NCT05292586

CLINICAL STUDY PROTOCOL

STUDY CODE No.: CLI-05993AB8-02

IND No: 153868

A 12 week, randomized, double-blind, multicenter, active controlled, 2-arm parallel group study testing the superiority of CHF 1535 pMDI 800/24µg total daily dose (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) compared to CHF 718 pMDI 800µg total daily dose (extrafine beclomethasone dipropionate) in adults with asthma on medium or high-dose inhaled corticosteroid.

Version No.: 2.0
Date: 01Jun2023

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

GENERAL INFORMATION

SPONSOR:	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
SPONSOR MEDICAL EXPERT (Clinical Research Physician)	[redacted], MD, MPH, MSCR [redacted] Readily available in case of medical questions
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VERSION HISTORY

Version	Date	Change History
1.0	01Mar2022	First issue
2.0	01Jun2023	Second Version For detailed list of changes see Summary of Changes from Protocol v 1.0 to Protocol v 2.0

Clinical Study Code No.: CLI-05993AB8-02	Version No. 2.0
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PROTOCOL OUTLINE

Study title	A 12 week, randomized, double-blind, multicenter, active controlled, 2-arm parallel group study testing the superiority of CHF 1535 pMDI 800/24µg total daily dose (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) compared to CHF 718 pMDI 800µg total daily dose (extrafine beclomethasone dipropionate) in adults with asthma on medium or high-dose inhaled corticosteroid.
Sponsor	Chiesi Farmaceutici S.p.A. – Via Palermo 26/A 43122 Parma – Italy
Name of the Product	CHF 1535 200/6µg pressurized metered dose inhaler (pMDI) (beclomethasone dipropionate [BDP] plus formoterol fumarate [FF])
Centre(s)	Approximately 90 sites
Indication	Asthma
Study design	Double-blind, randomized, multicenter, 2-arm parallel group study with active control group
Study phase	Phase III
Objectives	**Primary Objectives** • To demonstrate the superiority of CHF 1535 pMDI 800/24µg total daily dose (TDD) compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12. **Key Secondary Objective** • To demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12. **Secondary Objectives** • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 0. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 0. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in trough FEV_1 (i.e. average of 11.5h and 12h post-dose FEV_1 value) at Week 12. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average morning PEF over 12-week treatment period. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average evening PEF over 12-week treatment period. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e. change ≥100mL) for pre-dose morning FEV_1 at Week 4, 8 and 12.

	• To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e. change ≥100mL) for trough FEV_1 at Week 12. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in terms of Asthma Control Questionnaire-7 (ACQ-7) and Asthma Control Questionnaire-5 (ACQ-5) at Week 12. • To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in percentage of rescue medication free days and asthma symptom free days over 12-week treatment period. • To assess the safety and the tolerability of the study drugs.
Treatment duration	A 2-week run-in period on CHF 718 (BDP) pMDI 100µg, followed by a 12-week double-blind, treatment period.
Test product dose/route/regimen	**CHF 1535 pMDI 200/6µg** Fixed combination of extrafine BDP 200µg plus FF 6µg (BDP/FF) Dose regimen: BDP/FF 200/6µg per actuation, 2 inhalations (puffs) BID, total daily dose (TDD) 800/24µg
Reference product dose/route/regimen	**CHF 718 pMDI 100µg** Beclomethasone dipropionate (BDP) 100µg Dose regimen: BDP 100µg per actuation, 4 inhalations (puffs) BID, total daily dose (TDD) 800µg
Number of subjects	A total of about 580 subjects will be randomized according to a 1:1 ratio to either CHF 1535 pMDI 800/24µg TDD (290 subjects) or CHF 718 pMDI 800µg TDD (290 subjects)
Study population	Adult subjects with asthma on medium or high dose inhaled corticosteroids (ICS) or on medium dose ICS plus long-acting β2-agonist (LABA)
Inclusion/exclusion criteria	**Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible for participation into the study: 1. **Informed consent:** A signed and dated written informed consent obtained prior to any study-related procedures. 2. **Sex and age:** Male or female aged ≥18 and ≤75 years. 3. **Diagnosis of asthma:** A documented history of asthma for at least 1 year, with onset before age 40 4. **Stable asthma therapy:** Use of medium-dose ICS with or without a LABA or high-dose ICS alone for 3 months (at a stable dose for at least 4 weeks prior to screening).

Estimated Comparative Total Daily Dosages for US Approved Inhaled Corticosteroids		
Inhaled Corticosteroid*	**Medium daily dose**	**High daily dose**
Beclomethasone dipropionate (DPI or pMDI, extrafine particle, HFA)	>160-320µg	>320-640µg
Budesonide DPI	>360-720µg	>720µg
Ciclesonide (pMDI, extrafine particle, HFA)	>160-320µg	>320µg
Fluticasone furoate (DPI)	100µg	200µg
Fluticasone propionate (pMDI, standard particle, HFA) *	>220-440µg	>440µg
Fluticasone propionate (DPI)	>250-500µg	>500µg
Mometasone furoate (DPI)	220-440µg	>440µg
Mometasone furoate (pMDI, standard particle, HFA)	200-400µg	>400µg

** Note: This is not a table of equivalence. For questions on Inhaled corticosteroid + long-acting beta agonist (LABA) dual therapy where dose ranges do not fall within table ranges, please contact Medical Monitor for guidance.*

(Table adapted from Global Initiative for Asthma (2022) and Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007))

5. **Lung function:** Subjects with a pre-bronchodilator $FEV_1 \geq 40\%$ and $\leq 85\%$ of predicted, after appropriate washout from bronchodilators, at the screening *and* randomization visits. In addition, the ***absolute value*** of the first pre-dose FEV_1 at randomization (V2) must be at least 80% of the pre-bronchodilator value attained at screening.

6. **Reversibility post-bronchodilator:** Subjects with a positive reversibility to bronchodilator at screening, defined as an increase in $FEV_1 > 12\%$ *and* > 200mL compared to baseline within 30 minutes after 4 inhalations of albuterol HFA pMDI 90µg/actuation.

Note for IC#5 and IC#6: In case the reversibility and/or quality threshold is not met at screening, the test can be performed once before randomization.

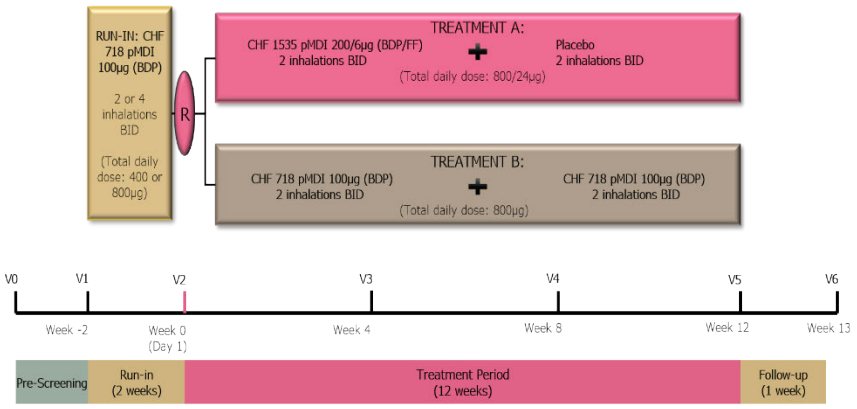
7. **Female subjects:**
    a. WOCBP fulfilling one of the following criteria:
        i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signing of the

	informed consent form and until the follow-up contact or ii. WOCBP with non-fertile male partners (contraception is not required in this case). For the definition of WOCBP and of fertile men and the list of highly effective birth control methods, refer to Appendix 2. Highly effective contraception should be maintained until the follow-up call. Subjects should then refer to the pregnancy recommendations and precautions, related to their asthma treatment prescribed after the study drug discontinuation. Or b. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile as per definitions given in Appendix 2). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges). 8. **Cooperative attitude** and ability to demonstrate correct use of the pMDI inhalers and eDiary/peak flow meter. The following inclusion criteria must be confirmed at the randomization visit prior to dosing: 5, 6, 7 and 8. **Exclusion Criteria** Any of the following will exclude a subject from participation: 1. **Pregnancy or lactation:** where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive pregnancy test (serum and urine pregnancy test to be performed at screening visit and urine pregnancy test to be performed prior to randomization). 2. **Poor compliance** with run-in medication or eDiary completion <50% before randomization. 3. **History of "at risk" asthma:** History of near-fatal asthma or of a past hospitalization for asthma in intensive care unit which, in the judgement of the investigator, may place the subject at undue risk. 4. **Recent asthma exacerbation:** Hospitalization, emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period. 5. **Unresolved respiratory tract infection (RTI)** in the 4 weeks prior to the screening visit or during run-in period. Documented coronavirus disease 2019 (COVID-19) diagnosis within the last 8

	weeks or complications from this disease, which have not resolved within 14 days prior to screening. 6. **Unstable ICS dose** during the 4 weeks prior to screening visit, including any change in dose, schedule, or formulation. 7. **Use of systemic corticosteroid** medication in the 4 weeks prior to screening or slow-release corticosteroids in the 12 weeks before screening. 8. **Respiratory disorders other than asthma:** History of a diagnosis of cystic fibrosis, bronchiectasis, COPD (as defined by the current GOLD Report), alpha-1 antitrypsin deficiency, interstitial lung disease, sarcoidosis, pulmonary hypertension, or any other significant lung disease which may interfere with study evaluations. 9. **Smoking status:** Current smokers or ex-smokers with total cumulative exposure equal to or more than 10 pack-years (pack-years = the number of cigarette packs per day times the number of years smoked) or having stopped smoking within one year prior to screening visit. 10. **E-cigarette status:** Current e-cigarettes users at the time of the screening visit or having stopped ≤ 6 months prior to screening visit). 11. **Cannabis usage:** Current use of inhaled or oral cannabis products (e.g. marijuana). 12. **Substance abuse:** Subjects with a history of alcohol or substance/drug abuse within 12 months prior to screening. 13. **Cardiovascular diseases:** Subjects who have clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV heart failure, acute ischemic heart disease within one year prior to study entry, known history of atrial fibrillation or history of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to screening, not controlled with a rate control strategy. *Note: Subjects with Permanent Atrial Fibrillation (for at least 6 months) with a resting ventricular rate <100/min, controlled with a rate control strategy (i.e., selective β-blocker, calcium channel blocker, pacemaker placement, digoxin, or ablation therapy) can be considered for the enrollment.* 14. **ECG criteria:** An abnormal and clinically significant 12-lead electrocardiogram (ECG) which may impact the safety of the subject according to Investigator's judgement. In terms of the QTcF,

	subjects with QTcF >450ms for males or QTcF >470ms for females at screening or at randomization visits (criterion not applicable for subject with pacemaker or permanent atrial fibrillation). 15. **Other medical conditions:** Other active severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. 16. **Vaccination:** Subjects having received a vaccination within 2 weeks prior to screening or during the run-in period. 17. **Subjects' wellbeing:** Subjects mentally or legally incapacitated, including but not limited to subjects who are institutionalized or incarcerated. 18. **Hypersensitivity:** Subjects with known intolerance, hypersensitivity or contraindication to treatment with ß2-agonists, ICS, or propellant gases/excipients. 19. **Surgery:** Subjects with major surgery in the 3 months prior to the screening visit or planned surgery during the study. 20. **Additional treatment:** Subjects treated with non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening), non-selective beta-blocking drugs, quinidine, quinidine-like anti-arrhythmic, or any medication with a QTc prolongation potential or a history of QTc prolongation. 21. Subjects treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. 22. Subjects with concomitant immunosuppressive therapy, use of oral or injected corticosteroids, anti-IgE, anti-IL5 or other monoclonal or polyclonal antibodies within 12 weeks prior to screening. 23. Subjects who are receiving any therapy that could interfere with the study drugs according to investigator's opinion. 24. **Participating in other investigational trial:** Subjects who have received an investigational drug within 1 month or 5 half-lives (whichever is greater) prior to screening visit, or have been previously randomized in this trial, or are currently participating in another clinical trial.

	25. **Spacer:** The need to use a spacer for correct self-administration of a pMDI. Exclusion criteria # 1, 2, 4, 5, 14 and 16 must be confirmed at the randomization visit prior to dosing.
Study plan	A total of 6 clinic visits (V0 to V5) and a follow-up call will be performed during the study, as follows: • A pre-screening visit (V0) will be carried out in order to fully explain the study to potential subjects, to obtain the written informed consent from the subject and to instruct the subject on screening visit procedures (such as medication restrictions). Eligible subjects entering the study will be instructed to refrain from taking their current asthma medication morning dose in addition to rescue medication as well as all non-permitted medications in accordance with section 5.2 unless absolutely necessary prior to the screening visit (V1). • A screening visit (V1) will help establish the eligibility of subjects for inclusion in the study (including routine hematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead ECG, spirometry including FEV_1 reversibility after albuterol intake, and training for the use of inhalers and diary/peak flow meter). • This visit will be followed by a 2-week open-label run-in period, where subjects entering the study on ICS/LABA therapy will be switched to a similar dose of extrafine BDP as the ICS dose contained in the ICS/LABA combination for the full run-in period. Subjects on ICS alone will be switched to similar dose of extrafine BDP during the run-in. • After the run-in period, eligible subjects will be randomized to one of the 2 study treatment arms (V2, Day 1). • After the randomization visit (V2), subjects will be assessed after 4, 8 and 12 weeks of treatment (from V3 to V5) at the clinic. At visit 2 (Week 0) and visit 5 (Week 12), ACQ-7 will be performed prior to spirometry. Spirometry will be performed at -45 min and -15 min pre-dose and at 5 min, 15 min, 30 min, 1hr, 2hr, 3hr, 6hr, 9hr, 11.5hr and 12hr post-dose. Vital signs and 12-lead ECG will be performed pre-dose and at 30 mins, 1h, 4h, and 12h post-dose. At Visits 3 (Week 4) and 4 (Week 8), only pre-dose spirometry will be performed (i.e., no serial spirometry will be performed), pre-dose vital signs and 12 lead ECG, as well as ACQ-7 will be performed. • A safety follow-up phone call will be done by the investigator 1 week after V5 or Early Treatment Discontinuation visit to check the status of unresolved adverse events (AEs) and to record any new AEs that have occurred after the last visit as well as the related concomitant medications. • AEs and SAEs will be monitored throughout the study. The study duration from V0 to V6 will be about 16 weeks. The subjects who discontinue study drug should not be considered automatically withdrawn from the study (except if the reason is consent withdrawal or lost to follow up). These subjects will be encouraged to remain

	in the study and complete all remaining protocol-specified visits (while off study drug) to assess lung function, adverse events, serious adverse events (SAEs) and concomitant medications post investigational treatment. 
Most relevant allowed concomitant treatments	The following medications are allowed during the study (run-in and randomization periods): 1. Inhaled short-acting β2-agonist, SABA, (albuterol) as rescue medication. A minimum of 6 hours should elapse between the use of rescue albuterol and the start of spirometric measurements, otherwise visits must be postponed. 2. Other asthma treatments (e.g., leukotriene modifiers, theophylline) if already taken at stable doses for at least 2 months prior to screening visit (the dose must remain constant for the entire study period). 3. Nasal corticosteroids and antihistamines for the treatment of hay-fever during the randomized treatment-period. 4. Treatment for allergic desensitization at the "maintenance" phase if already taken at stable doses for at least 1 month prior to screening visit (the dose must remain constant for the entire study period). 5. One short course (<10 days) of oral/parenteral corticosteroid and/or brief use of short-acting β2-agonists, and/or ipratropium (via nebulizer or inhaler) and/or steroids (via nebulizer), for asthma exacerbation during the randomized treatment-period. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluation parameters and does not qualify under the section "non permitted medications".
Most relevant forbidden concomitant treatments	The following medications are not permitted during the study (run-in and randomized treatment periods). Intake of such a drug during run-in constitutes a screening failure and the subject will not be randomized into the study. If any of these medications are taken during the treatment period, the subject will be carefully evaluated by the Investigator if they may continue taking the study drug or not, but they may remain in the study.

	1. Inhaled corticosteroids other than the study drugs 2. Inhaled LABAs 3. Inhaled fixed combinations ICS/LABAs (e.g., fluticasone propionate/salmeterol, budesonide/formoterol other than the study drugs 4. Oral β2-agonists 5. Oral/parenteral corticosteroids (except to treat an asthma exacerbation as described above) 6. Tricyclic antidepressants and Monoamine oxidase inhibitors (MAOIs) 7. Long-acting anticholinergics and short-acting anticholinergics (with the exception of a short course of nebulized or inhaled ipratropium to treat an asthma exacerbation as described above) 8. Non-selective β-blocking drugs (including eye drops) 9. Non-potassium sparing diuretics 10. Quinidine, quinidine-like anti-arrhythmic, or any medication with potential to prolong the QTc 11. Any biologic therapy for asthma (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab) 12. Any medication that could interact with the study drug, according to Investigator's judgement
Efficacy variables	**Primary Variable** • Change from baseline in FEV_1 AUC_{0-12h} at Week 12. **Key-Secondary Variable** • Change from baseline in peak FEV_1 within the first 3 hours post dosing at Week 12. **Secondary Variables** • Change from baseline in FEV_1 AUC_{0-12h} at Week 0. • Change from baseline in peak FEV_1 within the first 3 hours post dosing at Week 0. • Change from baseline in trough FEV_1 at Week 12. • Change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12. • Change from baseline in average morning PEF measured by subjects at home over the 12-week treatment period. • Change from baseline in average evening PEF measured by subjects at home over the 12-week treatment period. • Proportion of subjects classified as responder (change from baseline ≥100mL) in pre-dose morning FEV_1 at Week 4, 8 and 12. • Proportion of subjects classified as responder (change from baseline ≥100mL) in trough FEV_1 at Week 12. • Change from baseline in ACQ-7 and ACQ-5 score at Week 12. • Change from baseline in percentage of rescue medication free days over 12-week treatment period. • Change from baseline in percentage of asthma symptom free days over 12-week treatment period.

Safety variables	• Adverse Events (AEs), Adverse Drug Reactions (ADRs) and Class related Adverse Events. • Vital signs (systolic and DBP). • 12-lead ECG parameters: HR, QTcF, PR and QRS. • Standard hematology and blood chemistry.
Sample size calculation	**Sample Size** The sample size has been calculated to demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD over CHF 718 pMDI 800µg TDD in terms of the primary and key secondary endpoint. A discontinuation rate from the randomized study drug of approximately 10% at Week 12 has been considered. A total of 580 subjects will be randomized according to a 1:1 ratio to either CHF 1535 pMDI 800/24µg TDD or CHF 718 pMDI 800µg TDD (*i.e.,* 290 subjects per group). This sample size will provide, using the main estimand: • Approximately 89% power to detect a mean difference of 108mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 at a two-sided significance level of 0.05, assuming a SD of 409mL. The assumed mean difference of 108mL represents a weighted average between two means: a mean difference between groups of 120mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0mL while off-treatment (assuming 10% of the randomized subjects). • Approximately 90% power to detect a mean difference of 117mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12 at a two-sided significance level of 0.05, assuming a SD of 434mL. The assumed mean difference of 117mL represents a weighted average between two means: a mean difference between groups of 130mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0mL while off treatment (assuming 10% of the randomized subjects). Thus, considering the main estimand analysis, an overall study power of at least 80% for the primary and the key-secondary efficacy endpoint will be ensured.
Statistical methods	**Analysis Sets** The following analysis sets will be considered: • *Safety set*: all randomized subjects who receive at least one dose of study drug (analyzed as treated). • *ITT set*: all randomized subjects who receive at least one dose of the study drug (analyzed as randomized).

Primary efficacy variable

Main Estimand

Population: Subjects with asthma.

Treatment: Randomized study drug (CHF 1535 pMDI 800/24µg TDD or CHF 718 pMDI 800µg TDD) including rescue medication and any other asthma treatments that may be administered during the study.

Variable: Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.

Population-level summary: Adjusted between treatment difference comparing CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD.

Strategy for intercurrent events and events leading to missing data:

- *Early discontinuation from the randomized study drug*: Data collected after discontinuation from the randomized study drug (i.e. off-treatment data) will be included in the analysis (i.e. targeting a treatment policy strategy).

- *Early discontinuation from the study*: The collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms **[1]**.

Note: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.

- *Use of not allowed medications and other important protocol deviations*: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).

- *Wrong study drug intake*: If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug (i.e. targeting a treatment policy strategy).

Sensitivity analyses – Strategy for intercurrent events and events leading to missing data:

- *Early discontinuation from the study*: A two-dimensional tipping point analysis varying assumptions about the missing outcomes in the two treatment arms will be performed to explore the plausibility

of missing data assumptions under which the conclusions change (i.e. under which treatment effect is no longer statistically significant).

Analysis

Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 will be analyzed on the ITT set using an ANCOVA model including treatment, US region and prior asthma therapy as fixed effects and baseline (i.e. pre-dose FEV_1 at Week 0) value as covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 12 will be estimated by the model. Superiority of CHF 1535 pMDI 800/24µg TDD will demonstrated by a statistically significant difference between treatments at Week 12 (defined as $p<0.05$) favoring CHF 1535 pMDI 800/24µg TDD.

Key-secondary efficacy variable

Main Estimand

Population: Subjects with asthma.

Treatment: Randomized study drug (CHF 1535 pMDI 800/24µg TDD or CHF 718 pMDI 800µg TDD) including rescue medication and any other asthma treatments that may be administered during the study.

Variable: Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12.

Population-level summary: Adjusted between treatment difference comparing CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD.

Strategy for intercurrent events and events leading to missing data:

- *Early discontinuation from the randomized study drug*: Data collected after discontinuation from the randomized study drug (i.e. off-treatment data) will be included in the analysis (i.e. targeting a treatment policy strategy).

- *Early discontinuation from the study*: The collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms **[1]**.

Note: *In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.*

- *Use of not allowed medications and other important protocol deviations*: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).

- *Wrong study drug intake*: If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug (i.e. targeting a treatment policy strategy).

Sensitivity analyses – Strategy for intercurrent events and events leading to missing data:

- *Early discontinuation from the study*: A two-dimensional tipping point analysis varying assumptions about the missing outcomes in the two treatment arms will be performed to explore the plausibility of missing data assumptions under which the conclusions change (i.e. under which treatment effect is no longer statistically significant).

Analysis

Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12 will be analyzed on the ITT set using an ANCOVA model including treatment, US region and prior asthma therapy as fixed effects and baseline (i.e. pre-dose FEV_1 at Week 0) value as covariate. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 12 will be estimated by the model. Superiority of CHF 1535 pMDI 800/24µg TDD will demonstrated by a statistically significant difference between treatments at Week 12 (defined as $p<0.05$) favoring CHF 1535 pMDI 800/24µg TDD.

Control Type 1 Error

The primary and key-secondary efficacy variables will be tested following a hierarchical strategy to control the familywise type I error rate. Any p-values generated at each step will be considered exploratory in nature if at least one of the preceding steps in the hierarchy is not successful. The hierarchy for the primary and key secondary efficacy analyses is as follows:

- *Step 1*: Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 using the main estimand.
- *Step 2*: Change from baseline in peak FEV_1 within 3 hours post dose at Week 12 using the main estimand.

Secondary efficacy and safety variables

- Analyses of secondary efficacy variables are planned to target the same estimand as described for the primary and key-secondary efficacy variables in sections 12.3.4 and 12.3.5 (i.e. with collected

	off-treatment data included in the analysis and used to impute possible missing off-treatment data). • Safety analysis will be based on Safety set. For subjects who discontinue the study drug but remain in the study, assessments conducted following 1 week after the last dose of study drug will not be considered in the analysis or presentation of safety data. Details for the analysis of secondary efficacy and safety variables are defined in the Section 12 of protocol.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
β-HCG	Beta Human Chorionic Gonadotropin
B17MP	Beclomethasone 17-Monoproprionate
BDP	Beclomethasone Diproponate
BID	Twice a Day
BTPS	Body Temperature, Pressure, Saturated with Water Vapor
BUN	Blood Urea Nitrogen
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CR	Copy Reference
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DPB	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ER	Emergency Room
ET	Early Termination
ETD	Early Treatment Discontinuation
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FEV_1	First Forced Expiratory Volume
FF	Formoterol Fumarate
FSH	Follicle Stimulating Hormone
FU	Follow-up
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practices
Hb	Hemoglobin
Hct	Hematocrit
HFA	Hydrofluoroalkane
HR	Heart Rate
ICF	Informed Consent Form

ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intention to Treat
LABA	Long Acting β2-adrenergic receptor Agonist
LAMA	Long Acting Muscarinic Antagonist
LSLV	Last Subject Last Visit
MAOIs	Monoamine Oxidase Inhibitors
MART	Maintenance and Reliever Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MMAD	Mass Median Aerodynamic Diameter
MMRM	Mixed Model for Repeated Measured
NDA	New Drug Application
NYHA	New York Heart Association
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PLT	Platelet Count
pMDI	Pressurized Metered Dose Inhaler
PT	Preferred Term
QTc	QT Corrected for Heart Rate
QTcF	Corrected QT Interval by Fridericia
R&D	Research and Development
RBC	Red Blood Cells Count
RR	Respiratory Rate
RTI	Respiratory Tract Infection
SABA	Short Acting β2-adrenergic receptor Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SD	Standard Deviation
SITT	Single Inhaler Triple Therapy
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDD	Total Daily Dose
TEAE	Treatment Emergent Adverse Event
TLC	Total Lung Capacity
US	United States
WBC	White Blood Cell Count
WOCBP	Women of Childbearing Potential

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1. INTRODUCTION

1.1 Background Information and Study Rationale

Asthma is a chronic inflammatory disease of the airways characterized by heterogeneity in terms of phenotype and underlying mechanism(s) [2], [3]. Airway remodeling is also a cardinal histologic feature of asthma [3]. The clinical presentation typically includes a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, or cough and variable airflow obstruction. Asthma symptoms can vary over time and in intensity depending upon the presence of classic triggers like exercise, environmental/occupational exposures or viral respiratory infections [4], [5].

According to the World Health Organization, asthma affected an estimated 262 million people in 2019 and led to 461,000 deaths [6]. It impacts people of all races, ages and both sexes although there are ethnic and sex disparities with higher death rates in minority groups and in women [7], [8].

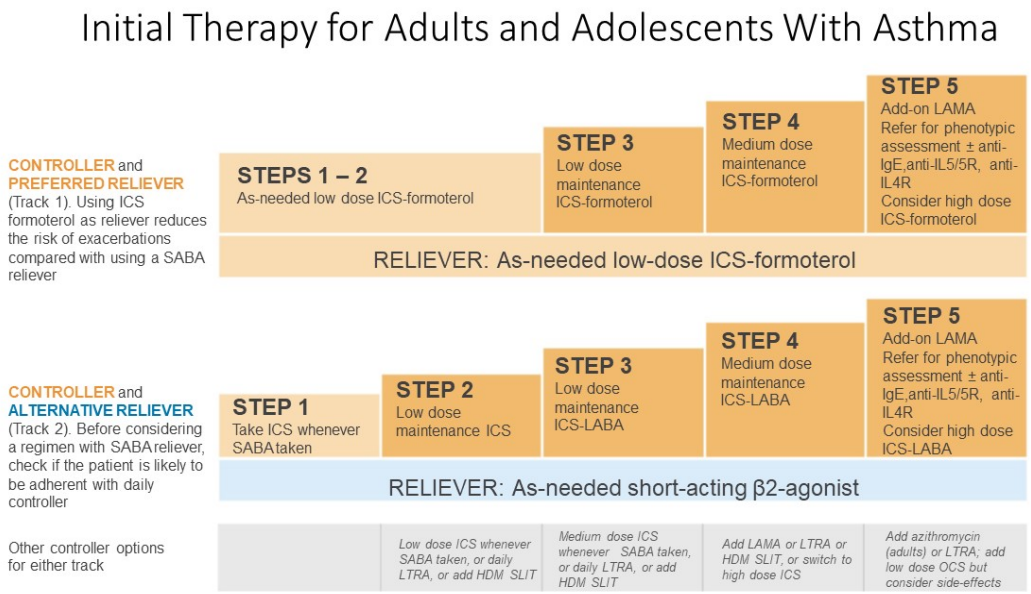
Current consensus guidelines for asthma management [9] have as a major goal to achieve disease control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation and side effects of medications. Figure 1 shows the step therapy for starting treatment in adults and adolescents who carry an asthma diagnosis. It is apparent from the figure that the combination of Inhaled Corticosteroids (ICS) and Long Acting β2-adrenergic receptor Agonists (LABA) plays an important role in asthma treatment as both maintenance and reliever therapy (MART). Notably, formoterol is the only LABA recommended by the 2021 GINA Report as a reliever therapy in combination with an ICS due to its proven fast bronchodilator effect.

Despite adherence to ICS/LABA therapy, 30-50% of patients with asthma remain symptomatic and poorly controlled [10], [11], [12]. GINA 2021 guidelines recommend triple therapy [addition of long-acting muscarinic antagonists (LAMA) to ICS-LABA] for patients ≥18 years old at step 5. Evidence suggests that addition of LAMA therapy to medium or high dose ICS/LABA can improve lung function and in some cases, lead to a reduction in exacerbations [13], [14]. Single inhaler triple therapy (SITT) is more convenient for patients than taking multiple inhalers and can potentially improve adherence [15]. Currently there is only one SITT marketed in the United States under the name of Trelegy® Ellipta® (fluticasone furoate/umeclidinium/vilanterol), a dry powder inhaler.

In January 2021, Chiesi's SITT, CHF 5993 with the trade name of Trimbow® [medium strength (beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide, BDP/FF/GB 100/6/12.5mcg) and high strength (BDP/FF/GB 200/6/12.5mcg)] pMDI was approved for the asthma indication in the European Union (EU). Trimbow® is not yet approved for asthma in the United States.

A fixed dose combination (FDC) consisting of the ICS BDP at 100µg and LABA FF at 6µg (Foster® or CHF 1535) was developed by Chiesi in the same Hydrofluoroalkane (HFA) pMDI solution formulation as CHF 5993, with a high extrafine inhaled particle fraction (i.e., mass median aerodynamic diameter [MMAD] around 1.1µm) for both active ingredients. CHF 1535 pMDI was nationally approved in Europe for asthma in 2006.

The FORCE2 study was designed as a pivotal clinical study to demonstrate the added benefit of the LABA component (FF) within BDP/FF to serve as a key piece of information to support a new drug application (NDA) for the BDP/FF/GB triple combination product for asthma in the United States.



1.2 Study Rationale

CHF 1535 pMDI is a FDC consisting of the ICS beclomethasone dipropionate (BDP) and the LABA formoterol fumarate (FF) developed by Chiesi with a high extrafine inhaled particle fraction (i.e. mass median aerodynamic diameter [MMAD] around 1.1 µm) for both active ingredients. CHF 1535 pMDI has been approved in Europe first for adults with asthma in 2006 and then, in 2014 via a Type II variation for adults with COPD under several brand names (Foster®, Fostair®). Currently the 100/6 mcg/actuation dose strength pMDI is approved in 77 countries and the 200/6 mcg/actuation dose strength pMDI in 39 countries. CHF 1535 is not FDA-approved for any indication.

At the time of its initial development, CHF 1535 100/6µg was a new HFA134a pMDI formulation of known active constituents, BDP and formoterol, which were individually marketed as pMDIs (both CFC and HFA) and dry powder inhaler (DPI) products. A clinical "bridging" strategy undertaken within the CHF 1535 HFA pMDI 100/6µg clinical development program confirmed the suitability of the use of the comparators in the pivotal clinical trials CT03 and CT04. CT03 demonstrated the non-inferiority of CHF 1535 HFA pMDI 100/6µg to corresponding equipotent daily doses of the free combination of BDP CFC pMDI plus formoterol DPI (as dry powder capsules), the superiority of CHF 1535 HFA pMDI 100/6µg over monotherapy with the corresponding equipotent daily dose of BDP CFC pMDI, and the safety and tolerability profile of CHF 1535 100/6µg. CT04 established the superiority of CHF 1535 HFA pMDI 100/6µg over double the equipotent corresponding daily dose of BDP CFC pMDI.

During the CHF 1535 pMDI product development, two additional late-stage pre-market phase III clinical trials in asthma generated data on the comparative efficacy and safety compared to other marketed products and supported product reimbursement. In one study, CHF 1535 100/6 µg 2 puffs bid (total daily dose BDP/FF 400/24µg) was demonstrated to be non-inferior to Symbicort® Turbuhaler® DPI (Budesonide/Formoterol Fumarate 640/18µg TDD) based on morning pre-dose peak expiratory flow (PEF) rate in adult patients with moderate-to-severe asthma without any difference in frequency of AEs **[16]**. CHF 1535 was also found to be non-inferior to Seretide® pMDI (Fluticasone Propionate/Salmeterol 500/100µg TDD) in a second phase III trial based on changes in lung function measured by morning pre-dose peak expiratory flow (PEF) rate in adult patients with moderate-to-severe asthma **[17]**.

The clinical program in support of the high strength CHF 1535 pMDI 200/6µg (developed as "step-up" in therapy in those patients not adequately controlled either on high dose ICS monotherapy or on moderate doses of ICS within a fixed combination ICS/LABA, with the aim to get better asthma control) was based on two single dose PK studies investigating the dose proportionality of Beclomethasone 17-Monopropionate (B17MP) total systemic exposure and lung bioavailability, respectively, after administration of CHF 1535 at increasing dose strengths (BDP/FF 50/6, 100/6 and 200/6µg per actuation) in healthy subjects and on the following two clinical studies: 1) A 6-month study demonstrated that CHF 1535 pMDI (BDP/FF 200/6µg per actuation, 2 puffs bid), administered at 800/24µg/day, is as safe as fluticasone 500µg + salmeterol 50µg/actuation (Seretide®) at 1000/100µg/day in patients with severe asthma **[18]**, and 2) a 12-week clinical study that established the superiority of CHF1535 200/6µg (800/24µg/day) vs. extrafine BDP (QVAR®, 800µg/day) in terms of the primary lung function outcome **[19]**. Although this data package was acceptable at that time for a European registration of the FDC BDP/FF (CHF 1535 pMDI), it does not meet today's FDA's requirement of FDC product development due to the differences in the devices between QVAR® and CHF 1535 pMDI.

FORCE2 was therefore designed to fulfil the FDA's regulatory requirement for combination product development in order to adequately characterize BDP/FF as an acceptable ICS/LABA comparator as used in the pivotal phase III studies with the SITT BDP/FF/GB (CHF 5993 pMDI) **[20]**. If the study meets its specified primary and key secondary endpoints, it will provide support for the NDA for the BDP/FF/GB triple combination product for asthma in the United States.

1.3 Risk/Benefit Assessment

1.3.1 Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with CHF 1535 can be found in the Investigator's Brochure. Several findings were identified as potential risks associated with the mono-components of CHF 1535 which will be monitored in the study.

Risk of Oropharyngeal Candidiasis with ICS: Local effects of ICS include oropharyngeal candidiasis and assessment for this will be performed on a regular basis at each study visit. As a mitigation strategy, subjects will be instructed to gargle with water and to rinse out their mouths each time they use their ICS.

Risk of Systemic Effects with ICS: Systemic effects such as bone disorders, bone mineral density decrease and associated fractures, and cortisol suppression have been described with the use of corticosteroids. Although a decrease in bone mineral density and the risk of fractures is a class concern for ICS containing medications, the proposed dose of inhaled BDP in this study is considered unlikely to have a clinically significant impact on hypothalamic pituitary axis particularly given the short-term nature of the study and the fact that the described systemic effects will be monitored during ongoing assessment of AEs and SAEs. In addition, systemic ocular effects of corticosteroids, including glaucoma and cataract formation, have been described although these effects are much less likely to occur with inhaled corticosteroids compared with oral corticosteroids and will be monitored during AE/SAE reviews.

Risk of Cardiovascular Events with LABAs: Cardiovascular events are a documented class effect associated with LABAs, including FF. The randomized controlled trial, TRIGGER, provides extensive long-term safety data to support the safety of FF 24µg TDD when used as a component of BDP/FF in subjects with uncontrolled asthma using high dose ICS in combination with a LABA **[20]**. This high range of ICS dose is consistent with other FDA-approved ICS/LABA combination products for asthma (e.g., DULERA®, SYMBICORT®, ADVAIR® DISKUS®, and BREO® ELLIPTA®). To mitigate potential cardiovascular risks associated with FF, subjects with clinically significant cardiovascular disease (as outlined in section 4.3, Exclusion Criteria) will be excluded from the study and ECGs and vital sign assessments will be performed as per protocol.

1.3.2 Benefit Assessment

A previously completed 12-week, multinational ex-US randomized phase III study with CHF 1535 demonstrated the clinical benefit of using pMDI BDP/FF 200/6µg (two actuations bid) compared to BDP 100µg (QVAR®, four actuation bid) in a population of 376 adult asthmatics not adequately controlled with high dose of ICS or medium dose of ICS plus LABA (the primary endpoint was improvement in lung function) **[19]**. BDP/FF and BDP showed a comparable safety profile, with no adverse events of clinical concern observed with either treatment. CHF1535 is commercialized as Foster® in more than 50 countries ex-US since it launched 15 years ago.

1.3.3 Overall Risk: Benefit Conclusion

Current risks that have been identified for the BDP/FF (200/6µg) combination are based on the known pharmacology of the individual active components BDP and FF. These include risks of oropharyngeal candidiasis, ocular effects and bone disorders/fractures from ICS and the risk of adverse cardiovascular effects from LABA. The BDP/FF combination is widely commercialized ex-US. A comprehensive safety monitoring strategy is being proposed for all the risks. Given the overall clinical experience with BDP and FF and the fact that that the associated risks with these compounds are anticipated from their known pharmacology, the risk: benefit ratio of using CHF 1535 in subjects with asthma on medium or high-dose ICS in order to provide support for the NDA for the BDP/FF/GB triple combination product for asthma seems justified.

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

2. STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.

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

Population	Subjects with asthma. Further details about the population are provided in Section 4.
Treatments	Randomized study drug (CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD) including rescue medication and any other asthma treatments that may be administered during the study.
Variable	Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.
Strategy for intercurrent events / events leading to missing data	*Early discontinuation from the randomized study drug:* Data collected after discontinuation from the randomized study drug (i.e. off-treatment data) will be included in the analysis (i.e. targeting a treatment policy strategy).
	Early discontinuation from the study: The collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms **[1]**. *Note*: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.
	Use of not allowed medications and other important protocol deviations: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	Wrong study drug intake: If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug (i.e. targeting a treatment policy strategy).
Population-level summary	Adjusted treatment difference comparing CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD

2.2 Key-Secondary Objective

To demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12.

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

Population	Subjects with asthma. Further details about the population are provided in Section 4.
Treatments	Randomized study drug (CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD) including rescue medication and any other asthma treatments that may be administered during the study.
Variable	Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12.
Strategy for intercurrent events / events leading to missing data	*Early discontinuation from the randomized study drug:* Data collected after discontinuation from the randomized study drug (i.e. off-treatment data) will be included in the analysis (i.e. targeting a treatment policy strategy).
	Early discontinuation from the study: The collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms **[1]**. *Note*: *In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.*
	Use of not allowed medications and other important protocol deviations: Data will be used regardless of whether or not the intercurrent event occurs (i.e. targeting a treatment policy strategy).
	Wrong study drug intake: If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug (i.e. targeting a treatment policy strategy).
Population-level summary	Adjusted treatment difference comparing CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD

2.3 Secondary Objectives

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 0.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 0.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in trough FEV_1 at Week 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average morning PEF over 12-week treatment period.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average evening PEF over 12-week treatment period.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e. change ≥100 mL) for pre-dose morning FEV_1 at Week 4, 8 and 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e. change ≥100 mL) for trough FEV_1 at Week 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in terms of ACQ-7 and ACQ-5 at Week 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in percentage of rescue medication free days and asthma symptom free days over 12-week treatment period.

- To assess the safety and the tolerability of the study drugs.

3. STUDY DESIGN

This is a phase III, randomized, double-blind, active controlled, 2-arm parallel group study to demonstrate the superiority of CHF 1535 pMDI 800/24µg total daily dose (TDD) compared to CHF 718 pMDI 800µg in terms of change from baseline in FEV_1 AUC_{0-12} at Week 12.

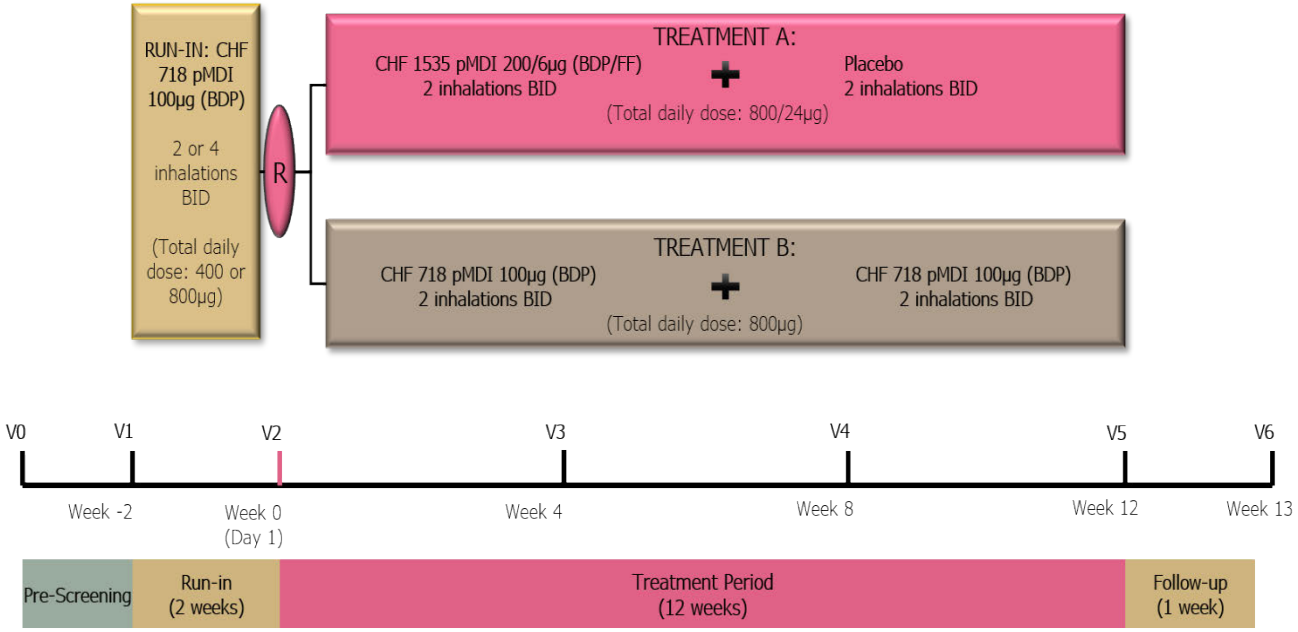
Approximately 580 subjects over the age of 18 will be randomized into the study.

A total of 6 clinic visits (V0- V5) and a follow-up call (V6) will be performed during the study as noted in section 7.

Screened subjects who were on a medium dose ICS or medium dose ICS-LABA prior to the study will be put on CHF 718 pMDI 100µg 2 inhalations BID (TDD 400µg) during the 2-week run in period. Screened subjects who were on a high dose ICS prior to the study will be

put on CHF 718 pMDI 100µg 4 inhalations BID (TDD 800µg) during the 2-week run in period.

Following the run-in period, eligible subjects will be randomized to one of two study drug arms (using a 1:1 allocation ratio) for 12 weeks.



The total study duration (V0 to FU call) is approximately 16 weeks for any subject completing the trial.

The start of the trial is defined as the date of first site initiation visit in the trial.

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

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Approximately 580 subjects (290 subjects per group) will be randomized. Recruitment will occur at participating outpatient study centers.

The end of recruitment will be communicated to study sites by Chiesi (or designee).

If a subject is screen failed, he/she can be rescreened (at least 1 month from the screen failure date) providing the medical conditions of the subject are appropriate with the inclusion in the

study according to the investigator judgement and after sponsor approval. The subject should sign a new informed consent and will be assigned with a new subject number.

4.2 Inclusion Criteria

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

1. **Informed consent:** A signed and dated written informed consent obtained prior to any study-related procedures.

2. **Sex and age:** Male or female aged ≥18 and ≤75 years.

3. **Diagnosis of asthma:** A documented history of asthma for at least 1 year, with onset before age 40

4. **Stable asthma therapy:** Use of medium-dose ICS with or without a LABA or high-dose ICS alone for 3 months (at a stable dose for at least 4 weeks prior to screening).

Estimated Comparative Total Daily Dosages for US Approved Inhaled Corticosteroids		
Inhaled Corticosteroid*	**Medium daily dose**	**High daily dose**
Beclomethasone dipropionate (DPI or pMDI, extrafine particle, HFA)	>160-320µg	>320-640µg
Budesonide DPI	>360-720µg	>720µg
Ciclesonide (pMDI, extrafine particle, HFA)	>160-320µg	>320µg
Fluticasone furoate (DPI)	100µg	200µg
Fluticasone propionate (pMDI, standard particle, HFA) *	>220-440µg	>440µg
Fluticasone propionate (DPI)	>250-500µg	>500µg
Mometasone furoate (DPI)	220-440µg	>440µg
Mometasone furoate (pMDI, standard particle, HFA)	200-400µg	>400µg

** Note: This is not a table of equivalence. For questions on Inhaled corticosteroid + long-acting beta agonist (LABA) dual therapy where dose ranges do not fall within table ranges, please contact Medical Monitor for guidance.*
(Table adapted from GINA 2022 and Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007))

5. **Lung function:** Subjects with a pre-bronchodilator FEV_1 ≥40% and ≤85% of predicted, after appropriate washout from bronchodilators, at the screening *and* randomization visits. In addition, the ***absolute value*** of the first pre-dose FEV_1 at randomization (V2) must be at least 80% of the pre-bronchodilator value attained at screening.

6. **Reversibility post-bronchodilator:** Subjects with a positive reversibility to bronchodilator at screening, defined as an increase in FEV_1 > 12% *and* > 200mL compared to baseline within 30 minutes after 4 inhalations of albuterol HFA pMDI 90µg/actuation.

Note for IC#5 and IC#6: In case the reversibility and /or quality threshold is not met at screening, the test can be performed once before randomization.

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

      For the definition of WOCBP and of fertile men and the list of highly effective birth control methods, refer to Appendix 2. Highly effective contraception should be maintained until the follow-up call. Subjects should then refer to the pregnancy recommendations and precautions, related to their asthma treatment prescribed after the study drug discontinuation.

   or

   b. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile as per definitions given in Appendix 2). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges).

8. **Cooperative attitude** and ability to demonstrate correct use of the pMDI inhalers and eDiary/Peak Flow Meter.

The following inclusion criteria must be confirmed at the randomization visit prior to dosing: 5, 6, 7 and 8.

4.3 Exclusion Criteria

Any of the following will exclude a subject from participation:

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

2. **Poor compliance** with run-in medication or eDiary completion <50% before randomization.

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

4. **Recent asthma exacerbation:** Hospitalization, emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period.

5. **Unresolved respiratory tract infection (RTI)** in the 4 weeks prior to the screening visit or during run-in period. Documented coronavirus disease 2019 (COVID-19) diagnosis within the last 8 weeks or complications from this disease, which have not resolved within 14 days prior to screening.

6. **Unstable ICS dose** during the 4 weeks prior to screening visit, including any change in dose, schedule, or formulation.

7. **Use of systemic corticosteroid** medication in the 4 weeks prior to screening or slow-release corticosteroids in the 12 weeks before screening.

8. **Respiratory disorders other than asthma:** History of a diagnosis of cystic fibrosis, bronchiectasis, COPD (as defined by the current GOLD Report), alpha-1 antitrypsin deficiency, interstitial lung disease, sarcoidosis, pulmonary hypertension, or any other significant lung disease which may interfere with study evaluations

9. **Smoking status:** Current smokers or ex-smokers with total cumulative exposure equal to or more than 10 pack-years (pack-years = the number of cigarette packs per day times the number of years smoked) or having stopped smoking within one year prior to screening visit.

10. **E-cigarette status:** Current e-cigarettes users at the time of the screening visit or having stopped ≤ 6 months prior to screening visit).

11. **Cannabis usage:** Current use of inhaled or oral cannabis products (e.g. marijuana).

12. **Substance abuse:** Subjects with a history of alcohol or substance/drug abuse within 12 months prior to screening.

13. **Cardiovascular diseases:** Subjects who have clinically significant cardiovascular condition such as, but not limited to, unstable ischemic heart disease, NYHA Class III/IV heart failure, acute ischemic heart disease within one year prior to study entry, known history of atrial fibrillation or history of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to screening, not controlled with a rate control strategy.

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

14. **ECG criteria:** An abnormal and clinically significant 12-lead electrocardiogram (ECG) which may impact the safety of the subject according to Investigator's judgement. In terms of the QTcF, subjects with QTcF >450ms for males or QTcF

>470ms for females at screening or at randomization visits (criterion not applicable for subject with pacemaker or permanent atrial fibrillation).

15. **Other medical conditions:** Other active severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

16. **Vaccination:** Subjects having received a vaccination within 2 weeks prior to screening or during the run-in period.

17. **Subjects' wellbeing:** Subjects mentally or legally incapacitated, including but not limited to subjects who are institutionalized or incarcerated.

18. **Hypersensitivity:** Subjects with known intolerance, hypersensitivity or contraindication to treatment with ß2-agonists, ICS, or propellant gases/excipients.

19. **Surgery:** Subjects with major surgery in the 3 months prior to the screening visit or planned surgery during the study.

20. **Additional treatment:** Subjects treated with non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug or changed to potassium sparing before the screening), non-selective beta-blocking drugs, quinidine, quinidine-like anti-arrhythmic, or any medication with a QTc prolongation potential or a history of QTc prolongation.

21. Subjects treated with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants.

22. Subjects with concomitant immunosuppressive therapy, use of oral or injected corticosteroids, anti-IgE, anti-IL5 or other monoclonal or polyclonal antibodies within 12 weeks prior to screening.

23. Subjects who are receiving any therapy that could interfere with the study drugs according to investigator's opinion.

24. **Participating in other investigational trial:** Subjects who have received an investigational drug within 1 month or 5 half-lives (whichever is greater) prior to screening visit, or have been previously randomized in this trial, or are currently participating in another clinical trial.

25. **Spacer:** The need to use a spacer for correct self-administration of a pMDI.

Exclusion criteria # 1, 2, 4, 5, 14 and 16 must be confirmed at the randomization visit prior to dosing.

4.4 Discontinuation from study drug

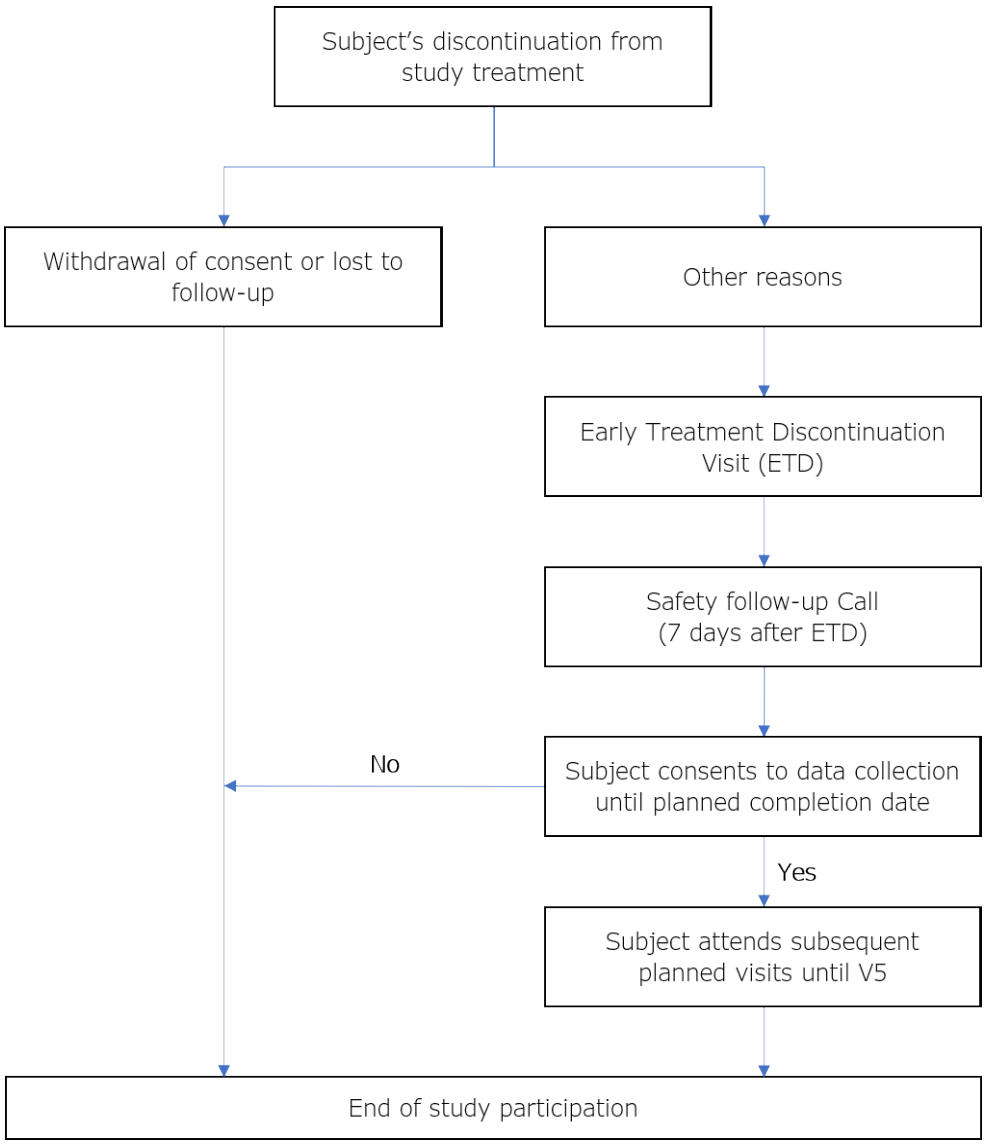
A subject who discontinues study drug **should not be considered automatically withdrawn from the study** (except if the reason is consent withdrawal or lost to follow up). The investigator and study staff must discuss with the subject who will be asked to continue attending the remaining study visits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

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

In accordance with ICH E9-R1 and corresponding guidance from regulatory agencies it is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided.
However, should a subject discontinue the study drug, all efforts will be made to complete the study procedures per protocol and report the observations as thoroughly as possible.

It will be the Investigator's judgement to withdraw the subject from the study drug if he/she deems it will place the subject at undue risk by continuing his/her participation.

Actions following Permanent Discontinuation from Study Drug:



The investigator is responsible for assessing the optimal treatment prescription for each study subject after the study drug discontinuation. The post study drug asthma medications should be recorded in the eCRF.

The investigator/designee must register the subject's **Early Study Drug Discontinuation** in the IRT (Interactive Response Technology) system. The Investigator/designee must report in the eCRF the main reason for Early treatment discontinuation.

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

Subject who consents to data collection till the planned V5 visit will continue attending study visits according to the study visit schedule. Before each visit, the wash-out periods for

concomitant medications detailed in section 5.2 must be respected. The following assessments will be performed:

- Spirometry (pre/post of the subject's maintenance inhaled therapy for asthma, including the serial spirometry when planned by the study protocol).
- The subject should continue to complete eDiary data (except for the study drug questions) and to measure PEF at home.
- The investigator (or designee) will check the concomitant medications and adverse events that occurred since last visit.
- Urine or serum pregnancy tests in all women of childbearing potential.
- Questionnaires- subjects will complete the ACQ-7 questionnaire (section 7.2.1).

4.5 Study Discontinuation

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

- The subject is lost to follow-up
- The subject withdraws consent
- The subject experiences an adverse event which makes participation in the study not possible
- Chiesi or the regulatory authorities or the Institutional Review Board(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular subject.
- The subject is unwilling or unable to adhere to the study requirements, i.e. non-compliance.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided. Every effort will be made to retain the subject in the study.

The investigator must document the reason (if specified by the subject) for withdrawal of consent in the eCRF. Subjects who wish to withdraw from further participation in the study should be encouraged to return to the clinic as soon as possible to complete the Early Termination Visit and to complete the follow-up phone call in order to collect important safety information. If a subject is lost to follow-up or withdraws consent no further information will be collected.

If a subject is withdrawn/dropped-out of the study, the subject number should not be reassigned to another subject.

The investigator is responsible for the optimal individual treatment prescription after the study discontinuation. The post study drug asthma medications should be recorded in the eCRF.

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

The following medications are allowed during the study (run-in and randomization periods):

1. Inhaled Short-acting β2-agonist, SABA, (albuterol) as rescue medication. A minimum of 6 hours should elapse between the use of rescue albuterol and the start of spirometric measurements, otherwise the visit must be postponed.
2. Other asthma treatments (e.g., leukotriene modifiers, theophylline) if already taken at stable doses for at least 2 months prior to screening visit (the dose must remain constant for the entire study period).
3. Nasal corticosteroids and antihistamines for the treatment of hay-fever during the randomized treatment-period.
4. Treatment for allergic desensitization at the “maintenance” phase if already taken at stable doses for at least 1 month prior to screening visit (the dose must remain constant for the entire study period).
5. One short course (<10 days) of oral/parenteral corticosteroid and/or brief use of short-acting β2-agonists, and/or ipratropium (via nebulizer or inhaler) and/or steroids (via nebulizer), for asthma exacerbation during the randomized treatment-period.

In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study drugs or the study evaluation parameters and does not qualify under the section "non permitted medications".

5.2 Non-permitted Concomitant Medications

The following medications are not permitted during the study (run-in and randomized treatment periods). Intake of such a drug during run-in constitutes a screening failure and the subject will not be randomized into the study. If any of these medications are taken during the randomized treatment period, the subject will be carefully evaluated by the Investigator to determine if they may continue taking the study drug or not, but they may remain in the study.

1. Inhaled corticosteroids other than the study drugs.
2. Inhaled LABAs.
3. Inhaled fixed combinations ICS/LABAs (e.g., fluticasone propionate/salmeterol, budesonide/formoterol) other than the study drugs
4. Oral β-2-agonists.
5. Oral/parenteral corticosteroids (except to treat an asthma exacerbation as described above).
6. Tricyclic antidepressants and Monoamine oxidase inhibitors (MAOIs),
7. Long-acting anticholinergics and short-acting anticholinergics (with the exception of a short course of nebulized or inhaled ipratropium to treat an asthma exacerbation as described above)
8. Non-selective β-blocking drugs (including eye drops).
9. Non-potassium sparing diuretics.

10. Quinidine, quinidine-like anti-arrhythmics, or any medication with potential to prolong the QTc.
11. Any biologic therapy for asthma (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab)
12. Any medication that could interact with the study drug, according to Investigator's judgement.

Prior to screening spirometry at Visit 1 the following wash-out intervals for concomitant medications must be respected:

Medication	**No use within the following time intervals prior to Screening**
Inhaled/nebulized short-acting β2-agonists	6 hours
Inhaled/nebulized short acting muscarinic antagonists	12 hours
Inhaled/nebulized SABA/SAMA fixed combinations	12 hours
Caffeinated substances	6 hours

During the treatment period, the following wash-out intervals for concomitant medications must be respected prior to spirometry:

Medication	**No use within the following time intervals prior to Spirometry**
Inhaled and/or nebulized short-acting β2-agonists	6 hours
Caffeinated substances	6 hours

6. TREATMENT(S)

The study drugs (randomized treatment, training medication and run-in medication) will be supplied to the clinical site under the responsibility of the Chiesi, who will also provide the pharmacist/investigator with appropriate certificates of analytical conformity.

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

6.1 Appearance and Content

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

- ***CHF 1535 pMDI 200/6µg (Test product_Treatment A)***

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

- ***CHF 718 pMDI 100µg (Run-In and Reference product_ Treatment B)***
  Active ingredients *HFA Beclomethasone Dipropionate*
  Excipients: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 doses
  Appearance: Aluminum canister + white actuator

- ***CHF 5993 Placebo (Training kit and placebo_Treatment A)***
  Active ingredients: None
  Excipients: HFA-134a propellant, ethanol anhydrous
  Presentation: Each canister contains 120 doses
  Appearance: Aluminum canister + white actuator

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

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

The selection of the dose for CHF 1535 200/6µg is the same as for the EU marketed product FOSTER®.

CHF 718 100µg are based on the EU marketed dose of Clenil® Modulite® (beclomethasone dipropionate).

6.2.2 Dosage

6.2.2.1 Run-in period

- **CHF 718 100µg:** 2 or 4 inhalations BID (puffs); total daily dose of BDP 400 or 800µg according to the subject's pre-trial asthma therapy ICS dose.

6.2.2.2 Randomized Treatment period

According to the allocation based on the randomization list, eligible subjects will be administered with one of the following study drugs:

- **Treatment A:**
  CHF 1535 200/6µg and Placebo: 2 puffs from each inhaler BID: 8 total inhalations (puffs); total daily dose of BDP/FF: 800/24µg

- **Treatment B:**
  CHF 718 100 µg: 2 puffs from each inhaler BID: 8 total inhalations (puffs); total daily dose of BDP: 800µg

6.2.3 Administration

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

6.2.3.1 Priming of the pMDI inhalers and inhalation

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

6.2.3.2 Run-in kits

During the run-in period, each subject will receive 1 run-in kit (containing 2 inhalers of CHF 718) covering the 2-week run-in period.

At screening visit (V1), the Investigator/designee, will contact the IRT system to assign each subject 1 run-in kit of CHF 718, **to be taken as 2 or 4 inhalations BID,** to replace the subject's current asthma regimen of medium or high dose ICS**.**

Note: The first dose of run-in medication must be administered at clinic at Visit 1.

The run-in medication will be administered BID from inhalers A and B as follows:

- **Morning administration (preferably between 7 am and 9 am):**
  - 1 or 2 inhalations (puffs) from inhaler A and 1 or 2 inhalations (puffs) from inhaler B according to what the investigator prescribes.
- **Evening administration (preferably between 7 pm and 9 pm):**
  - 1 or 2 inhalations (puffs) from inhaler A and 1 or 2 inhalations (puffs) from inhaler B according to what the investigator prescribes.

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

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

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

6.2.3.3 Study treatment kits

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

From Visit 2 to Visit 4 each subject will receive:

- One box containing **4 pMDIs** (Treatment A: 2 CHF 1535 pMDIs and placebo pMDIs, or Treatment B: 4 CHF 718 pMDIs)

Each of the four canisters will be labeled with the letters A, B, C, D. Subjects will be instructed to take the medication starting with inhalers A and B.

He/she will **switch** to inhalers C and D after 2 weeks according to the date written on the labels by the study staff for inhalers A and B.

The study drug will be administered BID from the same inhalers (A, B, C, D):

- **Morning administration (preferably between 7 am and 9 am):**
  - 2 inhalations (puffs) from inhaler A and 2 inhalations (puffs) from inhaler B (until the subject switches to inhalers C and D after 2 weeks according to the date written by the study staff on the label of the inhalers A and B)

- **Evening administration (preferably between 7 pm and 9 pm):**
  - 2 inhalations (puffs) from inhaler A and 2 inhalations (puffs) from inhaler B (until the subject switches to inhalers C and D after 2 weeks according to the date written by the study staff on the label of the inhalers A and B)

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

Newly Assigned Kit

The first morning dose from inhalers A and B of each newly assigned kit will be taken at the site under the supervision of the Investigator/designee.

Prior to dosing, study drug stored between 2°C and 8°C, should be removed from the refrigerator and the canister should be taken out of the actuator and warmed with hands for a few minutes before administration to the subject. The canister should never be warmed by artificial means. The subject should never inhale a cold medication (section 6.9 for storage conditions).

The priming of the inhalers “A” and “B” will be performed at site by Investigator/designee while for inhalers “C” and “D” the subjects will be instructed to perform the priming at home prior to start the administration with the new inhalers.

On study visit days, study drug **should not** be taken before coming to the site.

6.2.4 Subject Training

At screening visit (V1), the Investigator/designee will contact the IRT system to assign a training kit to each subject. Subjects will use the same training kit at screening (V1) and randomization visit (V2) if applicable.

At screening (V1) and at randomization visit (V2), the correct use of the pMDI (according to the product leaflets provided by Chiesi) will be explained to the subjects and they will be trained by using training inhalers identical to the devices used for the administration of the study drug containing placebo. The investigator/designee should make sure the subject is properly using their study drug inhaler at each clinic visit. Additional re-training should be done if needed.

The training kit will be kept at the site by the investigator (will not be dispensed to the subjects) and they will be used again if needed in order to retrain the subject.

For more details concerning the use of the pMDI please refer to the corresponding subject leaflets.

6.3 Packaging

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

6.3.1 Treatment Kits (Blinded)

Treatment A Kit:

One box will contain 4 pMDIs, labeled A-B-C-D (on the top of the canister).

Two CHF 1535 inhalers and two placebo inhalers (4 total inhalations BID).

The label will include a space on inhalers A and B for the study staff to note the date for the subject to switch from inhalers A and B to inhalers C and D, after a 2-week period (since there is no dose counter).

- *Primary packaging: 4 labeled canisters (with study label in English only) and 4 labeled actuators (with an English and Spanish label). The four inhalers will be named with letters A-B-C-D.*
- *Secondary packaging:* 1 carton box labeled (with an English and Spanish label) with a tear/peel off portion

Treatment B Kit:

One box will contain 4 pMDIs, labeled A-B-C-D (on the top of the canister).

Four CHF 718 inhalers (4 total inhalations BID)

The label will include a space on inhalers A and B for the study staff to note the date for the subject to switch from inhalers A and B to inhalers C and D, after a 2-week period (since there is no dose counter).

- *Primary packaging: 4 labeled canisters (with study label in English only) and 4 labeled actuators (with an English and Spanish label). The four inhalers will be named with letters A-B-C-D.*
- *Secondary packaging:* 1 carton box labeled (with an English and Spanish label) with a tear/peel off portion

6.3.2 Run-In Kit

One box will contain 2 CHF 718 inhalers labeled A and B (on the top of the canister).

- *Primary packaging*: 2 labeled canisters (with a study label in English only) canister plus 2 labeled actuators (with an English and Spanish label). The two inhalers will be named with letters A and B.

- *Secondary packaging:* 1 carton box labeled (with an English and Spanish label) with a tear/peel off portion

6.3.3 Training Kit

One box will contain 1 CHF 5993 placebo pMDI.

- *Primary packaging*: 1 labeled canister (with a study label in English only) plus 1 labeled actuator (with an English and Spanish label)

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

6.4 Labeling

All labeling will be in local language and according to local law and regulatory requirements and will be compliant with Annex 13 to the Volume 4 of the GMP and 21 CFR 312.6 "Labeling of an Investigational New Drug".

6.5 Treatment allocation

A balanced block randomization scheme stratified by prior asthma therapy at screening/study entry (i.e., "medium dose ICS/LABA", "medium dose ICS" and "high dose ICS") and US region (i.e., "Northeast", "Midwest", "South" and "West") will be prepared via a computerized system. Subject will be centrally assigned to one of the two treatment arms with a 1:1 ratio.

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

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

Subject numbers will consist of a 9 digit-number:

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

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

6.6 Treatment Code

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

6.7 Emergency Unblinding

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

In case of emergency, where he/she considers it essential to know what treatment the subject was taking, unblinding of the treatment code will be done through IRT and the treatment group will be disclosed. The IRT will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the Investigators, including unblinding. The IRT will also promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.

Users from Chiesi Global Pharmacovigilance will have their own credentials to unblind subjects in case of SUSARs to be reported to the IRB.

6.8 Study Drug Compliance

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

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

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

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each subject. A range of 65-135 % will be taken into account for a satisfactory level of compliance, while a level of compliance equal or superior to 50 % will be considered as satisfactory for the run-in medication. Subjects with compliance levels less than 75% will receive additional coaching from the site staff.

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

6.9 Drug Storage

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

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

- **Run-in and Treatment kits**

Run-In and Treatment kits must be stored between 2˚C (36˚F) and 8˚C (46˚F) by pharmacist/investigator at the hospital pharmacy or clinical site.

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

- **Training Kits**

Training kits must be kept on site and not dispensed to the subjects. Training kits must be stored between 2˚C (36 ˚F) and 8˚C (46 ˚F) by pharmacist/investigator and they must be removed from the refrigerator before priming and administration.

Once used, the training pMDI must be kept at the site at ambient temperature not above 25°C (77 ˚F), and outside the refrigerator. At this temperature condition the residual shelf life of the training pMDI will be four months (120 days). Therefore, the pharmacist/investigator at the hospital or study site must write the use-by-date on the kit labels once the pMDI is removed

from the refrigerator, before using it. The use-by-date corresponds to the dispensing date plus 4 months. Please note that the use-by-date must not exceed the total shelf life of the product.

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

6.10 Drug Accountability

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

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

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

All the study medications supplied, used or unused, will be returned to the designated distributor to be destroyed centrally or destroyed directly on site (according to the sites guidelines). If destroyed on site, a destruction certificate must be provided by the site and filed both at the site and Chiesi. The return of study medication(s) must be done only after full study medication accountability and reconciliation are completed. The destruction of study medication(s) will not occur until authorized by Chiesi.

6.11 Provision of Additional Care

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

7. STUDY PLAN

7.1 Study Schedule

	Pre-screening	Run-in	Treatment Period				Follow Up Call	Early** Term
Visits	V0	V1 Screening	V2 Rand.*	V3	V4	V5	V6	
Time (weeks)	-3	-2	0	4	8	12	13	
Visit Windows (days)			± 2	± 2	± 2	±2	± 2	
Informed Consent Form	✓							
Demographic Data	✓							
IRT Visit Confirmation Call	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion/ Exclusion Criteria		✓						
Eligibility Recheck[1]			✓					
Medical History/ Previous Meds & Smoking History		✓						
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓
Adverse Events Assessment		✓	✓	✓	✓	✓	✓	✓
Full Physical examination		✓				✓		✓
Oropharyngeal examination		✓	✓	✓	✓	✓		✓
Hematology and Blood Chemistry		✓				✓		✓
Serum pregnancy test (WOCBP)		✓				✓		✓
Urine pregnancy test (WOCBP)		✓	✓	✓	✓	✓		✓[6]
Spirometry pre/post albuterol[2], Vital signs & ECG pre-albuterol		✓						
Spirometry V2 & V5: serial[4,5] V3 & V4: pre-dose only			✓	✓	✓	✓		✓[7]
Vital signs V2 & V5: serial[3] V3 & V4: pre-dose vital signs only			✓	✓	✓	✓		✓[7]
ECG: V2 & V5: serial ECG[3] V3 & V4: pre-dose ECG only			✓	✓	✓	✓		✓[7]
ACQ-7 Questionnaire			✓	✓	✓	✓		✓
Training (pMDI, eDiary, Peak Flow Meter)		✓	✓					
eDiary/Peak Flow Meter completion		(daily)	(daily)	(daily)	(daily)			
Dispensation of rescue albuterol		D	D/R	D/R	R			
Dispensation of run-in medication		✓	R					
Study Drug dispensation (D)/ return & Accountability (R)			D	D/R	D/R	R		R
Subject eDiary/Peak Flow Meter dispensation (D)/ Return (R)		✓	D/R	D/R	D/R	R		R
Morning dose of Study Drug Administration			✓	✓	✓	✓		✓
Review of eDiary/Peak Flow Meter and study drug compliance			✓	✓	✓	✓		✓

*Rand.: Randomization

**Early Term: Early Termination for randomized subjects withdrawn from study treatment before week 12

1- Eligibility re-check only for inclusion criteria 5, 7, 8. 9 and exclusion criteria 2, 3, 13, 16, 26.
2- Spirometry will be carried out at baseline and repeated within 30 minutes after the inhalation of 4 puffs of albuterol.
3- Vital signs and 12-Lead ECG- pre-dose and 30 min, 1h, 4 h and 12 h post-dose
4- Pre-dose FEV1: -45min and -15min before administration of study drug at (V2 and V5/ET).
5- Post-dose serial spirometry (FEV1): 5min, 15min, 30min, 1h, 2h, 3h, 6h, 9h, 11.5h, 12h (V2 and V5/ET)
6- Urine pregnancy test to be done only if serum is not collected.
7- Early Termination visit – Pre-dose vital signs, ECG and spirometry.

7.1.1 Visit 0 - Pre-screening visit

A pre-screening visit (Visit 0) will be carried out in order to fully explain the study to potential eligible asthmatic subjects. The investigator or his/her designee should provide the subject with ample time and opportunity to inquire about details of the trial and to decide whether or not to participate.

If subject agrees to participate, the signed and dated **informed consent** must be obtained before any study related procedures.

This visit can be the same day as Visit 1 (V1) if the washout period has been respected.

The following procedures will take place:

- As soon as the informed consent is signed, the investigator (or his/her designee) will connect to IRT to assign a unique subject number. This number will be sequentially assigned.

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

Before leaving the site:

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

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

- **Subjects will be instructed:**
  - To fast overnight (at least 8 hours) before the next visit in order to perform blood sampling (only water is allowed);
  - To refrain from taking their current asthma regimen morning dose before the screening visit.
  - To refrain from taking rescue medications (albuterol), caffeinated substances in the 6 hours preceding the next visit, and to abstain from all non-permitted medications in accordance with section 5.2 unless absolutely necessary.

Note: *Visit 0 and Visit 1 can be combined, in case the subject has not taken his/her usual asthma treatment when he/she arrives at the clinic, the wash-out period is respected as well as he/she has fasted overnight (at least 8 hours),*

7.1.2 Visit 1- Screening Visit (Week -2)

A screening visit will be carried out in order to identify eligible consenting subjects for the study (preferably before 7-9 am).

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

The following procedures will take place:

- Inclusion/exclusion criteria check
- **Medical History:** The medical history including asthma history will be recorded.
- **Smoking history:** smoking status with all the data needed to calculate the pack year will be recorded.
- **Previous and concomitant medication:** all medications taken by the subjects in the last 3 months will be recorded. Intake of non-permitted medication constitutes non-eligibility criterion for enrollment in the study.
- **Adverse Events (AEs):** The occurrence of any AE between informed consent signature and screening visit will be checked. In case of any clinically significant abnormality revealed during the physical examination or screening procedures, it will be recorded in the subjects' medical history, unless its onset date is after the informed consent signature date and it is not due to a pre-existing condition. In this case it will be recorded as an AE.
- A full **physical examination (**section 7.2.4**)** will be performed.
- **Oropharyngeal examination (**section 7.2.4**)**
- **Vital Signs:** Pre-bronchodilator vital signs will be recorded (pulse rate, systolic [SBP] and diastolic [DBP] blood pressure, after 10 minutes of rest, in sitting position) (section 7.2.2).
- **12-Lead ECG:** Single pre-bronchodilator 12-lead ECG will be recorded after at least 10 minutes of rest (section 7.2.3).

  Eligible subjects must have a mean QTcF ≤450 ms (males) and ≤470 ms (female). (criterion not applicable for subjects with pacemaker or permanent atrial fibrillation) (exclusion criterion #14).
- **Blood samples:** A blood sample will be collected before albuterol administration and after an overnight fasting for the assessments of:
  - standard hematology and blood chemistry;
  - serum β-HCG tests in women of childbearing potential.

  The blood samples must be collected **after vital signs and 12-lead ECG recording.** The central laboratory will analyze the samples and provide the subjects' reports to the site. In case of non-interpretable data, another determination must be performed as soon as possible and prior to Visit 2 (randomization visit) (section 7.2.6).

- A **urine pregnancy test** will be performed in women of childbearing potential. This test will allow confirmation that the woman tested is not pregnant before the serum pregnancy test results are made available by the central laboratory (section 7.2.5).

- **Pre-bronchodilator and Post-bronchodilator spirometry** – pre- and post-albuterol, in order to assess eligibility and bronchodilator responsiveness (section 7.2.10)

- If the subject is **not eligible**, the investigator or site staff will access IRT to record the subject as screening failure.

- If the subject is eligible, the site staff will request a run-in kit from the IRT system. One **Run-in Medication kit** (CHF 718 (BDP) pMDI 100µg 2 or 4 inhalations BID (TDD) 400 or 800µg) for the run-in period will be dispensed with instructions for use. The number of inhalations the subject should take and the use-by-date must be filled-in on the label by the site staff.
- The subject will be trained on the proper use of pMDI (section 6.2.4) using the training kit containing placebo. The corresponding tear-off label will be placed in the subject specific dispensation tracking form. The training kit will remain at the site.

- **The morning dose of run-in medication** (first administration) will be administered at the clinic visit (preferably before 10:00 am) under medical supervision. The run-in medication will be primed by site staff.

- **eDiary/Peak Flow Meter dispensed** - Subjects will be trained on how to record the run-in medications and rescue medication, respiratory symptoms in the eDiary (section 7.2.8) and the use of the Peak Flow Meter (section 7.2.7).

- **Rescue Medication dispensed** - Subjects will keep the rescue medication throughout the study period (will be re-supplied if needed); subject will be instructed to bring the rescue medication at each visit in order to check the need for replacement.

Before leaving the site:

- An **appointment** for Visit 2 will be scheduled within 14 days (± 2-days) in the morning (approximately the same time of day).

- **Subjects will be instructed:**
  - To inhale 1 or 2 puffs in the morning and evening from each run-in inhaler depending on what is prescribed (depending upon what ICS dose the subject was on prior to screening). In addition, subject will also be instructed to take albuterol as rescue if necessary (sections 6.2.2 and 6.2.3).
  - To answer twice daily eDiary questions on symptoms, medication intake (run-in and rescue).
  - To perform home PEF measurements twice daily (am/pm) (the morning PEF measurement should be done prior to visit 2).

- **Not** to take the morning dose of run-in medication before coming to visit 2.
- To refrain from taking rescue medications (albuterol), caffeinated substances in the 6 hours preceding the next visit, and to abstain from all non-permitted medications in accordance with section 5.2 unless absolutely necessary.
- To bring back the run-in medication (in the boxes), and eDiary/Peak Flow Meter with them at the next visit.

7.1.3 Visit 2 – Randomization Visit (Week 0), Serial Spirometry Visit

The subjects will visit the site for the randomization visit (2 weeks (± 2 days) after Visit 1) in the morning, approximately the same time of day (preferably before 7-9 am).

PEF measurement is done at home in the morning before the visit.

If the wash-out of the medications (including rescue and run-in) has not been respected (section 5.2), the visit needs to be re-scheduled within 2 days. Only one re-schedule is allowed. If wash-out is still not respected in the morning of the re-scheduled visit, the subjects will be recorded as screen failure in the IRT system.

The following assessments and procedures will take place:
Eligibility criteria will be rechecked: (inclusion criteria # 5, 6, 7, and 8 and exclusion criteria # 1, 2, 4, 5, 14 and 16). At the discretion of the investigator, a subject who fails to meet all inclusion/exclusion criteria (screen failure) at V2 may be re-screened again, up to one additional time, after 1 month from the date of the initial screen failure. The screen failure should be entered into the IRT system. In case of rescreening, the subject should sign a new informed consent and will be assigned a new subject number; a link to prior subject number will be recorded in the eCRF.

- **Run-in Medication** taken during the run-in period will be collected and accounted for.

- **eDiary/Peak Flow Meter:** The investigator (or designee) will check the eDiary/Peak Flow Meter portal whether the subject has completed the expected daily questions on symptoms and medications intake, as well as performing daily PEF measurements (am/pm) for compliance.

  In case of **non-compliance**, the investigator (or designee) will retrain the subjects on how to complete the eDiary, perform home PEF maneuvers, and the medication intake (rescue and study drug). While retraining the subjects, the investigator (or designee) will verify subjects' cooperative attitude and ability to correctly use the eDiary/Peak Flow Meter. If the subjects are not cooperative and do not meet inclusion criteria #8, they will be recorded as screen failure in the IRT system.

- **Adverse Events assessment** – the occurrence of any AE since the last visit will be recorded. The status of ongoing AEs will be checked and updated.

- **Concomitant Medications** – the investigator or designee will check that the subject did not take any of the non-permitted medications since the screening visit. Any change in medications will be recorded.

- **Oropharyngeal Examination (**section 7.2.4**)**

- **Questionnaire:** Subjects will complete the ACQ-7 questionnaire (section 7.2.1).

- **A urine pregnancy** test will be performed in women of childbearing potential (section 7.2.5).

- Pre-dose Spirometry- A spirometry measurement at -45 and -15 minutes pre-dose will be completed (section 7.2.10).

- Pre-dose Serial Vital signs (section 7.2.2) and Serial ECG (section 7.2.3) will be performed.

If **eligibility criteria are confirmed**:

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

- **The morning dose of study drug (first administration)** will be administered at the clinic visit (before 9:00 am preferably) (the time of first inhalation corresponds to Time 0 of spirometry). Subjects will be instructed to inhale **2 puffs from the inhaler labeled A and 2 puffs from inhaler labeled B**.

- **Post-dose spirometry-** Serial spirometry will be conducted at the following time points: 5 min, 15 min, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12 hour

- Post-dose Serial Vital signs and Serial ECG: 30 min, 1h, 4h, and 12-hour post-dose

- Re-training on pMDI/eDiary/Peak Flow Meter (if necessary)

- Dispensation of rescue medication if needed

Before leaving the site:

- An **appointment** for Visit 3 will be scheduled in 4 weeks ± 2 days in the morning approximately between 7:00-9:00 am.

- **Study drug** (1 kit containing 4 inhalers labeled as A-B-C-D) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study drug by the site staff. The site will provide the subject instructions when to switch to canisters labeled (C & D).

- **Subjects will be instructed:**
  - To answer twice daily: questions on symptoms, study drug intake and rescue medication in the eDiary.
  - To take the rescue medication as needed, but to refrain 6 hours prior to the next visit (if possible).
  - To perform home PEF measurements twice daily (am/pm) (the morning PEF measurement should be done prior to visit 3).
  - **Not** to take the morning dose of the study drug before coming to the next visit.
  - To bring back the study drug (in the boxes), and eDiary/Peak Flow Meter with them at the next visit.
  - To refrain from taking caffeinated substances in the 6 hours preceding the next visit, and to abstain from all non-permitted medications in accordance with section 5.2 unless absolutely necessary.

7.1.4 Visit 3 - (Week 4) and Visit 4 (Week 8)

The subject will visit the site for Visit 3 (Week 4) and/or Visit 4 (Week 8) 4 weeks (± 2 days) after the last visit in the morning, approximately the same time of day (preferably before 7-9 am).

PEF measurement is done at home in the morning before the visit.

If the wash-out of the medications has not been respected (section 5.2), the visit needs to be re-scheduled within 2 days. Only one re-schedule is allowed. If wash-out is still not respected in the morning of the re-scheduled visit, the site should note the deviation from the protocol and the reason.

The following assessments and procedures will take place:

- The subject will bring in their rescue medication for accountability.
- The investigator (or designee) will update the IRT system with the current visit date and dispense the study drug kit allocated by the IRT system.
- **eDiary/Peak Flow Meter:** The investigator (or designee) will check the eDiary/Peak Flow Meter portal to determine whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF measurements (am/pm) for compliance.

  In case of **non-compliance**, the investigator (or designee) will retrain the subjects on how to complete the eDiary, perform PEF maneuvers, and the medication intake (rescue and study drug).
- **Adverse Events assessment** – the occurrence of any AE since the last visit will be recorded. The status of ongoing AEs will be checked and updated.

- **Concomitant Medications** – the investigator or designee will check that the subject did not take any of the non-permitted medications since the screening visit. Any change in medications will be recorded.

- **Oropharyngeal Examination (**section 7.2.4).

- **Questionnaire:** Subjects will complete the ACQ-7 questionnaire (section 7.2.1).

- **A urine pregnancy** test will be performed in women of childbearing potential (section 7.2.5).

- **Pre-dose Spirometry** only (section 7.2.10)

- **Vital signs and ECG** – pre-dose only (section 7.2.2 and section 7.2.3)

The morning dose of new study drug will be administered at the clinic visit (before 9:00 am preferably) (the time of first inhalation corresponds to Time 0 of spirometry). Subjects will be instructed to inhale 2 puffs from the inhaler A and 2 puffs from inhaler B.

- Dispensation of rescue **medication** if needed

Before leaving the site:

- An **appointment** for the next visit will be scheduled in 4 weeks ± 2 days in the morning approximately between 7:00-9:00 am.

- **Study drug** (1 kit containing 4 inhalers labeled as A-B-C-D) will be dispensed with instructions for use. The use-by-date must be filled-in on the label of study drug by the site staff. The site will provide the subject instructions when to switch to canisters labeled (C & D).

- **Subjects will be instructed:**
  - To answer twice daily: questions on symptoms, study drug intake and rescue medication in the eDiary.
  - To take the rescue medication as needed
  - To perform home PEF measurements twice daily (am/pm) (the morning PEF measurement should be done prior to next visit).
  - **Not** to take the morning dose of the study drug before coming to the next visit.
  - To bring back the study drug (in the boxes), and eDiary/Peak Flow meter with them at the next visit.
  - To refrain from taking rescue medications (albuterol), caffeinated substances in the 6 hours preceding the next visit, and to abstain from all non-permitted medications in accordance with section 5.2 unless absolutely necessary.

- To fast overnight (at least 8 hours) before **Visit 5** in order to perform blood sampling (only water is allowed).

7.1.5 Visit 5 – (Week 12) End of Treatment

The subjects will visit the site for Visit 5 (End of Treatment) 4 weeks (± 2 days) after Visit 4 in the morning, approximately the same time of day (preferably before 7-9 am).

PEF measurement is done at home in the morning before the visit.

If the wash-out of the medications has not been respected (section 5.2), the visit needs to be re-scheduled within 2 days. Only one re-schedule is allowed. If wash-out is still not respected in the morning of the re-scheduled visit, the site should note the deviation from the protocol and the reason.

The following assessments and procedures will take place:

- **eDiary/Peak Flow Meter:** The investigator (or designee) will check the eDiary/Peak Flow Meter portal to determine whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF measurements (am/pm) for compliance.
- The investigator (or designee) will update the IRT system with the current visit date.
- **Subject will return the eDiary/Peak Flow Meter and Study Drug kit**
- **Adverse Events assessment**
- **Concomitant Medications** will be reviewed
- **A full physical examination (**section 7.2.4**)** will be performed.
- **Oropharyngeal Examination (**section 7.2.4**)**
- **Questionnaire:** Subjects will complete the ACQ-7 questionnaire (section 7.2.1).
- **Blood samples:** A blood sample will be collected before study drug administration and after an overnight fasting for the assessments of (section 7.2.6) :
  - standard hematology and blood chemistry.
  - serum β-HCG tests in women of childbearing potential (section 7.2.5).

  The blood samples must be collected **before serial spirometry.** The central laboratory will analyze the samples and provide the subjects' reports to the site.
- **A urine pregnancy** test will be performed in women of childbearing potential (if the serum pregnancy test is not conducted).

- **Pre-dose Spirometry**- A spirometry measurement -45 and -15 minutes pre-dose will be completed (section 7.2.10).

- Pre-dose Serial Vital signs and Serial ECG (section 7.2.2 and section 7.2.3)

The morning dose of study drug will be administered on site (**from kit dispensed at Visit 4/Week 8)** (before 9:00 am preferably) (the time of first inhalation corresponds to Time 0 of spirometry). Subjects will be instructed to inhale **2 puffs from the inhaler labeled C and 2 puffs from inhaler labeled D**.

- **Post-dose spirometry-** Serial spirometry will be conducted at the following time points: 5 min, 15 min, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12 hour

- **Post-dose Serial Vital signs and Serial ECG**: 30 min, 1h, 4h, and 12-hour post-dose

Before discharge:
- A follow-up safety phone call (Visit 6) will be scheduled approximately 1 week after Visit 5/End of Treatment.
- The investigator will prescribe the most appropriate treatment or restore the initial therapy the subject was taking prior to the study.

7.1.6 Visit 6 - Follow-up Safety Visit

A follow-up safety phone call will be performed by the investigator or designated staff no later than 1 week after the final visit (Visit 5) or Early Termination from study drug visit to check the status of unresolved AEs/SAEs and to record any new AEs/SAEs that may have occurred after Visit 5 (or last visit), as well as related concomitant medications.

Investigator will access IRT in order to record completion of the study visit.

7.1.7 Early Termination Visit from Study

If a subject prematurely withdraws from the study, all efforts will be made to perform an Early Termination visit at the time of discontinuation from study. This visit will include the following assessments, providing there are no safety issues for the subject and in accordance with the subject's agreement:

- At the investigator's discretion, the subject will resume their pre-study therapy regimen or change if appropriate

- **eDiary/Peak Flow Meter:** The investigator (or designee) will check the eDiary/Peak Flow Meter portal to determine whether subject has completed the expected daily questions on symptoms and medications intake as well as performing daily PEF measurements (am/pm) for compliance.

- Investigator or designee will update the IRT system

- **Subject will return** the eDiary/Peak Flow Meter and Study Drug kit

- **Adverse Events assessment**
- **Concomitant Medications** will be reviewed
- A full **physical examination (**section 7.2.4**)** will be performed.
- **Oropharyngeal Examination** (section 7.2.4)
- **Questionnaire:** Subjects will complete the ACQ-7 questionnaire (section 7.2.1).
- A **blood sample** will be collected, after an overnight fasting (at least 10h, when possible) after vital signs and 12-lead ECG recordings and before dosing, for the assessments of (section 7.2.6):
  - standard hematology and blood chemistry
  - a serum β-HCG test in women of childbearing potential

The following **(pre-dose)** procedures will be performed (the administration of the morning dose of study drug will take place during the clinic visit, if possible):

- **Spirometry** (section 7.2.10)
- **Vital signs and ECG**: An appointment will be made 1-week from the Early Termination visit for the follow-up safety phone call (section 7.2.2 and section 7.2.3)

7.1.8 Early Discontinuation Visit from Study Drug

If a subject prematurely discontinues from study drug but remains in the study after randomization (Visit 2), all efforts will be made to perform an Early Termination visit at the time of discontinuation from study drug and the follow-up safety call will be conducted.

Subjects who consent to data collection until the planned V5 visit will continue attending study visits according to the study visit schedule. Before each visit, the wash-out periods for concomitant medications detailed in section 5.2 must be respected. The following assessments will be performed:

- Spirometry (pre/post of the subject's maintenance inhaled therapy for asthma, including the serial spirometry when planned by the study protocol).
- The subject should continue to complete eDiary data (except for the study drug questions) and to measure PEF at home.
- The investigator (or designee) will check the concomitant medications, adverse events that occurred since last visit.
- Urine pregnancy tests in all women of childbearing potential.
- Questionnaires- subjects will complete the ACQ-7 questionnaire (section 7.2.1).

7.2 Study Assessments and Procedures

7.2.1 Asthma Control Questionnaire (ACQ-7)

Asthma control will be evaluated by the completion of the Asthma Control Questionnaire© (ACQ-7) [21], [22]. The ACQ-7 is able to identify the adequacy of asthma control in individual subjects. The first 6 items of the questionnaire refer to symptoms and rescue use in the previous 7 days while the 7th item (related to FEV_1), is completed by the clinical staff.

The ACQ-7 is administered at Visit 2, Visit 3, Visit 4 and Visit 5/ET.

Subjects are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment).

Item 7 should be populated **using the pre-dose FEV_1 % predicted (-15 minutes from V2 to V5)**. If the -15 minute FEV1 % predicted is missing, the -45 minute assessment will be used as item 7.

The ACQ-7 will be completed by subjects on an electronic device in a quiet place before the pulmonary function testing, only question 7 will be completed after the testing.

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

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

The ACQ-5 score will be derived and analyzed from the ACQ-7 questionnaire data, considering the first five questions of the ACQ-7 questionnaire administered to subjects.

7.2.2 Vital signs

Pulse rate, systolic and diastolic blood pressure (SBP, DBP) will be measured after 10 min rest in sitting position:

- Visit 1 - pre-albuterol
- Visit 2 & 5 pre-dose and 30 min, 1h, 4h, and 12h post-dose
- Visit 3 & 4 pre-dose spirometry
- ET visit (if applicable, pre-dose)

The vital signs should be assessed **before the blood sampling.**

7.2.3 12-lead ECG

A centralized vendor will provide standardized ECG equipment to all the sites. A 12-lead ECG will be performed at the site for eligibility check (all subjects). The evaluation will be done by the site.

- Visit 1 - pre-albuterol
- Visit 2 & 5 pre-dose and 30 min, 1h, 4h, and 12h post-dose
- Visit 3 & 4 pre-dose spirometry
- ET visit (if applicable, pre-dose)

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

Standard electrode placement will be used for these ECG, including placing the limb leads, dual snap electrodes will be used for the precordial leads.

Single 12-lead ECG tracing will be recorded according to the study schedule. QTc value will be calculated using the Fridericia formula (Fridericia-corrected $QTc=QT/\sqrt[3]{RR}$). It will be calculated automatically by the ECG recorder. Heart rate (HR), PR and QRS values will be also evaluated from ECG at all visits.

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

ECG will be evaluated and interpreted at ERT and in case of any abnormality requiring urgent action ECG should be also evaluated on site (before sending to central vendor).

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

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

7.2.4 Physical Examination (Visit 1 and Visit 5)

A full physical examination including body weight, height (height only at visit 1) an assessment of general appearance, eyes, ears, nose, skin, head and neck, mouth and throat, respiratory,

cardiovascular, renal and urinary, lymph nodes, gastrointestinal, musculoskeletal, and nervous systems will be performed at the site by the investigator or designee.

Oropharyngeal Examination:

Oropharyngeal candidiasis is a condition commonly associated with the use of ICS and is caused by the Candida fungus. This side effect may be attributed to the topical effects of these medications on the oral mucosa **[23]**. Generalized immunosuppressive and anti-inflammatory effects of steroids are thought to play a major role in the pathogenesis of candidiasis **[24]**.

The subject's mouth and throat will be visually inspected by the investigator at V1- V5/ET to look for the presence of characteristic-looking white lesions / oral thrush. If deemed necessary by the investigator to confirm the diagnosis, the suspected lesion should be swabbed/scraped with a sterile cotton and the tissue sample sent to a laboratory for microscopic and culture identification.

Appropriate treatment of oropharyngeal thrush (e.g. using topical rinses and oral anti-fungal agents) can be prescribed at the discretion of the study investigator as deemed necessary throughout the study.

7.2.5 Serum and Urine Pregnancy Tests

Serum pregnancy tests will be performed at V1 and V5 for WOCBP.

A urine pregnancy test will be administered at V1 to V4 (V5 only if serum is not collected) for WOCBP, using a commercial urine β-HCG pregnancy test strip. This test strip is used to obtain a quick (within a few minutes), visual, qualitative result for the early detection of pregnancy. The test performed at V1 will allow confirmation that the woman tested is not pregnant before the serum pregnancy results are made available by the central laboratory.

7.2.6 Blood Hematology and Chemistry

Blood samples of approximately 9 mL (total) will be collected at the site for hematology and serum chemistry, after an overnight fast of at least 10 hours. The blood withdrawal should be performed after vital signs and 12-lead ECG recording and before administration of albuterol or study drug. An additional blood sample will be collected for serum pregnancy test in women of childbearing potential.

The following evaluations will be performed in a central laboratory:

7.2.6.1 Table. Laboratory Assessments

Serum chemistry	Blood urea nitrogen (BUN), cholesterol, triglycerides, creatinine, creatine phosphokinase (CPK), uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase (GGT), total bilirubin, bilirubin direct and indirect, alkaline phosphatases, albumin, total serum protein, and electrolytes (sodium, potassium, calcium, and chloride), fasting glucose, phosphate
Hematology	Red blood cells count (RBC), white blood cell count (WBC), with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes - absolute and %), total hemoglobin (Hb), hematocrit (Hct), platelet count (PLT)
Other	Serum pregnancy test (serum β-HCG) in WOCBP COVID-19 diagnostic swab test (as needed)

Blood collection and sample preparation will be performed according to procedures provided by the central laboratory which will be in charge to transmit the results to the investigator. In case of clinically significant abnormality, findings will be reported in the medical history or as AE (section 10.8).

7.2.7 Daily PEF measurements with Electronic Peak Flow Meter

PEF (L/min) will be monitored twice daily in the morning and in the evening (during the run-in and the study periods, from V1 to V4) by subjects at home using a portable electronic Peak Flow Meter.

This will be done before the intake of the study drug for both morning and evening PEF assessments.

A specific question will be included in the eDiary to ask if PEF measurements have been performed before the intake of study medication.

Subjects will be educated on the purpose and technique of PEF measurements. Specific instructions for use will be made available to the subjects.

During each measurement session (morning or evening before the intake of the study drug) the subjects will perform 3 blows. Data will be recorded in the device.

Morning measurements should be done between approximately 7:00 am and 9:00 am and evening measurements should be done between approximately 7:00 pm and 9:00 pm. An alarm will remind the subjects to perform measurements.

Data from the Peak Flow Meter will be automatically transmitted from subjects' home to ERT's central database on a daily basis. **A regular check of the recorded data will be done by the Investigator** (or designee) through a dedicated portal to verify the correct use of the device, to detect any clinical abnormality and to check subjects' compliance. **In case of poor compliance**

and/or worsening of asthma control during the study, phone call(s) to the subjects will be done by the site and instructions will be given again to the subjects if appropriate.

In case of Early Treatment Discontinuation, if the subject agrees to continue with the study assessments as planned in the study protocol, PEF measurements will continue to be monitored twice daily in the morning and in the evening by the subject at home as previously described.

7.2.8 Electronic Diary (eDiary)

Asthma symptoms, study drug and rescue medication

During the run-in and study periods (from V1 to V4), the subjects will answer the following questions in the electronic diary twice daily in the morning and in the evening before the PEF measurements:

- the asthma symptom scores;
- the nocturnal awakening occurrence due to asthma requiring rescue medication;
- the use of study medication (rescue and study treatment).

In case of Early **Treatment** Discontinuation, if the subject agrees to continue with the study assessments as planned in the study protocol, the subjects will answer twice a day in the morning and in the evening and before the PEF measurements the following questions in the electronic diary:

- the asthma symptom scores;
- the nocturnal awakening occurrence due to asthma requiring rescue medication;
- the use of rescue medication.

The data will be automatically transmitted from the subjects' home to the ERT's central database on a daily basis **and checked by the Investigator on a regular basis.**

- **Asthma symptoms** (overall symptoms, cough, wheeze, chest tightness and breathlessness) will be scored, as occurred respectively during the night and during the day, as follows:
  - **Morning (night-time asthma symptom score):**
    0 No symptom
    1 Mild: symptoms not causing awakening
    2 Moderate: discomfort enough to cause awakenings
    3 Severe: causing awakenings for most of the night / do not allow to sleep at all
  - **Evening (daytime asthma symptom score):**
    0 No symptom
    1 Mild: aware of symptoms which can be easily tolerated
    2 Moderate: discomfort enough to cause interference with daily activity
    3 Severe: incapacitating with inability to work/take part in usual activity
- **Nocturnal awakening occurrence due to asthma requiring rescue medication**

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

- **Study Drug**
  The intake of study drug will be recorded twice daily as follows: the number of puffs taken in the morning and in the evening. Note: These questions are not applicable after the early treatment discontinuation, even if the subject agrees to continue with the study assessments as planned in the study protocol.

- **Rescue medication**
  The daily use of rescue medication will be recorded as follows: the number of puffs taken during the night will be recorded each morning on awakening, while the number of puffs taken during the day will be recorded each evening, before taking the study drug.

Asthma control day

The derived variable of asthma control days will be calculated according to the following definition (both the two conditions below should occur to define an asthma control day):

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

7.2.9 Asthma exacerbations during the treatment period

In a case of an asthma exacerbation, treatment needs to be delivered in the way that the treating physician deems appropriate and in the best interest of the subject. Subjects will be instructed on recognition of symptoms and signs signaling a developing asthma exacerbation.

Asthma exacerbations (as per ATS/ERS guidelines and Virchow paper **[25]**, **[26]**) are defined as follows:

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

a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights or increase of ≥ 0.75 from baseline in daily symptom score on 2 consecutive days.

b) Increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day)

c) ≥ 20% decrease in PEF from baseline on at least 2 consecutive mornings/evenings or ≥ 20% decrease in FEV1 from baseline

d) Visit to the ER/trial site for asthma treatment not requiring systemic corticosteroids

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

A severe asthma exacerbation is defined as an asthma worsening requiring the initiation of treatment with systemic corticosteroids for at least 3 days.

Note: courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations. A severe exacerbation requiring an emergency room visit or a hospitalization will be documented accordingly. Asthma worsening treated with depot corticosteroids (for sustained systemic effect of at least 3 days) are considered as severe exacerbations.

Eligible subjects should remain free of exacerbation requiring hospitalization, emergency room admission or use of systemic corticosteroids within 4 weeks prior to screening and during the run-in period (according to exclusion criterion #4).

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

After randomization, if the subject experiences a severe asthma exacerbation requiring systemic corticosteroid and/or use of nebulizer containing β2-agonists and/or corticosteroids and/or antibiotic therapy, hospitalization or emergency care visit, the following study visit should only occur after subject's stabilization. In addition, a minimum timeframe of 2 weeks between the end of the exacerbation and the clinic visit should elapse. Otherwise, the clinic visit should be delayed.

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

At each visit (starting Visit 1), the investigator will assess the occurrence of any asthma exacerbation since the last visit. If not already notified by the subject, the investigator will also check whether the subject has taken systemic corticosteroids meeting the criteria for a severe exacerbation or whether the subject has been in the emergency room or been hospitalized due to asthma.

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

The investigator is supported in the detection of asthma worsening by the eDiary data.

In case of asthma exacerbations during the study, the subjects will be allowed to receive short courses (≤ 10 days) of systemic corticosteroids (section 5.1).

The intake of study medication should be maintained in case of asthma exacerbation to the extent possible. Only in case of absolute need, a temporary discontinuation of study treatment intake no longer than 2 weeks is allowed (if longer, the subjects will be withdrawn). The

investigators will carefully record all additional treatments taken for the exacerbation. Any necessary unscheduled visit will be performed in order to evaluate the subjects' clinical condition.

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

An asthma exacerbation is not a reason to withdraw the subject from the study treatment, unless the investigator deems it necessary. The decision to withdraw the subject from the study drug will be at the investigator's discretion, however the subject may stay on study, but off study drug.

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

7.2.10 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 **[27]**. All sites will be provided with a spirometer. It is recommended that, in each center, the same spirometer is used for a given subject during the course of the study. **Calibration of the spirometer must be performed by the same investigator or designee (to the extent possible) at each visit prior to any spirometry maneuvers and the reports must be kept with the source documents.**

The specific procedures for centralized spirometry will be provided to the investigator by the centralized spirometry vendor.

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

The following parameters will be recorded at Visits V1 to V5/ET (if applicable):

- Forced Expiratory Volume in the 1st second (FEV_1, L)
- Forced Vital Capacity (FVC, L)

Predicted values of FEV_1 and FVC will be calculated according to formulas reported by Quanjer et al **[28]**.

Subjects should be relaxed (shoulders down and relaxed) with the nose clipped after at least 10 minutes rest and asked to breathe regularly for several breaths until the end expiratory lung volume is stable (this usually requires at least three tidal maneuvers). They are then urged to take a deep breath to TLC (Total Lung Capacity) and exhale forcefully without hesitation. FEV_1 and FVC will be recorded at each clinic visit from a forced vital capacity maneuver. The highest

FVC and the highest FEV_1 (values corrected for BTPS) will be selected after examining the data from all of the usable spirograms, even if they do not come from the same maneuver. An adequate test requires a minimum of 3 acceptable FVC maneuvers [27]. Acceptable repeatability, for the purposes of this study, is achieved when the difference between the two largest FEV_1 and the two largest FVC values is ≤ 200mL). If these criteria are not met in 3 maneuvers, additional trials should be attempted, up to, but usually no more than 8.

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

The run-in or the study drug should not be taken at home in the morning of the visit. If the drug is taken at home, the measurements should be deferred (i.e. the visit needs to be re-scheduled to take place within 2 days). If rescue or study drug intake occurs again in the previous 6 hours before the re-scheduled visit:

- at V1 and V2, the subject will be a screen failure
- from V3 to V5, the visit will be performed and details of the intake (time and quantity) documented.

At **Visits 2 and 5**, serial spirometry will be conducted at T-45 and T-15 minutes pre-morning dose and 5, 15, 30, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-morning dose. Time points for serial spirometry should be followed as closely as possible.

Visits 3 and 4 pre-dose spirometry only (i.e. no serial spirometry will be performed).

ET (if applicable) pre-dose spirometry only

7.2.11 Rescue medication

The daily use of rescue medication will be recorded as follows: the number of puffs taken during the night will be recorded each morning on awakening before taking the morning dose of the study drug while the number of puffs taken during the day will be recorded each evening before taking the evening dose of the study drugs.

In case of Early Treatment Discontinuation, if the subject agrees to continue with the study assessments as planned in the study protocol, the daily use of rescue medication will continue to be recorded by the subject as previously described.

8. EFFICACY ASSESSMENTS

Primary efficacy variable:

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.

Key-Secondary efficacy variable:

- Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12.

Secondary efficacy variables:

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 0.
- Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 0.
- Change from baseline in trough FEV_1 at Week 12.
- Change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12.
- Change from baseline in average morning PEF over 12-week treatment period.
- Change from baseline in average evening PEF over 12-week treatment period.
- Responder analysis (i.e. change ≥100 mL) for pre-dose morning FEV_1 at Week 4, 8 and 12.
- Responder analysis (i.e. change ≥100 mL) for trough FEV_1 at Week 12.
- Change from baseline in terms of ACQ-7 and ACQ-5 at Week 12.
- Change from baseline in percentage of rescue medication free days over 12-week treatment period.
- Change from baseline in percentage of asthma symptom free days over 12-week treatment period.

9. SAFETY ASSESSMENTS

9.1 Safety Variables

- Adverse Events (AEs), Adverse Drug Reactions (ADRs), Class-related Adverse Events.
- Vital signs (systolic and diastolic blood pressure).
- 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS.
- Standard hematology and blood chemistry.

9.2 COVID-19 Infection

COVID-19 is a contagious illness caused by a coronavirus. It may present with a wide range of symptoms from mild to severe and the investigator/site staff should maintain vigilance in detecting these symptoms which include, but are not limited to cough, shortness of breath, difficulty breathing, fever, chills, muscle pain, sore throat, and new loss of taste or smell.

A person can become infected from respiratory droplets transmitted when an infected person coughs, sneezes, or talks or from inhalation of the aerosolized particles that may linger in the air for extended periods of time. One may also be able to get it by touching a surface or object that has the virus on it, and then by touching their mouth, nose, or eyes. Everyone is at risk of getting COVID-19. Older adults and people of any age who have serious underlying medical conditions may be at higher risk for more severe illness.

The investigator/site staff must take all necessary precautions to minimize and avoid the risk of transmission and exposure to study subjects and site staff, according to local guidelines.

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

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

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

To date, there are several vaccines approved for prevention of COVID-19 caused by SARS-CoV-2. For all confirmed cases of COVID-19/SARS-CoV-2 the investigator must follow the standard of care in accordance with local treatment guidelines. COVID-19 vaccination status and all concomitant treatments must be recorded in the eCRF.

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 unfavourable 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 anemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalization or prolongation of existing hospitalization**

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

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

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

- Is a congenital anomaly or birth defect

- **Is a medically significant adverse event**

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

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

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

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

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

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (included in the Investigator's Brochure for CHF 1535 pMDI and CHF 718 pMDI). Otherwise, it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the reference safety information would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

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

10.3 Intensity of Adverse Event

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

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

10.4 Causality Assessment

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

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

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

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

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

10.5 Action taken with the study drug due to an AE

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

10.6 Other actions taken

- Specific therapy/Medication
- Concomitant Procedure

10.7 Outcome

Each Adverse Event must be rated by choosing among:

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

10.8 Recording Adverse Events

All Adverse Events occurring during the course of the study must be documented in the eCRF. If the Adverse Event is serious, the Serious Adverse Event Form must also be completed.

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

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

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

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

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

10.9 Reporting Serious Adverse Events to Chiesi

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

Safety Contact	Telephone no.	Fax no.	E-mail
Parexel Safety Contact	[redacted]	Northamerica_medicalparexel.com	PV_FORCE2@parexel.com
Chiesi Safety Contact	Not applicable	+39 0521 1885003	CT_CDS@chiesi.com

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be

reported if the investigator becomes aware of them and considers them related to study drug.
- Up to the closure of the site, SAE reports should be reported to the Parexel Safety Contact. New serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities and IRBs

All SUSARs/IND safety reports which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported to Regulatory Authority in compliance with the timelines and standards for reporting SUSARs/IND safety reports set out in the 21CFR Part 312.32 IND Safety Reporting and linked FDA guidance [Guidance for Industry and Investigators, Safety Reporting Requirements for INDS and BA/BE Studies] and according to local reporting requirements.

Investigational Review Boards/Ethic Committees and Investigators will also receive the report, if required.

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

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Parexel Safety Contact together with the Serious Adverse Event form, retaining a copy on site.
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Parexel Safety Contact as soon as available, retaining a copy on site.
- All documents provided by the Investigator or site staff to the Parexel Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- In case of pregnancy, the subject will be immediately discontinued from the study drug and she will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and until the age of one year to detect any congenital anomaly or birth defect. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail/via Monitor to the Parexel Safety Contact using the paper Pregnancy Report Form. The Parexel 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 Parexel Safety Contact. Information collected in specific sections relative to the pregnancy will be recorded in the form only upon signature of the specific ICF by the subject/subject's partner. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome, together with a follow-up of the first two pages, if necessary (e.g. an update in the medications received during pregnancy by the mother). If it meets the criteria for immediate

classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.

- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed, but the subject participating to the study should not be discontinued from the study.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in/rescue medication, or if the pregnancy occurs after the follow-up call (i.e, at least 7 days after the last study drug intake) the pregnancy does not need to be reported and followed.
- Any Adverse Drug Reaction occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority and/or to the relevant Marketing Authorisation Holders of the involved medicinal products, according to the applicable laws. Additionally, also conditions of use outside the marketing authorisation of the medicinal products (i.e. off-label, overdose, misuse, abuse and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy should be reported.

11. DATA MANAGEMENT

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

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

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.
Medical history, adverse events and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC).

External data (ECG readings, spirometry, laboratory samples, eDiaries, electronic questionnaires and IRT) will be processed centrally, sent to the designated CRO and reconciled with the corresponding information recorded in the CRF. Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

After the completion of data collection and cleaning, a review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened, and the planned statistical analysis will be performed.

If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by Chiesi.

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

12. STATISTICAL METHODS

12.1 Sample Size

The sample size has been calculated to demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD over CHF 718 pMDI 800µg TDD in terms of the primary and key secondary endpoint.

A discontinuation rate from the randomized study drug of approximately 10% at Week 12 has been considered.

A total of 580 subjects will be randomized according to a 1:1 ratio to either CHF 1535 pMDI 800/24µg TDD or CHF 718 pMDI 800µg TDD (i.e., 290 subjects per group). This sample size will provide, using the main estimand:

- Approximately 89% power to detect a mean difference of 108 mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 at a two-sided significance level of 0.05, assuming a SD of 409 mL. The assumed mean difference of 108 mL represents a weighted average between two means: a mean difference between groups of 120 mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0 mL while off-treatment (assuming 10% of the randomized subjects).

- Approximately 90% power to detect a mean difference of 117 mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12 at a two-sided significance level of 0.05, assuming a SD of 434mL. The assumed mean difference of 117 mL represents a weighted average between two means: a mean difference between groups of 130mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0mL while off treatment (assuming 10% of the randomized subjects).

Thus, considering the main estimand analysis, an overall study power of at least 80% for the primary and the key-secondary efficacy endpoint will be ensured.

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

- *Step 1*: Primary endpoint (i.e. change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12) using the main estimand - Tested at a 2-sided 5% significance level.

- *Step 2*: Key-secondary endpoint (i.e. change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12) using the main estimand - Tested at a 2-sided 5% significance level.

12.2 Populations for analysis

- Safety set: All randomized subjects who receive at least one dose of study drug (analyzed as treated).

- ITT set: All randomized subjects who receive at least one dose of the study drug (analyzed as randomized).

12.3 Statistical analysis

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

12.3.1 Descriptive Statistics

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

12.3.2 Missing data

- FEV_1 $AUC_{0\text{-}12h}$: In the calculation of FEV_1 $AUC_{0\text{-}12h}$ normalised by time, missing values will be replaced as follows:
  - If the pre-dose FEV_1 value is not available, the entire curve will be considered as missing.
  - In case the 12h value is missing, the value of the previous timepoint will be carried over; the time associated with this timepoint will be the time of study medication intake plus 12 hours.
  - Single, isolated missing FEV_1 values (not pre-dose or last value) will be replaced by linear interpolation using the adjacent values.
  - If 2 or more consecutive post-dose time points have missing FEV_1 values, the FEV_1 $AUC_{0\text{-}12h}$ will be considered as missing.
  - If in total 3 or more of the post-dose time points have missing FEV_1 values, the FEV_1 $AUC_{0\text{-}12h}$ will be considered as missing.

- Pre-dose FEV_1: Pre-dose FEV_1 is defined as the mean of 45 minutes and 15 minutes pre-dose FEV_1 measurements. If one of the measurements at 45 minutes and 15 minutes pre-dose is not available, then the non-missing measurement will be taken as the pre-dose value. If no pre-dose measurement is available, then the pre-dose FEV_1 value will be considered as missing.

- Trough FEV_1: Trough FEV_1 is defined as the mean of 11.5h and 12h post-dose FEV_1 measurements. If one of the FEV_1 measurements at 11.5h and 12h post-dose is not available, then the non-missing measurement will be taken as the trough FEV_1 value. If no measurement is available, then the trough FEV_1 value will be considered as missing.

- Peak FEV_1: Peak FEV_1 is defined as the maximum value among those collected at 5 min, 15 min, 30 min, 1h, 2h and 3h post-dose. If 2 or more FEV_1 measurements at 5 min, 15 min, 30 min, 1h, 2h and 3h post-dose are not available, then the peak FEV_1 value will be considered as missing.

- Daily data: A minimum of 7 days with available measurements will be required in the run-in period and in each inter-visit period (i.e. [Week 0 – Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) to consider the following variables as non-missing: morning and evening PEF, use of rescue medication, daily asthma symptoms, percentage of rescue medication free days and asthma symptom free days.

- ACQ-7 and ACQ-5 questionnaire: For ACQ-7 and ACQ-5 questionnaire, the total score will be calculated only if all the scores derived from all the seven items (for ACQ-7) or from all the five items (for ACQ-5) are recorded.

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

12.3.3 Subject demographics and baseline characteristics

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

12.3.4 Primary efficacy variables

Main estimand

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

Intercurrent event / event leading to missing data	Strategy	Strategy for sensitivity analyses

Early discontinuation from the randomized study drug	*Treatment policy*: Data collected after discontinuation from the randomized study drug (i.e. off-treatment data) will be included in the analysis.	
Early discontinuation from the study	*Hypothetical:* The collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms **[1]**. This approach targets the off-treatment effect that would have been observed if all subjects discontinued from study drug had consented to continue the study. Note: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.	*Sensitivity 1*: A two-dimensional tipping point analysis varying assumptions about the missing outcomes in the two treatment arms will be performed to explore the plausibility of missing data assumptions under which the conclusions change (i.e. under which treatment effect is no longer statistically significant).
Use of not allowed medications and other important protocol deviations	*Treatment policy*: Data will be used regardless of whether or not the intercurrent event occurs.	
Wrong study drug intake	*Treatment policy*: If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug.	

Analysis

Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 will be analyzed on the ITT set using an ANCOVA model including treatment group, US region and prior asthma therapy as fixed effects and baseline value (i.e. Week 0, FEV_1 pre-dose) as covariate.. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 12 will be estimated by the model. Superiority of CHF 1535 pMDI 800/24µg TDD will demonstrated by a statistically significant difference between treatments at Week 12 (defined as $p<0.05$) favoring CHF 1535 pMDI 800/24µg TDD.

12.3.5 Key-Secondary efficacy variable

The attributes of the main estimand in terms of population, treatments, variable and population-level summary are provided in section 2.1. The strategy for intercurrent events and events leading to missing data for the key-secondary efficacy analyses and the sensitivity analyses targeting this estimand is the same as the one reported for the primary efficacy variable (section 12.3.4).

Analysis

Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12 will be analyzed on the ITT set using an ANCOVA model including treatment group, US region and prior asthma therapy as fixed effects and baseline value (i.e. Week 0, FEV_1 pre-dose) as covariate.. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs at Week 12 will be estimated by the model. Superiority of CHF 1535 pMDI 800/24µg TDD will demonstrated by a statistically significant difference between treatments at Week 12 (defined as $p<0.05$) favoring CHF 1535 pMDI 800/24µg TDD.

12.3.6 Secondary efficacy variable

Analyses of secondary efficacy variables are planned to target the same estimand as described for the primary and key-secondary efficacy variables in sections 12.3.4 and 12.3.5 (i.e., with collected off-treatment data included in the analysis and used to impute possible missing off-treatment data) with:

- *Early discontinuation from the randomized study drug* managed with a treatment policy strategy with off-treatment data included in the analysis.

- *Early discontinuation from the study* managed with a hypothetical strategy with off-treatment data observed on all subjects used for the imputation of missing data after study discontinuation for both treatment arms **[1]**.

  Note: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms

- *Use of not allowed medications and other important protocol deviations* managed with a treatment policy strategy, with data used regardless of whether or not the intercurrent event occurs.

- *Wrong study drug intake* managed with a treatment policy strategy, with data used regardless of whether or not the intercurrent event occurs (i.e. considering the randomized study drug).

No sensitivity analysis will be performed for the secondary efficacy analyses.

Secondary efficacy variables will be analyzed as follows:

- ***Change from baseline in FEV_1 AUC_{0-12h} at Week 0*** will be analyzed with an ANCOVA model as described for the analysis of the primary and key-secondary efficacy variable.

- ***Change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 0*** will be analyzed with an ANCOVA model as described for the analysis of the primary and key-secondary efficacy variable.

- ***Change from baseline in trough FEV_1 at Week 12*** will be analyzed with an ANCOVA model as described for the analysis of the primary and key-secondary efficacy variable.

- ***Change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12*** will be analyzed with an ANCOVA model as described for the analysis of the primary and key-secondary efficacy variable.

- ***Change from baseline in average morning PEF over 12-week treatment period*** will be analyzed using an ANCOVA model including treatment group, US region and prior asthma therapy as fixed effects, and baseline value (i.e. average of the values collected during the run-in period) as covariate.

- ***Change from baseline in average evening PEF over 12-week treatment period*** will be analyzed with an ANCOVA model as described for morning PEF.

- ***Responder analysis (i.e. change from baseline ≥100 mL) for pre-dose morning FEV_1 at Week 4, 8 and 12*** will be analyzed separately at each visit with a logistic regression model including treatment, US region and prior asthma therapy as factors and baseline FEV_1 value (i.e. Week 0, FEV_1 pre-dose) as covariate.

- ***Responder analysis (i.e. change from baseline ≥100 mL) for trough FEV_1 at Week 12*** will be analyzed with a logistic regression model including treatment, US region and prior asthma therapy as factors and baseline FEV_1 value (i.e. Week 0, FEV_1 pre-dose) as covariate.

- ***Change from baseline in terms of ACQ-7 and ACQ-5 at Week 12*** will be analyzed with an ANCOVA model as described for the analysis of the primary and key-secondary efficacy variable, including baseline value (i.e. ACQ-7 or ACQ-5 at Week 0) as covariate.

- ***Change from baseline in percentage of rescue medication free days over 12-week treatment period*** will be analyzed with an ANCOVA model as described for morning PEF.

- ***Change from baseline in percentage of asthma symptom free days over 12-week treatment period*** will be analyzed with an ANCOVA model as described for morning PEF.

12.3.7 Safety variables

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

Adverse Events

Classification

- All adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake will be classified as treatment emergent adverse even (TEAE).

- Any adverse events started after the informed consent signature and before the first study drug intake will be classified as pre-treatment adverse events.

- Any adverse events started later than 1 week after the last dose of study drug will be considered as post-treatment adverse events.

Descriptive Analysis of TEAEs

- The number of subjects who experienced:

  - at least one TEAE
  - at least one drug related TEAE (i.e. ADR)
  - at least one serious TEAE
  - at least one non-serious TEAE
  - at least one serious related TEAE
  - at least one TEAE leading to study drug discontinuation
  - at least one TEAE leading to death

  will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events and incidence density [i.e. number of subjects with at least one event divided by the total person-time of exposure to study drug]) and by System Organ Class (SOC) and Preferred Term (PT) (number and percentage of subjects having at least one occurrence of that event and incidence density):

- Adverse events data will be also visualized with outputs including two-panels display with 1. proportions and incidence density and 2. plotted proportions.

- All adverse events will be listed.

- Pre-treatment adverse event and post-treatment adverse events will be listed only.

Analysis of TEAEs comparing treatment groups

- The number of subjects who experienced:

- at least one TEAE
- at least one drug related TEAE (i.e. ADR)
- at least one serious TEAE
- at least one non-serious TEAEs
- at least one serious related TEAE
- at least one TEAE leading to study drug discontinuation
- at least one TEAE leading to death

will be compared between treatment groups in terms of risk difference. The risk difference will be calculated considering the proportion of subjects with the selected event in the two treatment groups (i.e. number of subjects of the treatment group with the selected event / number of subjects of the treatment group). The 95% CIs for the risk difference will be calculated using the Newcombe hybrid score method **[29]**. Note: For each category defined above, the appropriateness of this analysis will be further evaluated in the SAP considering the actual number of events occurred in the overall safety set.

- The number of subjects who experienced:

  - at least one TEAE by SOC
  - at least one serious TEAE by SOC
  - at least one TEAE by PT
  - at least one serious TEAE by PT

  will be compared between treatment groups with the same methodology described in the previous bullet point.

- Adverse events data will be also visualized with outputs including two-panels display with 1. plotted proportions and 2. forest plot with risk differences (95% CI).

Class-related Adverse Events

Class-related Adverse Events will be grouped into the following medical concepts according to the TEAE SOC and PT. The final categorization of TEAEs into medical concepts will be defined by the study team during the blinded review of the data, reported in the SAP and finalized before the database lock.

Class related Adverse Events	
Medical concept 1	**Medical concept 2**
ICS class related AEs	Lower Respiratory Tract Infections (including pneumonia)
	Candidiasis
	Ocular effects
	Decreased bone density
	Adrenal suppression
LABA class related AEs	Cardiovascular effects

	Effects on glucose
	Effects on potassium
	Muscle spasms
	Tremor

Descriptive Analysis of class related TEAEs

- The number of subjects who experienced:

  - at least one class related TEAE
  - at least one class related ADR
  - at least one serious class related TEAE
  - at least one non-serious class related TEAE
  - at least one serious class related ADR
  - at least one class related TEAE leading to study drug discontinuation
  - at least one class related TEAE leading to death

  will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events and incidence density [i.e. number of subjects with at least one event divided by the total person-time of exposure to study drug]) and by medical concepts (number and percentage of subjects having at least one occurrence of that event and incidence density):

- Adverse events data will be also visualized with outputs including two-panels display with 1. proportions and incidence density and 2. plotted proportions.

Analysis of class-related TEAEs comparing treatment groups

- The number of subjects who experienced:

  - at least one class related TEAE
  - at least one class related ADR
  - at least one serious class related TEAE
  - at least one non-serious class related TEAE
  - at least one serious class related ADR
  - at least one class related TEAE leading to study drug discontinuation
  - at least one class related TEAE leading to death

  will be compared between treatment groups with the same methodology described for the TEAEs.

- The number of subjects who experienced:

  - at least one class related TEAE by medical concept 1
  - at least one serious class related TEAE by medical concept 1
  - at least one class related TEAE by medical concept 2
  - at least one serious class related TEAE by medical concept 2

will be compared between treatment groups with the same methodology described for the TEAEs.

- Adverse events data will be also visualized with outputs including two-panels display with 1. plotted proportions and 2. forest plot with risk differences (95% CI).

ECG
ECG parameters and change from baseline will be summarised by treatment group using descriptive statistics.

Vital signs
Vital signs and change from baseline will be summarised by treatment group using descriptive statistics.

Laboratory data
The laboratory values and the change from baseline for continuous laboratory will be summarised by treatment group using descriptive statistics.

12.3.8 Interim analysis

No interim analysis is planned.

13. INSTITUTIONAL REVIEW BOARD APPROVAL

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

The 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 IRB will be provided to the Chiesi.

The investigator should provide written reports to the IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the subjects.

14. REGULATORY REQUIREMENTS

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

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

15. INFORMED CONSENT

Written informed consent will be obtained from all subjects as per IRB guidelines before any study-related procedures are performed. Informed consent must be written in a language understandable to the subjects. It is the responsibility of the investigator to obtain written consent from each subject prior to any study related procedures taking place, by using the latest IRB approved version of the document.

The processing of subjects' data as well as subject inclusion in the study is based on subject's explicit consent as pointed out within the informed consent.

Adequate time shall be given to the subject to ask the Investigator or designee about any clarification needed and to consider his or her decision to participate to the trial.

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

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

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

Female subjects becoming pregnant during the study and partner of a subject participating in the study becoming pregnant will have to sign a specific informed consent form to provide permission to Chiesi to collect information about the pregnancy, its outcome and the birth and health of the newborn child.

In case of pregnancy during the study, if the subject's partner and his/her legal representative are unable to read, the specific informed consent for pregnancy follow-up will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the subject partner. The witness shall sign and date the informed consent document.

16. SOURCE DOCUMENTS/DATA

16.1 Recording of source data

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

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

16.2 Direct access to source document/data

The Investigator must permit trial-related monitoring, audits, Institutional Review Board(s) review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by Parexel who has been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/center before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data, provided that subject confidentiality is respected.

The purposes of these visits are:

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

Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

The sponsor will implement processes to manage quality and oversight throughout all stages and activities of the trial based on data and processes identified as critical for the subjects' rights and safety as well as data reliability and robustness.

Quality management will include tools, and procedures for data collection, monitoring and processing, as well as the collection of information essential to decision making.
The quality management system will use a risk-based approach as described in ICH E6 with:

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

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

19. INSURANCE AND INDEMNITY

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

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

The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.

The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, and addresses and telephone numbers (according to country specific guidelines). 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 and Institutional Review Board providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

At the end of the trial a summary of the clinical study report will be provided to all Institutional Review Boards and the FDA.

23. RECORD RETENTION

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

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

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

24. PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities and, if they fall under the Chiesi commitments on Clinical Trial Transparency, to make them available on www.chiesi.com website.

Chiesi furthermore reserves the right to use such data for industrial purposes.
In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately.

Negative as well as positive results should be published or otherwise made publicly available according to the relevant regulatory requirements.

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

A 12 week, randomized, double-blind, multicenter, active controlled, 2-arm parallel group study testing the superiority of CHF 1535 pMDI 800/24µg total daily dose (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) compared to CHF 718 pMDI 800µg total daily dose (extrafine beclomethasone dipropionate) in adults with asthma on medium or high-dose inhaled corticosteroid.

Product: CHF 1535

Pharmaceutical Form: Pressurized metered dose inhaler

Approval of Clinical Study Protocol by the Investigator:

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

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

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

The undersigned agrees that the trial will be carried out in conformity with the 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

APPENDIX 2 – RECOMMENDATIONS RELATED TO CONTRACEPTION AND PREGNANCY TESTING IN CLINICAL TRIALS

Birth control methods, which may be considered as highly effective

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

Such methods include:

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

[1]Vasectomized partner is highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[2]Sexual abstinence is considered as highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

[3]Methods with low user dependency.

Definition of women of childbearing potential and of fertile men

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

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