-Vu antistatic provided at V3. He/she will use this AeroChamber Plus™ Flow-Vu antistatic until the end of the study.

Salbutamol used as rescue medication will be taken as needed in response to symptoms.

Administration will be done according to the package instruction leaflets. A package leaflet will be included with study medications in local language.

The study medications will be administered twice a day in the morning (preferably between 7.00 and 9.00 am) and in the evening (preferably between 7.00 and 9.00 pm) according to the leaflet instructions
Note: The first administration of the study medication (randomised treatment period) will take place at clinic in the morning of visit 3 under medical supervision.

#### *6.2.3.3 Subject Training*

At Visit 1, the Investigator, or designee, will contact the IRT system to get two training kits for each patient, one with placebo pMDI and one with placebo NEXThaler®.

The patient will be instructed by the Investigator on how to use the **Foster® NEXThaler®** and the **Foster® pMDI,** on the method of inhalation and duration of breath holding after inhalation, according to the instructions for use. The proper use of the inhalers will be checked again at randomization visit using the same training kits.

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

In case the patient needs to take asthma **Foster® pMDI** medications via a spacer, he/she will be trained on the use of **Foster® pMDI** with the AeroChamber Plus™ Flow-Vu antistatic provided at V1.

At Visit 1 and at randomization visit (V3), the patient will be trained with the same Aerochamber Plus™ dispensed at Visit 1.
For more details concerning the use of the **Foster®pMDI** with Aerochamber Plus™, please refer to the corresponding patient leaflets. Instructions will be provided in a separate document.

### 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).

Chiesi Farmaceutici S.p.A. will supply the study drugs for the run-in period and the randomised treatment period.

**Training kits**

At visit 1, the investigator will train the eligible patients using placebo, to the proper use of pMDI and NEXThaler® inhaler. The investigator will use two boxes.

One box will contain 1 Foster® pMDI placebo.

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

A second box will contain 1 Foster® NEXThaler® placebo.

- *Primary packaging*: one NEXThaler® placebo inhaler
- *Secondary packaging*: one aluminium pouch containing one NEXThaler® placebo inhaler
- *Tertiary packaging*: box containing one pouch containing one NEXThaler® placebo inhaler

In case patient needs to take pMDI medication via a spacer, he/she will be trained to inhale using 1 AeroChamber Plus™. In case patient is eligible, this spacer will be used also for Run-in period.

- *Secondary packaging*: box containing one AeroChamber Plus™ spacer.

**Run-in period**

At visit 1, the investigator will deliver to each eligible patient one box containing two Foster® 100/6µg pMDI inhalers.

- *Primary packaging*: one canister plus standard actuator
- *Secondary packaging*: box containing two canisters of Foster® 100/6µg pMDI plus standard actuators.

**Treatment period**

At randomisation (V3) and subsequent dispensing visits (V5 and V7), each patient will be provided with 2 boxes.

The first box will contain 2 pMDI inhalers of Foster® 100/6µg **or** placebo. One of the two inhalers will be labelled with a "sun" sticker identifying the one to be used for the morning administration. The second inhaler will be labelled with a "moon" sticker identifying the one to be used for the evening administration. Overall, there will be 3 pMDI boxes per patient, from V3 to V7.

- *Primary packaging*: canister plus standard actuator
- *Secondary packaging*: box containing 2 canisters plus 2 standard actuators

The second box will contain 2 inhalers of Foster® NEXThaler® 100/6µg **or** placebo. One of the two NEXThaler® will be labelled with a "sun" sticker identifying the one to be used for the morning administration. The second NEXThaler® will be labelled with a "moon" sticker identifying the one to be used for the evening administration. Overall, there will be 3 NEXThaler® boxes per patient, from V3 to V7.

- *Primary packaging*: one NEXThaler® inhaler
- *Secondary packaging*: one aluminium pouch containing one NEXThaler® inhaler
- *Tertiary packaging*: box containing two pouches, each one containing one NEXThaler® inhaler

In case the patient needs to take pMDI medication via a spacer, he/she will receive a new AeroChamber Plus™. This spacer will be used until the end of treatment.

- *Secondary packaging*: box containing one AeroChamber Plus™ spacer.

## 6.4 Labelling

All labelling 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.

## 6.5 Treatment allocation

A balanced block randomization scheme stratified by site will be prepared via a computerised system. Patients will be centrally assigned, in each centre, to one of the two treatment arms at the end of the run-in period through an Interactive Response Technology (IRT). Each Investigator will call the IRT at the pre-screening visit (when the informed consent form is signed) or whenever the informed consent is signed to obtain a patient's number, and also at the Visit 1to enrol patients and to randomise patients at randomization visit. The IRT will assign the patient to a certain treatment group using a list-based randomization algorithm and assign the study medication kit number corresponding to the treatment group assigned to the patient. The IRT will also generate a confirmation after every IRT transaction is performed.
Patient number will be centrally assigned, through the IRT, during the pre-screening visit (Visit 0).

### 6.6 Treatment Code

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 run-in and treatment kits as well as training kits and spacer (if needed). The IRT will track quantities, kit numbers, medication types, batch/code numbers, expiration dates and dispensing limiting dates. The IRT will monitor inventory levels at all sites and manage the re-supply. The IRT will track patient screen failures and withdrawals from the study.

In case of emergency, the patient will be provided with a card in which the phone numbers of Hospital site and Investigator are reported.

Note:
At pre-screening visit (Visit 0), the investigator will access IRT to register the patient in the system and obtain a patient number.

At all the other visits of the treatment period the investigator will call IRT to enter the patient status in the study (if patient is on-going, dropped-out or completed).

The randomization list will be provided to the labelling facility but will not be available to subjects, Investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency.
The Sponsor's clinical team will also be blinded during the study without direct access to the randomization list.

In case of emergency, unblinding of the treatment code will be done through IRT. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the Investigators. The Investigator will be provided with usernames and passwords for randomization purposes and to unblind the study treatment in case of emergency situation, where he/she considers essential to know what treatment the patient was taking. The IRT will promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.
Users from Chiesi Global Pharmacovigilance will have their own passwords to unblind patients in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees/IRB.

### 6.7 Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the subject in the electronic diary.
For **Foster® NEXThaler®** the compliance will also be checked through the dose-counter of the inhaler by the Investigator at visit.
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 patient. A range between 75-125% will be taken into account for a satisfactory level of compliance.

### 6.8 Medication Storage

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

***pMDI medication: used during the Run-in (Foster® 100/6µg), the Randomized treatment period (Foster® 100/6µg or placebo) and for Training (placebo)***

pMDI kits must be stored between 2˚C and 8˚C by Pharmacist/Investigator at the Hospital. At clinic visits, the medication kits should be removed from the refrigerator before patient's administration. If the inhaler has been exposed to severe cold, the canister has to be taken out of the mouthpiece and warmed with the hands for a few minutes before administration to the patient. It must never be warmed by artificial means. The patient should never inhale a cold medication. The canisters contain a pressurised liquid. They must neither be exposed to temperatures higher than 50°C nor pierced.

Once dispensed, the patients will be instructed to keep the boxes at home at ambient temperature not above 25°C but not in the refrigerator.
At this temperature condition the residual shelf life of the pMDI kits will be five months (**150 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the kit labels** once the kits are removed from the refrigerator, before assigning to the patients. The **use-by-date corresponds to the dispensing date plus 5 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

***DPI medication: used during the Randomized treatment period (Foster® NEXThaler® 100/6µg or placebo) and for Training (placebo)***

*Pouched inhaler*: it doesn't require any special storage conditions until the aluminium pouch is closed. After opening the pouch, the inhaler must be stored below 25ºC and protect from humidity (see below);
*Unpouched inhaler*: At clinic visits, the inhalers must be removed from the pouches before administration. Once removed from the pouch, the inhalers for treatment should be kept at ambient temperature not above 25°C. At this temperature condition the residual shelf life will be six months (**180 days**). Therefore, **the Pharmacist/Investigator at the Hospital must write the use-by-date on the treatment kit labels** once the inhalers are removed from the pouch. The **use-by-date corresponds to the dispensing date plus 6 months.** Please note that the use-by date must not exceed the total shelf life of the product.

The site must check the Min/Max temperatures once daily for adequate storage of refrigerated and ambient kits. The Min/Max temperatures must be recorded in a dedicated temperature tracking form. Any deviation to the requirement for storage will be promptly reported and Sponsor shall assess if the affected study can still be used.

Note*: A temperature recording must be performed, on site once daily for both storages*.

### 6.9 Medication 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 nominated individual), to include a signed account of all the test treatments 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 medication supply (used and unused) inventory. An explanation will be given for any discrepancies.

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

### 6.10 Provision of additional care

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

## 7. STUDY PLAN

### 7.1 Study Schedule

The study plan includes a total of 10 clinic visits (Visit 0 to Visit 9), as follows:

- *Visit 0 (**V0**)*: Pre-screening visit (at week -5 before the randomization visit);
- *Visit 1 (**V1**)*: Screening visit, start of 4-week run-in period;
- *Visit 2 (**V2**)*: after 2 weeks of run-in period;
- *Visit 3 (**V3**)*: randomization visit;
- *Visit 4 (**V4**)*: after 2 weeks of treatment;
- *Visit 5 (**V5**)*: after 4 weeks of treatment;
- *Visit 6 (**V6**)*: after 6 weeks of treatment;
- *Visit 7 (**V7**)*: after 8 weeks of treatment;
- *Visit 8 (**V8**)*: after 10 weeks of treatment;
- *Visit 9 (**V9**)*: after 12 weeks of treatment.
- *Follow-up phone contact for completed and discontinued patients*: after 7-10 days of last study medication intake or the Early Termination visit in order to check the status of any unresolved adverse event at the last visit.

During treatment period a "window" of ±3 days is allowed.

## Schedule of events:

| | Pre-screening | | Run-in | | Treatment Period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 0 (within 7 days before V1) | Visit 1 Screening Week -4 | Visit 2 Week -2 | Visit 3 Randomization Week 0 | Visit 4 Week 2 | Visit 5 Week 4 | Visit 6 Week 6 | Visit 7 Week 8 | Visit 8 Week 10 | Visit 9 Week 12/ ETV* /FU call** |
| Written informed consent | ✔ | | | | | | | | | |
| Demographic data | ✔ | | | | | | | | | |
| Instructions for screening visit | ✔ | | | | | | | | | |
| Patient card | ✔ | | | | | | | | | |
| Inclusion/Exclusion criteria | | ✔ | | ✔ | | | | | | |
| Medical history/Previous medications | | ✔ | | | | | | | | |
| Concomitant medications | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Physical examination | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Vital signs (HR and BP) [1] | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| 12-lead ECG [1] | | ✔ | | | | | | | | ✔ |
| $FEV_1$ reversibility test [2] | | ✔ | | | | | | | | |
| Lung function measurements at clinic visits: pre-dose spirometry | | ✔ [5,10] | ✔ [5] | ✔ [5,10] | ✔ [5] | ✔ [5] | ✔ [5] | ✔ [5] | ✔ [5] | ✔ [5] |
| Training to the use of pMDI and/or NEXThaler® spacer and Peak Flow Meter[8] | | ✔ | | ✔ | | | | | | |
| Asthma control questionnaire© (ACQ-6) | | ✔ | | ✔ | | | | | | ✔ |
| Peak flow meter dispensation and electronic daily diary dispensing | | ✔ | | | | | | | | |
| Daily diary returning | | | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Use of electronic Peak Flow Meter (Pre-dose morning and evening PEF) | | ← | | | **Daily** | | | | | → |
| Use of electronic diary morning and evening (rescue and run in / treatment | | ← | | | **Daily** | | | | | → |

| | Pre-screening | | Run-in | | Treatment Period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 0 (within 7 days before V1) | Visit 1 Screening Week -4 | Visit 2 Week -2 | Visit 3 Randomization Week 0 | Visit 4 Week 2 | Visit 5 Week 4 | Visit 6 Week 6 | Visit 7 Week 8 | Visit 8 Week 10 | Visit 9 Week 12/ ETV* /FU call** |
| Download of peak flow meter and recorded data check[9] | | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Haematology– Blood chemistry [3](with serum potassium and serum glucose) | | ✔ | | | | | | | | ✔ |
| Urinary pregnancy test [3,4] | | ✔ 6 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | |
| Serum pregnancy test[3,4] | | ✔ | | | | | | | | ✔ |
| Adverse events/Serious adverse events | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Recognition of developing asthma exacerbation | | ✔ | | | | | | | | |
| Occurrence of asthma exacerbation | | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| IRT call | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Run-in medication dispensation | | ✔ | | | | | | | | |
| Run-in medication collection | | | | ✔ | | | | | | |
| Study medication dispensation | | | | ✔ 7 | | ✔ 7 | | ✔ 7 | | |
| Study medication collection | | | | | | ✔ | | ✔ | | ✔ |
| Peak flow meter collection | | | | | | | | | | ✔ |

(1) After 10 minutes of rest, in sitting position.
(2) Within 10-30 min after 400 µg salbutamol (4x100 µg). This test will be performed only if there isn't any documented reversibility test or bronchial provocation test/challenge test within the last 24 months for the patient. In case the reversibility threshold is not met at screening, the test can be repeated once before Visit 2 or at Visit 2.
(3) Biology analysis will be done locally.
(4) For females of childbearing potential only.
(5) In case of rescue medication use, at least 6 hours must elapse between the intake and the spirometry measurements. No run-in medication or study medication intake at home in the morning of the visits after Visit 1. In the morning of V1, no medications for asthma must be taken
(6) Results must be available before the first run-in medication intake at the visit.
(7) 1 box with 2 Foster® pMDI inhaler (refrigerated) and 1 box with 2 Foster® NEXThaler® (ambient) will be distributed.
(8) Re-trainings can be done during the study if need be. Training for spacer.
(9) Data recorded in the electronic peak flow meter and in the electronic diary will be collected and checked at every visit from Visit 2 to Visit 9 or early termination
(10) In case inclusion criteria N° 3 is not met at Visit 1, the test can be repeated once before visit 2 or at visit 2. In case this criteria is not met at randomisation visit (visit 3) the test can be repeated once within 2 days after this visit.

*Early Termination Visit for randomised patients withdrawn before week 12
**FU call after 7-10 days maximum after the of last study medication intake to check the status of any unresolved adverse event adverse event.

### 7.1.1 Visit 0 (Pre-screening visit)

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

- Collection of the written informed consent signed by the patient, after the study has been fully explained by the investigator.
- Demographic data will be collected.
- Instructions will be given to the patient for the next visit (V1).
- The patient card will be given to the patient.
- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to allocate the unique patient's number. This number will be sequentially assigned.

An **appointment** for the screening visit (V1), will be taken in the morning between 7:00 and 9:00 a.m. (+/- 2 hours), **within 7 days maximum**. Patients will be instructed:

- To fast overnight (at least 8 hours) for the next visit in order to perform blood sampling (only water is allowed).
- Not to take salbutamol or other SABA used as rescue in the 6 hours preceding the next visit, unless absolutely necessary.
- Not to take fixed combination of ICS/LABA in the 24 hours and/or LABA in the 24 hours preceding the next visit and/ or ICS dose in the 12 hours preceding the next visit.

### 7.1.2 Visit 1 (Screening visit / Week -4)

A screening visit will be carried out between 7:00 and 9:00 a.m. (+/- 2 hours), in order to identify eligible patients for entering in the study.

If the wash-out for rescue (SABA) and /or wash out of ICS/LABA, have not been respected and/or if ICS has been taken on the morning of the visit, the visit needs to be re-scheduled **within 2 days**. This is allowed only once. If SABA intake occurs again in the previous 6 hours before the re-scheduled visit or if the wash-out of ICS/LABA or ICS and LABA are not respected again, the patient will be discontinued.

The following procedures will take place:

- The patient's eligibility for entry into the study will be assessed according to the inclusion and exclusion criteria.
- A medical and surgical history will be recorded. Previous medications in the past 3 months must be collected.
- Concomitant medications being taken by the patient will be recorded. Intake of non-permitted medication constitutes a non-eligibility criterion for enrolment in the study.
- A full physical examination will be performed.
- Vitals signs [heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure] will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A 12-lead ECG will be performed after 10 minutes of rest (see section 7.2).
- A blood sample will be collected at pre-dose and after an overnight fasting for the assessments of (see section 7.2):
  - routine haematology and routine blood chemistry (including serum potassium and serum glucose);

The blood sample must be collected after ECG.
In case of non-interpretable data, another determination must be performed as soon as possible and before randomization (V3)

- For female of childbearing potential, perform a urinary pregnancy test and a serum pregnancy (results must be available before entering in the run-in period)
- Spirometry will be carried out (see section 7.2): **$FEV_1$ percent must be > 80% of the patient's predicted normal value** after an appropriate wash-out from bronchodilators.
- Asthma control will be evaluated by the completion of the paper Asthma Control Questionnaire© (ACQ-6) to verify the eligibility of the patient (see section 7.2). Only patients with a score at the ACQ-6 < 0.75 are eligible.
- In case the patient doesn't have any documented positive response (within the last 24 months) to the bronchial provocation test/challenge test or the reversibility test, a $FEV_1$ reversibility test with 4 puffs (4 x 100 µg) of salbutamol pMDI will be performed to assess reversibility (i.e. a positive reversibility test is defined as above). In case of patient doesn't respect the appropriate wash-out from bronchodilators (as above specified) at this visit or if the test is negative at V1, reversibility should be re-tested at V2 or **before the visit 2.**
- In the case $FEV_1$ percent doesn't meet the eligibility criterion, the test can be repeated once before visit 2 or at Visit 2
- AEs occurred since the signature of the informed consent will be recorded. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the patient's medical history, unless its start date is after the informed consent signature date. In this case it will be recorded as an adverse event.
- If the patient is eligible, the investigator will access IRT in order to obtain the training kits to training the patient to the proper use of **Foster®**pMDI (with AeroChamber Plus™, if needed) and **NEXThaler®** (see section 6.2).
- Patients will be also trained in the early recognition of a developing asthma exacerbation and on appropriate early actions needed (moderate/severe - see Appendix II).
- The investigator will access IRT in order to obtain the run-in medication Foster® pMDI to be dispensed with instructions for use. Patients will be instructed to inhale 2 puffs of run-in medication in the morning (between 7:00 and 9:00 a.m.) and 2 puffs in the evening (between 7:00 and 9:00 p.m.). **The first administration of Foster® pMDI will take place at the clinic visit under medical supervision.** Patients must be informed to take their usual rescue medication (salbutamol) as needed in case of asthma symptoms.
- An electronic peak flow meter will be given to each patient at visit 1 for measuring of daily PEF. The patient will be instructed and trained on how to use the peak flow meter. **The measurement of PEF will take place every morning and every evening** during the run-in period, **before the intake of run-in medication**. The recording will start in the evening of Visit 1.
- Patient will be asked to record in electronic diary every morning and every evening the number of puff(s) of rescue taken (if any), the run in medication **(Foster® pMDI)** intakes and the asthma symptom scores. The recording will start in the evening of Visit 1.
- An appointment for Visit 2 will be made within 2 weeks (+/- 2 days) from Visit 1 (at approximately the same time of the day, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the run-in medication and the electronic peak flow meter/electronic diary.
  - To perform the morning PEF measurement before coming to the next visit

- To answer questions in the electronic diary.
- Not to take rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
- Not to take the morning dose of the run-in medication **(Foster® pMDI)** before coming to the clinic visit (it will be taken at the visit).

### 7.1.3 Visit 2 (2 week run-in period / Week -2)

The Visit 2 will start between 7:00 and 9:00 a.m. (+/- 2 hours).

If rescue salbutamol has been inhaled in the previous 6 hours, or the run in medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or run in medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded. Check that traditional medication have been stopped.
- The occurrence of adverse events (if any) will be checked and recorded.
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to run in medication, the rescue taken and the asthma symptom score.

    **In case of lack of compliance with the electronic peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**
- The occurrence of asthma exacerbations (if moderate / severe) will be evaluated and recorded in the eCRF. If any events, patient will be withdrawn.
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to run in medications administration. If the reversibility test was negative at Visit 1, it can be performed again during this visit (if not done before V2).
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT in order to enter the status of the patient.
- **Run-in medication will be administered at the clinic under supervision of the Investigator with the medication brought back by the patient at the visit.**
- Run-in medication (the one dispensed at Visit 1) will be returned to the patient together with instructions for use. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- For administration of run in medications, investigator will give to the patient the same instructions as the ones given at Visit 1.

- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking run in medication in the morning and in the evening.** He/she will also record the run-in medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 3 will be made within 2 weeks (+/-3 days) from Visit 2 (at approximately the same time as the other visits, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the run-in medication (in its box) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - **Not to take the morning dose of the run in medication before coming to the clinic visit.**

### 7.1.4 Visit 3 (Randomization / Start of Treatment Period / Week 0)

The visit 3 will start between 7:00 and 9:00 a.m. (+/- 2 hours). It is recommended to start the assessment by spirometry in the respect of wash out period described below.

In case of repeated V3, all the assessments should be performed again.

If rescue (salbutamol) has been inhaled in the previous 6 hours, or Foster® pMDI (run-in medication) has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. Only one re-schedule is allowed. If SABA intake occurs again in the previous 6 hours before the re-scheduled visit or Foster®pMDI intake occurs again on the morning of the re-scheduled visit, the patient will be discontinued.

The following procedures will be performed:

- Check the inclusion and exclusion criteria
- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- Asthma control will be evaluated by the completion of the paper Asthma Control Questionnaire© (ACQ) as at Visit 1, to confirm the eligibility of the patient (see section 7.2). Patients with ACQ score < 0.75 at V3 will be randomised.
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the electronic diary:** Patient's compliance to run in medication, the rescue taken and the asthma symptom score.

  **In case of lack of compliance with peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**

- Check if at least 7 valid pre-dose morning PEF measurements are present in the last 14 days of the run-in period
- The occurrence of asthma exacerbations (moderate/severe, if any) will be evaluated and recorded. In case of moderate/severe asthma exacerbation (see Appendix III), the patient will not be randomised.
- The investigator will collect the box containing the run-in medication.
- A pre-dose spirometry measurement (see section 7.2) will be performed prior to patient randomization in order to verify that $FEV_1$ percent is still > 80% of the patient's predicted normal value after an appropriate wash-out from bronchodilators. In the case $FEV_1$ percent doesn't meet the eligibility criterion, the test can be repeated once within 2 days after Visit 3.
- Patient will be trained to the proper use of Foster®pMDI (plus AeroChamber Plus™, if needed) and Foster® NEXThaler® with training kits (see section 6.2).

**For eligible patients:**

- The patient will be randomised and the treatment will be allocated according to a central randomization system. Investigator will access IRT in order to obtain the appropriate kit numbers for the next 4-week treatment period. **The first administration of the study medication will take place at the clinic visit under supervision of the Investigator.**
- Study medications (and AeroChamber Plus™, if needed) will be dispensed to the patient together with instructions for use. Patient will be instructed to take two inhalations from each morning device (Foster®pMDI, **Foster® NEXThaler®**) in the morning and two inhalations from each evening device in the evening. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 4 will be made within 2 weeks (+/-3 days) from Visit 3 (at approximately the same time as Visit 3, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the **study medications** (in their boxes) at the next visit.
  - To perform the morning PEF measurement with the peak flow meter before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - **Not to take the morning dose of the study medication before coming to the clinic visit** (the study medications will be administered at the clinic visit).

### 7.1.5 Visit 4 (Week 2 of Treatment Period)

The Visit 4 will start between 7:00 and 9:00 a.m. (+/- 2 hours)

If rescue salbutamol has been inhaled in the previous 6 hours, or the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- Used study medication will be collected (if needed).
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.

  **In case of lack of compliance with peak flow meter/electronic diary instructions on how to use it will be given again to the patient**
- The occurrence of asthma exacerbations (moderate and severe – see Appendix III) (if any) will be evaluated and recorded.
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to study medications administration.
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT to enter the status of the patient.
- **The study medication will be administered at the clinic under supervision of the Investigator with the medications dispensed at Visit 3 and brought back by the patient.**
- Study medications (dispensed at V3) will be returned to the patient together with instructions for use. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- For administration of study medications, investigator will give to the patient the same instructions as the ones given at V3.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see sections 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 5 will be made within 4 weeks (+/- 3 days) from Visit 3 (at approximately the same time as the other visits, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the study medications (in their boxes) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - Not to take the morning dose of the study medication before coming to the clinic visit (the study medication will be administered at the clinic visit).

### 7.1.6 Visit 5 (Week 4 of Treatment Period)

The Visit 5 will start between 7:00 and 9:00 a.m. +/- 2 hours.

If rescue salbutamol has been inhaled in the previous 6 hours, or the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- Used study medication will be collected.
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.

    **In case of lack of compliance with peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**
- The occurrence of asthma exacerbations (moderate and severe – see Appendix III) (if any) will be evaluated and recorded.
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to study medications administration.
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT in order to obtain the appropriate kit numbers for the next 4-week treatment period. **The morning dose of the study medication will be administered at the clinic under supervision of the Investigator.**
- Study medications will be dispensed to the patient together with instructions for use. Patient will be instructed to take two inhalations from each morning device (Foster®pMDI, Foster® NEXThaler®) in the morning and two inhalations from each evening device in the evening. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- For administration of study medications, investigator will give to the patient the same instructions as the ones given at V3.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 6 will be made within 6 weeks (+/- 3 days) from Visit 3 (at approximately the same time as the other visits, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the study medications (in their boxes) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.

- To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
- **Not to take the morning dose of the study medication before coming to the clinic visit** (the study medication will be administered at the clinic visit).

### 7.1.7 Visit 6 (Week 6 of Treatment Period)

The Visit 6 will start preferably between 7:00 and 9:00 a.m. (+/- 2 hours).

If rescue salbutamol has been inhaled in the previous 6 hours, or the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.
    **In case of lack of compliance with peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**
- The occurrence of asthma exacerbations (moderate and severe – see Appendix III) (if any) will be evaluated and recorded.

- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to study medications administration.
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT to enter the status of the patient.
- **The study medication will be administered at the clinic under supervision of the Investigator with the medications dispensed at Visit 5 and brought back by the patient.**
- Study medications dispensed at V5 will be returned to the patient together with instructions for use. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- For administration of study medications, investigator will give to the patient the same instructions as the ones given at V3.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.

- An appointment for Visit 7 will be made within 8 weeks (+/- 3 days) from Visit 3 (at approximately the same time as the other visits, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the study medications (in their boxes) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - **Not to take the morning dose of the study medication before coming to the clinic visit** (the study medication will be administered at the clinic visit).

### 7.1.8 Visit 7 (Week 8 of Treatment Period)

The Visit 7 will start between 7:00 and 9:00 a.m. (+/- 2 hours).

If rescue salbutamol has been inhaled in the previous 6 hours, or the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:
- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- Used study medication will be collected.
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.
    **In case of lack of compliance with peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**
- The occurrence of asthma exacerbations (moderate and severe – see Appendix III) (if any) will be evaluated and recorded.
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to study medications administration.
- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT in order to obtain the appropriate kit numbers for the next 4-week treatment period. **The morning dose of the study medication will be administered at the clinic under supervision of the Investigator.**
- Study medications will be dispensed to the patient together with instructions for use. Patient will be instructed to take two inhalations from each morning device (Foster®pMDI, Foster® NEXThaler®) in the morning and two inhalations from each evening device in the evening. Patient will be instructed to take his/her usual SABA as rescue if necessary.

- For administration of study medications, investigator will give to the patient the same instructions as the ones given at V3.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at Visit 1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 8 will be made within 10 weeks (+/- 3 days) from Visit 3 (at approximately the same time as the other visits, between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the study medications (in their boxes) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - **Not to take the morning dose of the study medication before coming to the clinic visit** (the study medication will be administered at the clinic visit).

### 7.1.9 Visit 8 (Week 10 of Treatment Period)

The Visit 8 will start between 7:00 and 9:00 a.m. (+/- 2 hours).

If rescue salbutamol has been inhaled in the previous 6 hours, or the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled again in the previous 6 hours before the re-schedule visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded.
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the electronic diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.
    **In case of lack of compliance with peak flow meter/electronic diary, instructions on how to use it will be given again to the patient.**
- The occurrence of asthma exacerbations (moderate and severe – see Appendix III) (if any) will be evaluated and recorded.

- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2).
- A spirometry measurement (see section 7.2) will be performed prior to study medications administration.

- For female of childbearing potential a urinary pregnancy test will be performed
- Investigator will access IRT to enter the status of the patient.
- **The study medication will be administered at the clinic under supervision of the Investigator with the medications dispensed at Visit 7 and brought back by the patient.**
- Study medications dispensed at V7 will be returned to the patient together with instructions for use. Patient will be instructed to take his/her usual SABA as rescue if necessary.
- For administration of study medications, you will give to the patient the same instructions as the ones given at V3.
- The patient will be instructed to continue measuring daily PEF in the morning and in the evening (as instructed at Visit 1) with the peak flow meter given at V1, starting from the evening of the visit (see section 7.2). **Measurements must be done before taking study medications in the morning and in the evening.** He/she will also record the study medication compliance, rescue taken (if any) and asthma symptom scores in the electronic diary.
- An appointment for Visit 9 will be made within 12 weeks (+/- 3 days) from Visit 3 (at approximately the same time as the other visits, preferably between 7:00 and 9:00 a.m. +/- 2 hours). The patient will be instructed:
  - To bring back the peak flow meter/electronic diary and the study medications (in their boxes) at the next visit.
  - To perform the morning PEF measurement before coming to the next visit and to answer questions in the electronic diary.
  - To avoid taking rescue (salbutamol) in the 6 hours preceding the next visit, unless absolutely necessary.
  - **Not to take the morning dose of the study medication before coming to the clinic visit** (the study medication will be administered at the clinic visit).

### 7.1.10 Visit 9 (Week 12 / End of Treatment Period)

The Visit 9 will start between 7:00 and 9:00 a.m (+/- 2 hours).

If the study medication has been taken in the morning of the visit, the visit needs to be re-scheduled to take place within 2 days. This is allowed only once. If rescue has been inhaled in the previous 6 hours before the re-scheduled visit or study medication intake occurs again on the morning of the re-scheduled visit, the visit will be performed anyway, but all the information regarding time of intake and number of puffs must be noted in the eCRF.

The following procedures will be performed:

- Changes of concomitant medications being taken by the patient will be recorded.
- The occurrence of adverse events (if any) will be checked and recorded
- The occurrence of asthma exacerbations (moderate/severe see Appendix III) and other adverse events will be checked and recorded (if any).
- A full physical examination will be performed.
- Vital signs (HR, SBP and DBP) will be measured, after 10 minutes of rest, in sitting position (see section 7.2.7).
- A 12-lead ECG will be performed after 10 minutes of rest (see section 7.2).
- A blood sample will be collected at pre-dose and **after an overnight fasting** for the assessments of (see section 7.2):
  - routine haematology and routine blood chemistry (including serum potassium and serum glucose);

- The blood sample must be collected after ECG
- Asthma control will be evaluated by the completion of the paper Asthma Control Questionnaire© (ACQ).
- Investigator will **collect and check:**
  - **Data recorded in the** electronic **peak flow meter:** PEF data will be verified to check the correct use of the device and to detect any clinical abnormality,
  - **Data recorded in the** electronic **diary:** Patient's compliance to treatment medication, the rescue taken and the asthma symptom score.
- A spirometry measurement (see section 7.2) will be performed prior to the last study medication intake.
- For female of childbearing potential a serum pregnancy test will be performed
- **The last dose of study medication will be administered at the clinic under supervision of the Investigator from the kit dispensed at Visit 7.**
- Study medications and peak flow meter/electronic diary will be collected.
- At investigator discretion, the pre-study patient's therapy will be resumed or changed if appropriate.
- At the end of the patient's participation in the trial, she/he will be discharged from the unit, providing that all her/his safety assessments are satisfactory.
- Investigator will access IRT to enter the status of the patient.

### 7.1.11 Early Termination Visit for a patient withdrawn before Week 12

In case of early study discontinuation, all the pre-dose procedures scheduled for Visit 9

(Week 12 / End of Treatment Period) will be performed.

If a patient is withdrawn before the end of treatment period, a final evaluation will be done.
The Investigator must fill in the Early Termination visit in the eCRF. The explanations regarding the reasons of withdrawal and all the assessments performed will be inserted.

### 7.1.12 Follow-up phone contact

The patient will be contacted within 7-10 days after the last study medication intake to check any unresolved AE/ SAEs at Visit 9 and any AEs/ SAEs that have occurred after Visit 9, as well as the related concomitant medications.

This safety follow-up call shall also be performed in case of premature discontinuation of patients' participation (1 week after the last dose intake and/or last visit).
The patient must be informed that he/she cannot participate in another clinical study for 4 weeks after this follow-up contact and the patient is exited from the study.

*Note:* SAEs that are still ongoing at the time of the last visit will be monitored until clinical recovery is complete, until progression has been stabilized or the patient is lost to follow-up.

## 7.2 Investigations

### 7.2.1 Spirometry

Lung function measurements and daily calibration of the spirometer will be done according to the recommendation of the Official Statement of the European Respiratory Society and American Thoracic Society [10, 11]. It is recommended that, in each centre, the same spirometer is used for a given patient during the course of the study. All sites will be provided with a machine. Lung function

measurements will be done with patients either standing or sitting (for each patient, this should be consistent throughout the study) with the nose clipped after at least 10 minutes rest. Values will be corrected for BTPS conditions. **Depending on the device used for the study a calibration may be necessary. If this is the case calibration of the spirometer must be performed by the same investigator or deputy (to the extent possible) at each visit prior to any spirometry manoeuvres and the reports must be kept with the source study documents.**
The specific procedures for the central spirometry will be provided to the investigator by the central spirometry company.

Throughout the study, the clinic visits and the lung function measurements will start in the morning between 7:00 and 9:00 a.m. (+/- 2 hours), approximately at the same time of the day for each patient. To avoid diurnal variation it is hardly recommended to not perform lung function measurements after 11:00 a.m.

The following parameters will be assessed pre-dose at all the clinical Visits:
- Forced Expiratory Volume in the 1st second ($FEV_1$, L).
- Forced Vital Capacity (FVC, L).

Note: some additional standard parameters (for instance PEF or ratio $FEV_1$/FVC) will be assessed by the spirometer during the visit only for information purpose of the investigator.

Predicted values of $FEV_1$ will be calculated according to formulas reported by Quanjer et al [11] (The predicted values will be adjusted according to local Chinese reference value).

Spirometry will be first performed at Visit 1 to verify the eligibility of the patient.
Will be rechecked at randomization and will be recorded at each clinic visit.

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 rescue medication (salbutamol) must be withheld as much as possible for at least 6 hours prior to starting the pre-dose assessment at each visit.**
**The run-in medication or the study medications should not be taken by the patient in the morning of the visit. If not, the measurements should be deferred (i.e. the visit needs to be re-scheduled to take place within 2 days).** It will be postponed only once.

### 7.2.2 Daily PEF measurements with electronic peak flow meter

Morning and evening PEF (L/min) will be monitored daily (during the run-in period and the randomised treatment period) by patients using an electronic peak flow meter.
**This will be done before the intake of the study medication.**
During each measurement session, the patient will perform 3 blows. Data will be recorded in the device.
Morning measurements should be done between 7:00 am – 9:00 am (+/- 2 hours) and evening measurements should be done between 7:00 pm – 9:00 pm (+/- 2 hours). An alarm will remind the patients to perform measurements.
Data from the device will be downloaded at each visit by the Investigator. A check of the recorded data will be done by the Investigator to verify the correct use of the device and to detect any clinical

abnormality and to check patient's compliance with the device. **In case of lack of compliance, instructions on how to use it will be given again to the patient.**

### 7.2.3 Electronic diary

Use of study medication (morning and evening doses) will be recorded in the electronic diary.
Use of rescue medication (salbutamol) will be recorded in the electronic diary in the morning and in the evening, before the PEF measurements.
The daily use of rescue medication will be recorded as follows: the number of puffs of salbutamol taken during the night will be recorded each morning on awakening before taking the morning dose of the study medications while the number of puffs taken during the day will be recorded each evening before taking the evening dose of the study medications.
The recorded data will be downloaded and checked by the Investigator at each visit.

### 7.2.4 Asthma symptoms scores

Asthma symptoms (cough, wheeze, chest tightness and breathlessness) will be recorded in the electronic diary in the morning and in the evening before the PEF measurements and 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 awakening
3. Severe: causing awakening 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.

**Asthma control days**

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

- Days (night-time plus daytime) with a total asthma score = 0
- No rescue medication use.

### 7.2.5 Asthma control questionnaire (ACQ-6)

Asthma control will be assessed at Visit 1, after the run-in period (Visit 3) and at the end of treatment period (Visit 9) through the 6-items Asthma Control Questionnaire©.

Only patients with a score at the ACQ < 0.75 will be enrolled and are eligible for randomization.
A paper ACQ will be filled in (which will be kept as source data) and the Investigator will record scores of each question in the eCRF form.

### 7.2.6 Asthma exacerbations

Patient will be instructed on recognition of symptoms (reported in Appendix II) signalling a potential asthma exacerbation and to call the investigator in this case.
During the run-in period, if the patient experienced any asthma exacerbation defined as moderate and severe the patient will not be randomised in the study at V3.

Patient re-screening may be allowed according to sponsor approval.

After randomization, in case the patient's condition does not require additional medication, or the additional medication used are allowed for the treatment of an episode of asthma exacerbation (as described in section 5.1), this patient will be maintained in the study. As soon as the exacerbation resolves, any additional treatment given for this asthma exacerbation needs to be discontinued.
The decision to withdraw the patient from further participation to the study will be at the investigator's discretion.

A moderate asthma exacerbation [13] is defined as:

Deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use for at least 3 days and/or hospitalization. E.R. visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, may be classified as moderate exacerbations.

A severe asthma exacerbation [13] is defined as:

At least one of the following:
1. Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.
2. A hospitalization or E.R. visit because of asthma, requiring systemic corticosteroids.

### 7.2.7 12-lead ECG

A local ECG will be used. The 12-lead single ECG measurements will be performed at Visit 1 and Visit 9 pre-bronchodilator. Prior to recording, the patient should be at rest in sitting position for at least 10 min. Investigator will check if the ECG is normal or abnormal (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female,) and if the patient can enter in the study, excluding any clinically significant ECG abnormalities that results in active medical problem.

### 7.2.8 Laboratory tests

The blood samples will be collected in the morning of Visit 1 and Visit 9 after an overnight fasting. Analysis will be done by local laboratories.
The following parameters will be assessed at Visit 1:

- *Blood Chemistry*: creatinine, BUN, fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, sodium, potassium, calcium, and chloride electrolytes (Na, K, Ca, Cl).

- *Haematology*: red blood cells count (RBC), white blood cells (WBC) and differential count (Neutrophils, Basophils Eosinophils, Lymphocytes, Monocytes), total haemoglobin (Hb), hematocrit (Hct), platelets count (PLT).
- *Pregnancy test*
  - *Serum β-HCG:* only for females of childbearing potential and only at Visit 1 and Visit 9.
  - *Urinary β-HCG:* only for females of childbearing potential from Visit 1 to Visit 8.

Blood collection and sample preparation will be performed according to procedures provided by the local laboratory.
The blood sample must be collected **after ECG**.

### 7.2.9 Vital signs

Heart rate, systolic and diastolic blood pressure (SBP, DBP) will be measured after 10 min rest in sitting position at pre-dose from Visit 1 to Visit 9.

## 8. EFFICACY ASSESSMENTS

Since the time interval between two visits during treatment period is 2 weeks with a window of +-3 days, in the analyses based on two-week treatment periods the actual inter-visit periods (in days) will be taken into account.

### 8.1 Primary variable

Change from baseline to the entire treatment period in average pre-dose morning PEF.

### 8.2 Secondary variables:

- Change from baseline to each 2-week (inter-visit) treatment period in average pre-dose morning PEF.
- Change from baseline to each 2-week (inter-visit) treatment period and to the entire treatment period in:
  - average pre-dose evening PEF;
  - daily PEF variability;
  - average use of rescue medication (number of puffs/day);
  - percentage of rescue-use free days;
  - average total morning asthma symptom scores;
  - average total evening asthma symptom scores;
  - percentage of asthma symptoms-free days;
  - percentage of asthma control days.
- Change from baseline in pre-dose morning $FEV_1$ and FVC at each clinic visit.
- Change from baseline to Week 12 in the Asthma Control Questionnaire (ACQ) score.

## 9. SAFETY ASSESSMENTS

- Adverse events and adverse drug reactions.
- Vital signs (heart rate, systolic and diastolic blood pressure).
- Moderate / severe asthma exacerbations.
- Abnormalities at 12-lead ECG

## 10. ADVERSE EVENT REPORTING

### 10.1 Definitions

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

An **Adverse Drug Reaction** is an "untoward and unintended responses to an investigational medicinal product related to any dose administered".
All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.
The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

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

- **Results in death**

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

- **Is life-threatening**

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

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

Hospitalization refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an 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 product information **(Investigator's Brochure for Foster® NEXThaler® and Summary of Product Characteristics for Foster® 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 Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

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

### 10.3 Intensity of Adverse Event

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

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

### 10.4 Causality Assessment

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

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

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

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

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

### 10.5 Action taken with the study drug due to the AE

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

### 10.6 Other actions taken

- Specific therapy/medication
- Surgical/medical procedure
- 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 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.

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

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

### 10.9 Reporting Serious Adverse Events to Chiesi

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

| Name and Title | Tel no. | Mobile no. | Fax no. | E-mail |
|---|---|---|---|---|
| PPD Safety Contact | PPD | | | Foster_NEXThaler_PhV@PPD .com |
| PPD<br>Global Pharmacovigilance Operations Specialist | PPD | | | PPD |

- 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 PPD Safety Contact. New SAEs occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

In regards to Regulations in force for Pharmacovigilance, the Investigator must also fulfil in his 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 PPD Safety Contact together with the Serious Adverse Event form, retaining a copy on site with the case report form;

- If an autopsy is performed, copy of redacted autopsy report should be actively sought by the Investigator and sent to the PPD Safety Contact as soon as available, retaining a copy on site with the case report form;
- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be followed with due diligence until the outcome of the pregnancy is known. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail/via Monitor to PPD Safety Contact using the paper Pregnancy Report Form. PPD 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 PPD Safety Contact. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome with a follow-up of the first two pages, if necessary (e.g. an update in the medications received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.
- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.

## 11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her designee.
All patients who will sign the informed consent will be databased. For patients who are screened but not randomized a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, adverse events and concomitant medications if any.
Questionnaires answers will be databased.
Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, 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).
External data (electronic diary data, PEF measurements from electronic peak flow meter,) will be processed centrally and reconciled against data recorded in the eCRF as part of cleaning activities.
Laboratory normal ranges will be collected prior to FPFV at each site and provided to data management via PPD results will be entered in the eCRF by the investigator.

After cleaning of data, a review meeting will be held to determine the occurrence of any protocol violation and to define the patient populations for the analysis.

Once the data have been declared to be complete and accurate, the database will be locked (eCRF locked and external data monitored by audit trails to apply data control), the randomization codes will be opened and the planned statistical analysis will be performed. Only authorised and well-documented updates to the study data are possible after database lock. Patient data on electronic support will be sent after database lock to the investigational site for archiving.

## 12. STATISTICAL METHODS

The following describes the statistical analysis as it is foreseen at the time of planning the trial. A detailed statistical analysis plan will be described in a separate document, which will include the statistical methods that will be used for conducting the analysis, to be finalized before breaking the blind.

### 12.1 Sample Size

A sample size of 220 evaluable patients per group will provide approximately 85% power to demonstrate the non-inferiority of Foster® NEXThaler® compared to Foster® in terms of change from baseline to the entire treatment period in average pre-dose morning PEF, with a non-inferiority margin of -15 l/min and a one-sided significance level of 0.025, assuming a mean difference of 0 l/min between treatments and a standard deviation of 52 l/min.
The non-inferiority margin of -15 L/min is widely reported in previous studies [14, 15]. Moreover, it is less than the minimal patient perceivable improvement of 18.8 L/min estimated by Santanello et al. [16].
Estimating a non-evaluable rate of 10%, a total of about 490 patients (245 per treatment group) will be randomized.Anticipating a screening failure rate of 50%, a total number of about 1000 patients will be screened.
Populations for analysis:

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

The primary efficacy variable will be analyzed both in the ITT and in the PP populations. The ITT and PP populations have equal importance in the evaluation of the non-inferiority hypothesis.
The secondary efficacy variables will be analyzed in the ITT population only.
Analysis of safety variables will be performed in the Safety population. In case of deviation between as-randomised treatment and treatment actually received, the treatment actually received will be used in the analysis of safety variables (i.e. an as-treated analysis will be performed).

### 12.2 Statistical analysis

The following describes the statistical analysis as it is foreseen at the time of planning the trial.
A detailed statistical analysis plan will be described in a separate document to be completed after having finalized the protocol. 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 and locking the database.

#### 12.2.1 Descriptive Statistics

Descriptive statistics will be provided for each variable in summary tables by treatment group. Quantitative variables will be summarized by using n (sample size), mean, standard deviation, median, minimum and maximum. For lung function parameters the 95% confidence interval (CI) of the mean will also be reported. Categorical variables will be summarized by using frequency count and percent distribution. Missing values will not be used in percentage calculations

### 12.2.2 Missing data

For the daily variables recorded by the patients, the availability of at least 50% of the measurements will be required between two adjacent visits in order to consider an inter-visit period as valid for the analysis; otherwise the entire inter-visit period will be considered missing for the analysis.

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 the review of the data. Decisions will be fully documented in the Data Review Report.

### 12.2.3 Patient demographics and baseline characteristics

Descriptive statistics will be presented at baseline for ITT and PP populations. The following parameters will be presented:

- Demographic characteristics (age, gender, race, height, weight, bmi);
- Disease specific history (asthma, smoking habits);
- Baseline spirometric data;
- Medical/surgical history and concomitant diseases;
- Previous and concomitant medications;

### 12.3 Principles of statistical analysis

For each two-week (inter-visit) period, the variables daily recorded by the patients will be summarized according to their type:

- for quantitative variables, all the available measurements will be averaged over the period;
- for categorical variables, percentages will be calculated considering all the days with available data.

For quantitative efficacy and safety variables, analysis within treatment groups will be presented. Mean changes from baseline and their 95% CIs will be calculated.
The least squares means and their differences obtained from the statistical models will be presented with the respective 95% CIs.
P-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.
For primary and secondary efficacy variables, baseline will be based on the last two weeks of the run-in period

### 12.3.1 Primary efficacy variables

Change from baseline to the entire treatment period in average pre-dose morning PEF will be analysed using an ANCOVA model including treatment, center and sex as factors and baseline as a covariate.

Non-inferiority will be demonstrated if the lower redundant limit of the 95% confidence interval (CI) of the adjusted mean difference between Foster® 100/6 µg NEXThaler®and Foster® 100/6 µg pMDI will be ≥ -15 L/min.

### 12.3.2 Secondary efficacy variables

- All the variables measured repeatedly during the randomized treatment period (see section 8.2) will be analysed using a linear mixed model for repeated measures (MMRM) including change from baseline at each inter-visit period as dependent variable, treatment, visit/period, treatment × visit/period interaction, center and sex as fixed effect, baseline and baseline × visit/period interaction as fixed covariates.

- All the variables calculated over the entire treatment period as change from baseline (see section 8.2) will be analysed using the same ANCOVA model as for the primary efficacy variable.

- Change from baseline at each clinical visit in pre-dose morning $FEV_1$ and FVC will be analysed using a linear mixed model for repeated measures (MMRM) including change from baseline at each visit as dependent variable, treatment, visit/period, treatment × visit/period interaction, center and sex as fixed effect, baseline and baseline × visit/period interaction as fixed covariates.

- Change from baseline to end of treatment (Week 12) in the ACQ score will be analysed using the same ANCOVA model as for the primary efficacy variable.

### 12.3.3 Safety variables

- *Adverse Events*
  - The number and the percentage of patients experiencing adverse events, adverse medication reactions, serious adverse events and adverse events leading to study withdrawal will be summarized by treatment group. Adverse events will also be summarized by System Organ Class and Preferred Term using the MedDRA dictionary.
- Vital Signs
  - Vital signs (heart rate, systolic and diastolic blood pressure) will be summarized by treatment group using descriptive statistics, (see 12.3.1) and changes from baseline with their 95% CIs will be presented.
- *12-Lead ECG data*
  - Mean absolute values at Visit 1 and at the end of Treatment (Visit 9) of HR, PR, QRS and QTcF will be analyzed using descriptive statistics, including the appropriate 95% CIs, as well as change at Visit 9 vs Visit 1
  - The number and percentage of subjects with an abnormal ECG (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female), will be summarized by treatment group at visit 1 and visit 9.
- *Asthma exacerbations*
  - The number of moderate / severe asthma exacerbations and the number and the percentage of patients experiencing moderate / severe asthma exacerbations will be summarized by treatment group.

No interim analysis is planned.

## 13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Ethics Committee/Institutional Review Board in accordance with the requirements of China.
The EC/IRB shall give its opinion in writing -clearly identifying the study number, study title and informed consent form approved, before the clinical trial commences.
A copy of all communications with the EC/IRB will be provided to the Sponsor.
The Investigator should provide written reports to the EC/IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the subjects (according to the requirements of each country).

## 14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in China.
Selection of the subjects will not start before the approval of the Ethics Committee/Institutional Review Board has been obtained and the study notified to Health Authorities (or authorized by).
The study will be conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practices guidelines and following all other requirements of local laws.

## 15. INFORMED CONSENT

It is the responsibility of the Investigator to obtain written consent from each subject or from the subject's legal representative prior to any study related procedures taking place.
If the subject and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the subject.
Consent must be documented by the subject's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.
Each subject's signed informed consent must be kept on file by the Investigator. One copy must be given to the subject.

## 16. DIRECT ACCESS TO SOURCE DOCUMENTS/DATA

The Investigators or designated must permit trial-related monitoring, audits, Ethics Committee/Institutional Review Board review or regulatory inspection, providing direct access to source data/documents.

## 17. STUDY MONITORING

Monitoring will be performed by PPD who has been designated by Chiesi.
It is understood that the monitor(s) will contact and visit the Investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data (source data is any data that is recorded elsewhere to the case report forms), provided that subject confidentiality is respected.

The purposes of these visits are:

- to assess the progress of the study;
- to review the compliance with the study protocol;
- to discuss any emergent problem;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the CRFs against the source documents;
- to assess the status of medication storage, dispensing and retrieval.

Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

## 18. QUALITY ASSURANCE

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

## 19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.
Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the medication was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.
The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

## 20. CONFIDENTIALITY

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

## 21. PREMATURE TERMINATION OF THE STUDY

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

## 22. CLINICAL STUDY REPORT

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 Chinese Competent Authority and to Investigators.

## 23. RECORD RETENTION

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

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

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

## 24. PUBLICATION OF RESULTS

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

## 25. REFERENCES

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## APPENDIX I - APPROVAL OF THE PROTOCOL BY CLINICAL INVESTIGATOR(S)

**A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma**

**Product:** Foster® 100/6µg NEXThaler®: Fixed combination of beclomethasone dipropionate 100 µg/unit dose plus formoterol fumarate 6 µg/unit dose

**Pharmaceutical Form:** Dry powder via NEXThaler® inhaler

**Approval of Clinical Study Protocol by the Coordinating Investigator:**

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

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

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

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

**Investigator's Name:** Pr Zheng Jinping 郑劲平,MD

_____ _____

Signature Date

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

| | |
|---|---|
| Clinical Study Code: CCD-01535BA0-01 | Version No.:7.0 |
| IND No.: 2015L06250 | Date: 31/08/2020 |

**A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma**

**Product:** Foster® 100/6µg NEXThaler®: Fixed combination of beclomethasone dipropionate 100 µg/unit dose plus formoterol fumarate 6 µg/unit dose

**Pharmaceutical Form:** Dry powder via NEXThaler® 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/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

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

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

**Investigator's Name:** _____,MD

**Centre No.** :_____

_____ _____
Signature Date

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

# APPENDIX II

## MINIMUM LIST OF SOURCE DATA REQUIRED

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

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

# APPENDIX III

**Signs and Symptoms of a Developing Moderate and Severe Asthma Exacerbation***

| Sign/Symptom | Moderate Exacerbation | Severe Exacerbation |
|---|---|---|
| Breathless | Prefers sitting | Hunched forward |
| Talks in | Phrases | Words |
| Respiratory rate | Increased | Often > 30/minute |
| Wheeze | Loud | Usually Loud |
| Pulse/min | 100-120 | >120 |

* *Modified from Box 4.4 (Management of Asthma exacerbations in primary care) of the Global Initiative for Asthma Document (GINA 2018) [www.ginasthma.org]

# SIGNATURE PAGE

**Document Code:** CLI-CCD-01535BA0-01-APP 16.1.1-02068
**Title:** Foster NEXThaler_Amendment N°1 to Protocol v7.0 dated 31082020
**Version:** 1.0,CURRENT
**Status:**Approved, since: 04-Mar-2021 03:12:28 UTC

**Electronic Signature:**
Signed by: PPD
Date: 04-Mar-2021 03:12:19 UTC
Meaning of Signature: Clinical Approval

**Note:** Each electronic signature above is equivalent to a handwritten signature since the computer system managing the electronic document fully complies with the international rules (i.e. FDACFR21part11, EU Annex11) concerning Electronic Records and Electronic Signatures Management. **Declaration**

PPD

Chiesi

**NON-SUBSTANTIAL,**

**GENERAL**

**AMENDMENT No.** 1

**DATE:** 24 February 2021

To Clinical Study Protocol
Version no.: *7.0*, Date: *31 August 2020*

**STUDY CODE No.: CCD-01535BA0-01**

**IND No.: 2015L06250**

# A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma



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

| Clinical Study Code No.: CCD-01535BA0-01 | IND No.: 2015L06250 |
|---|---|

**Information related to the Amendment**

| | | |
|---|---|---|
| **Regulatory Authority** | □ | **Notification** |
| | □ | **Approval** |
| | ♦ | **Not applicable** |
| **Ethics Committee/IRB** | ♦ | **Notification** |
| | □ | **Approval** |
| | □ | **Not Applicable** |
| **Informed Consent** | □ | **Modified** |
| | ♦ | **Unchanged** |
| **Case Report Form** | □ | **Modified** |
| | ♦ | **Unchanged** |
| **Other Study Documents** | □ | **Modified (specify)** |
| | ♦ | **Unchanged** |

- **SECTIONS OF THE PROTOCOL WHICH ARE MODIFIED**

The following changes were made in the protocol (changed elements are in bold italic and deleted text is crossed out)

| Previous version | New version | Rationale |
|---|---|---|
| **PROTOCOL OUTLINE**<br>**Inclusion criteria**<br>2. Clinical diagnosis of asthma for a minimum of 6 months prior to Visit 1 confirmed by a chest physician according to international guidelines updated 2018 (GINA). The evidence of asthma must be confirmed through a documented positive response (in the last twenty-four months) either to a bronchial provocation test/challenge test or a reversibility test.<br>~~3.~~ In case the patient does not have any documented reversibility test or provocation/challenge test, Salbutamol Reversibility Test will be performed at Visit 1 within 10 to 30 min after administration of 400 µg of salbutamol pMDI (ATS/ERS taskforce 2005). Positive test if $\Delta FEV_1 \geq 12\%$ and $\geq 200$ mL over baseline.<br>~~4.~~ Note: In case the reversibility threshold is not met at Visit 1, the test can be repeated once before Visit 2 or at Visit 2.<br>~~5.~~ $FEV_1$>80% of the predicted normal value after appropriate washout from bronchodilators (to be checked at Visit 1 and at randomization visit (Visit 3).<br>Note: If this criterion is not met:<br>• At Visit 1: the test can be repeated once before Visit 2 or at Visit 2.<br>• At randomization visit: the test can be repeated once | **PROTOCOL OUTLINE**<br>**Inclusion criteria**<br>2. Clinical diagnosis of asthma for a minimum of 6 months prior to Visit 1 confirmed by a chest physician according to international guidelines updated 2018 (GINA). The evidence of asthma must be confirmed through a documented positive response (in the last twenty-four months) either to a bronchial provocation test/challenge test or a reversibility test.<br>In case the patient does not have any documented reversibility test or provocation/challenge test, Salbutamol Reversibility Test will be performed at Visit 1 within 10 to 30 min after administration of 400 µg of salbutamol pMDI (ATS/ERS taskforce 2005). Positive test if $\Delta FEV_1 \geq 12\%$ and $\geq 200$ mL over baseline.<br>Note: In case the reversibility threshold is not met at Visit 1, the test can be repeated once before Visit 2 or at Visit 2.<br>3. $FEV_1$>80% of the predicted normal value after appropriate washout from bronchodilators (to be checked at Visit 1 and at randomization visit (Visit 3).<br>Note: If this criterion is not met:<br>• At Visit 1: the test can be repeated once before Visit 2 or at Visit 2.<br>• At randomization visit: the test can be repeated once | Due to the formatting problem, the numbering of inclusion criteria is different from the main body of the protocol, but the content is the same. |

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| within 2 days after this visit. | within 2 days after this visit. | |
| ~~6.~~ ACQ-6 (simplified version of the Asthma Control Questionnaire) score < 0.75 (to be checked at Visit 1and at randomization visits). | 4. ACQ-6 (simplified version of the Asthma Control Questionnaire) score < 0.75 (to be checked at Visit 1and at randomization visits). | |
| ~~7.~~ Patients on previous regular treatment at a stable dose for at least 1 month prior to Visit 1 with either medium daily dose of ICS monotherapy (e.g., BDP-CFC > 500 – 1000 µg/day or equivalent dose) or high daily dose of ICS monotherapy (e.g., BDP-CFC > 1000 µg/day or equivalent dose) OR low daily dose of ICS (e.g., BDP-CFC≥200 – 500 µg/day or equivalent dose)/ LABA free/fixed combination or medium daily dose of ICS (e.g., BDP- CFC > 500 – 1000 µg/day or equivalent dose)/ LABA free/fixed combination. | 5. Patients on previous regular treatment at a stable dose for at least 1 month prior to Visit 1 with either medium daily dose of ICS monotherapy (e.g., BDP-CFC > 500 – 1000 µg/day or equivalent dose) or high daily dose of ICS monotherapy (e.g., BDP-CFC > 1000 µg/day or equivalent dose) OR low daily dose of ICS (e.g., BDP-CFC≥200 – 500 µg/day or equivalent dose)/ LABA free/fixed combination or medium daily dose of ICS (e.g., BDP- CFC > 500 – 1000 µg/day or equivalent dose)/ LABA free/fixed combination. | |
| ~~8.~~ A cooperative attitude and ability to be trained to the proper use of DPI and pMDI devices and electronic peak flow meter (to be checked at Visit 1and at randomization visits). | 6. A cooperative attitude and ability to be trained to the proper use of DPI and pMDI devices and electronic peak flow meter (to be checked at Visit 1and at randomization visits). | |
| ~~9.~~ At least 7 valid pre-dose morning PEF measurements in the last 14 days of the run-in period are necessary (to be checked at randomization visit). | 7. At least 7 valid pre-dose morning PEF measurements in the last 14 days of the run-in period are necessary (to be checked at randomization visit). | |
| **PROTOCOL OUTLINE**<br>**Exclusion criteria** | **PROTOCOL OUTLINE**<br>**Exclusion criteria** | Due to the formatting problem, the numbering of exclusion criteria is different from the main body of the protocol, but the content is the same. |
| 1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are using one or more of the following highly effective contraceptive measures: | 1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) UNLESS they are using one or more of the following highly effective contraceptive measures: | |

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| • Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)<br>• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)<br>• Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)<br>• Bilateral tubal occlusion<br>• Vasectomised partner<br>• Sexual abstinence | • Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)<br>• Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)<br>• Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)<br>• Bilateral tubal occlusion<br>• Vasectomised partner<br>• Sexual abstinence | |
| Reliable contraception should be maintained throughout the study. | Reliable contraception should be maintained throughout the study. | |
| Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study. | Any postmenopausal women (physiologic menopause defined as "12 consecutive months of amenorrhea without an alternative medical cause") or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy) can be enrolled in the study. | |
| ~~2.~~ Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at Visit 1 and end of treatment (V9), urine pregnancy test will be performed at all visits except V0 and V9. | Pregnancy testing will be carried out during the course of the study in all women of childbearing potential: serum pregnancy test will be performed at Visit 1 and end of treatment (V9), urine pregnancy test will be performed at all visits except V0 and V9. | |
| ~~3.~~ Intermittent asthma or asthma occurring only during episodic exposure to an allergen or a chemical sensitizer. | 2. Intermittent asthma or asthma occurring only during episodic exposure to an allergen or a chemical sensitizer. | |
| ~~4.~~ History of near fatal asthma (e.g., brittle asthma, hospitalization for asthma | 3. History of near fatal asthma (e.g., brittle asthma, hospitalization for asthma | |

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| exacerbation in an Intensive Care Unit). | exacerbation in an Intensive Care Unit). | |
| ~~5.~~ Diagnosis of COPD as defined by the current GOLD guidelines updated 2016. | 4. Diagnosis of COPD as defined by the current GOLD guidelines updated 2016. | |
| ~~6.~~ Current smokers, or ex-smokers with total cumulative exposure equal or more than 10 pack-years, or having stopped smoking one year or less prior to Visit 1. | 5. Current smokers, or ex-smokers with total cumulative exposure equal or more than 10 pack-years, or having stopped smoking one year or less prior to Visit 1. | |
| ~~7.~~ Severe asthma exacerbation leading to intake of systemic corticosteroids (≥10 days) within 1 month prior to inclusion or moderate/severe asthma exacerbation [according to international guidelines updated 2018 (GINA) and Reddel et al. definition [13] during the run-in period (to be checked at Visit 1 and at Visit V3 (randomization). | 6. Severe asthma exacerbation leading to intake of systemic corticosteroids (≥10 days) within 1 month prior to inclusion or moderate/severe asthma exacerbation [according to international guidelines updated 2018 (GINA) and Reddel et al. definition [13] during the run-in period (to be checked at Visit 1 and at Visit V3 (randomization). | |
| ~~8.~~ Lower respiratory tract infections (e.g. pneumonia) affecting the patient's asthma within 1 month prior to inclusion. | 7. Lower respiratory tract infections (e.g. pneumonia) affecting the patient's asthma within 1 month prior to inclusion. | |
| ~~9.~~ History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease. | 8. History of cystic fibrosis, bronchiectasis or alpha-1 antitrypsin deficiency, or any other significant lung disease. | |
| ~~10.~~ Diagnosis of restrictive lung disease. | 9. Diagnosis of restrictive lung disease. | |
| ~~11.~~ Patients treated with oral or parenteral corticosteroids in the previous 2 months before Visit 1 (3 months for parenteral depot corticosteroids). | 10. Patients treated with oral or parenteral corticosteroids in the previous 2 months before Visit 1 (3 months for parenteral depot corticosteroids). | |
| ~~12.~~ Intolerance or contra-indication to treatment with β2-agonists and/or inhaled corticosteroids or allergy to any component of the study treatments. | 11. Intolerance or contra-indication to treatment with β2-agonists and/or inhaled corticosteroids or allergy to any component of the study treatments. | |
| ~~13.~~ Having received an investigational medication within 2 months before Visit 1. | 12. Having received an investigational medication within 2 months before Visit 1. | |

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| ~~14.~~ Patients who have a clinical or functional uncontrolled respiratory, haematological, immunologic, renal, neurologic, hepatic, endocrinal or other disease, or any condition (e.g. major surgery) that might, in the judgment of the investigator, represent for the patients an undue risk or that could compromise the results or interpretation of the study. | 13. Patients who have a clinical or functional uncontrolled respiratory, haematological, immunologic, renal, neurologic, hepatic, endocrinal or other disease, or any condition (e.g. major surgery) that might, in the judgment of the investigator, represent for the patients an undue risk or that could compromise the results or interpretation of the study. | |
| ~~15.~~ History or current evidence of uncontrolled heart failure, clinically relevant coronary artery disease, recent myocardial infarction, severe hypertension, uncontrolled cardiac arrhythmias. | 14. History or current evidence of uncontrolled heart failure, clinically relevant coronary artery disease, recent myocardial infarction, severe hypertension, uncontrolled cardiac arrhythmias. | |
| ~~16.~~ Clinically relevant laboratory abnormalities such as (but not limited to) hypokalemia (< 3.5 mEq/l), that might compromise patient's safety or compliance, interfere with evaluation, or preclude completion of the study, in the judgment of the investigator. Patients with uncontrolled diabetes including patients with a history of serum glucose levels consistently out of the normal range (> 140 mg/dl) or HbA1C >8.0%. | 15. Clinically relevant laboratory abnormalities such as (but not limited to) hypokalemia (< 3.5 mEq/l), that might compromise patient's safety or compliance, interfere with evaluation, or preclude completion of the study, in the judgment of the investigator. Patients with uncontrolled diabetes including patients with a history of serum glucose levels consistently out of the normal range (> 140 mg/dl) or HbA1C >8.0%. | |
| ~~17.~~ Patients who have an abnormal 12-lead ECG parameter (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female) or 12-lead ECG evaluated as abnormal clinical significant by the investigator, at Visit 1. | 16. Patients who have an abnormal 12-lead ECG parameter (i.e.: QRS > 120 msec and/or PR > 210 msec and/or HR < 45 bpm and/or HR > 110 bpm and/or QTcF > 450 ms for males or QTcF > 470 ms for female) or 12-lead ECG evaluated as abnormal clinical significant by the investigator, at Visit 1. | |
| ~~18.~~ Patients who have a concomitant disease of poor prognosis (e.g., cancer). | 17. Patients who have a concomitant disease of poor prognosis (e.g., cancer). | |

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| ~~19.~~ Patients treated with monoclonal antibodies (e.s anti-IgE antibodies). | 18. Patients treated with monoclonal antibodies (e.s anti-IgE antibodies). | |
| ~~20.~~ Patients treated with non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication), non-selective β-blocking medications, quinidine, quinidine-like antiarrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation. | 19. Patients treated with non-potassium sparing diuretics (unless administered at a fixed dose combination with a potassium conserving medication), non-selective β-blocking medications, quinidine, quinidine-like antiarrhythmics, or any medication with a QTc prolongation potential or a history of QTc prolongation. | |
| ~~21.~~ Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, unless already taken at stable doses in the month before the Visit 1 and without any safety concern. | 20. Patients treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, unless already taken at stable doses in the month before the Visit 1 and without any safety concern. | |
| ~~22.~~ Patients who are receiving therapy that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin). | 21. Patients who are receiving therapy that could interact with steroids, such as enzyme inhibitors [macrolides, antifungal therapy (not topical)] or induced (anticonvulsants, rifampicin). | |
| ~~23.~~ Inability to comply with study procedures or with study treatment intake. | 22. Inability to comply with study procedures or with study treatment intake. | |

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

A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® 100/6µg NEXThaler®, 2 inhalations b.i.d., versus Foster® 100/6µg pMDI, 2 puffs b.i.d., in patients with controlled asthma

**Product:** Foster® 100/6µg NEXThaler®: Fixed combination of beclomethasone dipropionate 100 µg/unit dose plus formoterol fumarate 6 µg/unit dose

**Pharmaceutical Form:** Dry powder via NEXThaler® 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/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

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.

**Investigator's Name**: _____, MD

**Centre No.**: _____

**Signature**: _____

**Date**: _____/_____/_____

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

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**Investigator's Name**: _____, MD

**Centre No.**: _____

**Signature**: _____

**Date**: _____/_____/_____

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