CLINICAL STUDY PROTOCOL

STUDY CODE No.: CLI-05993AB6-07

EUDRACT No.: 2022-000536-36

NCT05472662

A SINGLE-DOSE, RANDOMISED, DOUBLE-BLIND, CONTROLLED, 2-WAY CROSS-OVER STUDY TO ASSESS THE POTENTIAL FOR BRONCHOCONSTRICTION OF THE NEW PROPELLANT HFA-152a VERSUS THE MARKETED HFA-134A PROPELLANT, IN ADULT SUBJECTS WITH MILD ASTHMA.

Version No.: 2.0

Date: 30 August 2022

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

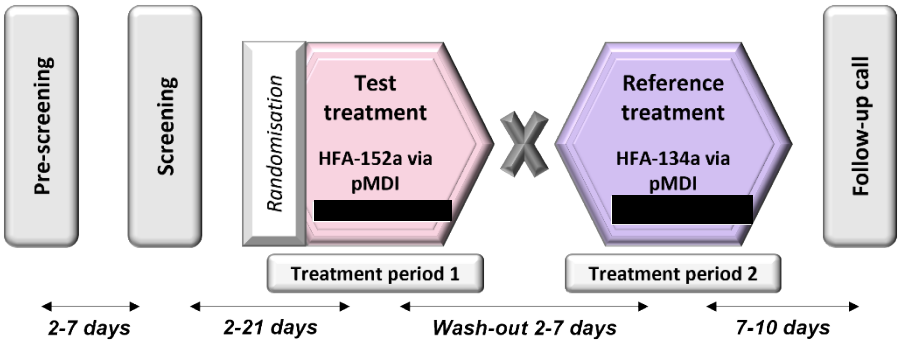
GENERAL INFORMATION

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 Clinical Research Physician Global Clinical Development Tel. [redacted] Mob. [redacted] e-mail: [redacted] Readily available in case of medical questions
COORDINATING INVESTIGATOR	Dave Singh Medicines Evaluation Unit The Langley Building Southmoor Road, Wythenshawe Manchester, M23 9QZ, United Kingdom Tel. +44 (0) 161 946 4052 Fax. +44 (0)161 946 1459 e-mail: dsingh@meu.org.uk
MONITORING CRO	[redacted]
CENTRAL SPIROMETRY LABORATORY	[redacted]

VERSION HISTORY

Version	Date	Change History
1.0	06 April 2022	First version
2.0	30 August 2022	Second Version The following non-substantial changes applied to the study protocol: - Numbering of the exclusion criteria have been adjusted; - Removal of the calibration for the centralized spirometer as the device is already calibrated; - Clarification that the spirometry for eligibility is performed locally; - Clarification of the re-screening procedure; - Removal of the rest period before ECG as not required; - Clarification regarding the ECG and Vital signs assessment pre-dose; - Clarification that the pregnancy test is applicable only for WOCBP; - Inclusion of the possibility to perform the ACQ-5 questionnaire at pre-screening visit.

PROTOCOL OUTLINE

Study title	A single-dose, randomised, double-blind, controlled, 2-way cross-over study to assess the potential for bronchoconstriction of the new propellant HFA-152a versus the marketed HFA-134a propellant, in adult subjects with mild asthma.
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	HFA-152a propellant via pressurised metered dose inhaler (pMDI).
Centres	Approximately 4 centres in the United Kingdom (UK).
Indication	Not Applicable
Study design	Single-dose, randomised, double-blind, controlled, 2-way cross-over study.  (HFA = Hydrofluoroalkane; pMDI = Pressurised metered dose inhaler) *The study design proposed in the figure is just an example of one of the possible sequences.*
Study phase	Phase IIa
Objectives	**Primary objective:** • To compare the potential for bronchoconstriction [redacted] of the HFA-152a propellant *versus* [redacted] the HFA-134a propellant when administered alone (not in combination with other active compounds). **Secondary objective:** • To evaluate the general safety and tolerability of the two different propellants. [redacted] • [redacted]
Treatment duration	Two treatment periods, each with a single-dose administration ([redacted]) of the study treatment, separated by a wash-out period of 2 to 7 days.
Test product dose/route/regimen	**Placebo HFA-152a propellant via pMDI:** • **Administration**: Single-dose administration [redacted]

Reference product dose/route/regimen	**Placebo HFA-134a propellant via pMDI:** • **Administration**: Single-dose administration [redacted].
Number of subjects	24 randomised subjects in order to have 20 evaluable subjects.
Study population	Male and female adult subjects with mild asthma (Step 1 of the Global Initiative for Asthma [GINA] 2021 guidelines).
Inclusion criteria	*Subjects must meet all of the following inclusion criteria at screening, to be eligible for enrolment into the study:* 1. Subject's **written informed consent** obtained prior to any study related procedure; 2. **Gender and age:** Male or female adults aged from 18 to 75 years old (inclusive); 3. **Diagnosis of asthma:** documented established diagnosis of mild asthma for at least 6 months according to Step 1 of the GINA 2021 guidelines; 4. **Lung function:** subjects with a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% of the predicted normal value and ≥1.5 L at screening and prior to randomisation, after appropriate wash-out from bronchodilators; *Note: In case of FEV_1 values <60% at screening, measures can be repeated once before randomisation in an unscheduled visit.* **5. Documented excessive variability in lung function (one or more of the following):** positive bronchodilator reversibility test**,** defined as an increase in FEV_1 of >12% and/or >200 mL from baseline within 30 minutes (min) after inhalation of 200-400 µg salbutamol (albuterol) according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) (ATS/ERS) standards; or positive bronchial challenge test, defined as a decrease from baseline in FEV_1 of ≥20% with standard doses of methacholine, or a decrease of ≥15% with standardised hyperventilation, hypertonic saline or mannitol challenge. Excessive variability in lung function must be documented within the past 2 years (*a copy of the original spirometry report must be included as source documentation*). In case evidence of documented excessive variability in lung function is not available, the test (bronchodilator reversibility or bronchial challenge) should be performed at screening; *In case the criterion of excessive variability in lung function is not met at screening, the test can be repeated once before randomisation in an unscheduled visit. A bronchial challenge test can be performed, if a bronchodilator reversibility test was unsuccessful and vice versa.* **6. Current asthma therapy:** as needed low-dose inhaled corticosteroids (ICS)-formoterol, as needed short-acting β2-agonists (SABA), or low-dose ICS whenever SABA is taken; taken not more than twice a week (2 events) in the 4 weeks prior to screening or in the 6 weeks prior to randomisation. For subjects using pMDI, spacer is allowed (as it improves delivery and reduces the risk of ICS local side-effects);

Low-dose ICS is defined by GINA 2021 (box 3-6) as follows:

Inhaled corticosteroid	Adults daily low dose
Beclometasone dipropionate (pMDI, standard particle, hydrofluoroalkane [HFA])	200-500 µg
Beclometasone dipropionate (dry powder inhaler [DPI] or pMDI, extrafine, HFA)	100-200 µg
Budesonide (DPI or pMDI, standard particle, HFA)	200-400 µg
Ciclesonide (pMDI, extrafine, HFA)	80-160 µg
Fluticasone furoate (DPI)	100 µg
Fluticasone propionate (DPI)	100-250 µg
Fluticasone propionate (pMDI, standard particle, HFA)	100-250 µg
Mometasone furoate (DPI)	See product information
Mometasone furoate (pMDI, standard particle, HFA)	200-400 µg

7. **Asthma control:** controlled or partly controlled based on an Asthma Control Questionnaire© (ACQ-5) score <1.5 at screening (or pre-screening) and prior to randomisation;
8. **Ability to use the inhalers:** subjects must have a cooperative attitude and the ability to be trained to use correctly the pMDI inhalers at screening;
9. **Ability to comply with the protocol:** subjects must have a cooperative attitude, the ability to perform the required outcome measurements, and the ability to understand the risks involved at screening and prior to randomisation;
10. **Female subjects** fulfilling one of the following criteria:
    a) **Women of non-childbearing potential** (WONCBP) defined as physiologically incapable of becoming pregnant (i.e. postmenopausal or permanently sterile, as per definitions given Section 4.1 of the Clinical Trials Facilitation and Coordination Group guidance). 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);
    b) **Women of childbearing potential** (WOCBP) fulfilling one of the following criteria:
        i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method preferably with low user dependency, from the signature of

	the informed consent form (ICF) and until the follow-up visit/call or; ii. WOCBP with non-fertile male partners (contraception is not required in this case). *Note: In case of hormonal contraception, an additional non-hormonal method (barrier method, preferably male condom) is required.* 11. **Male subjects** fulfilling one of the following criteria: a) Fertile male subjects with pregnant or non-pregnant WOCBP partners: they must be willing to use male condom from the signature of the ICF and until the follow-up visit/call, or; b) Non-fertile male subjects (contraception is not required in this case), or; c) Fertile male subjects with WONCBP partner (contraception is not required in this case). For the definition of WOCBP, fertile men and the list of highly effective birth control methods, refer to Section 4.1 of the Clinical Trials Facilitation and Coordination Group guidance. The following criteria will be re-checked at randomisation: #4, #6, #7, #9.
Exclusion criteria	*The presence of any of the following exclusion criteria will exclude a subject from study enrolment:* 1. **History of "at risk" asthma:** history of near fatal asthma, hospitalisation for asthma in intensive care unit which, in the judgement of the Investigator, may place the subject at undue risk; 2. **Recent exacerbation:** asthma exacerbation requiring systemic corticosteroids or emergency room admission or hospitalisation within 4 weeks prior to screening and prior to randomisation; 3. **Asthma requiring use of biologics:** asthma subjects treated with chronic systemic corticosteroids or anti-immunoglobulin E (IgE) or other monoclonal or polyclonal antibodies; 4. **Respiratory disorders other than asthma:** subjects with known respiratory disorders other than asthma. This can include, but is not limited to, diagnosis of chronic obstructive pulmonary disease (COPD) as defined by the current guidelines (e.g. Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease; 5. **Lung cancer or history of lung cancer:** subject with a diagnosis of lung cancer or a history of lung cancer; 6. **Lung resection:** subject with a history of lung volume resection; 7. **Lower respiratory tract infection:** subject with lower respiratory tract infection that required use of antibiotics within 4 weeks prior to screening and prior to randomisation; 8. **Documented coronavirus disease 2019 (COVID-19) diagnosis** within 2 weeks prior to screening, or associated

	complications/symptoms, which have not resolved within 2 weeks prior to screening; 9. **Smoking status:** current smoker, or ex-smoker with a smoking history of ≥10 pack-years (pack-years = the number of cigarette packs per day times the number of years). To be eligible for the study, ex-smokers with a smoking history of <10 pack-years must have stopped smoking for ≥1 year (≥6 months for e-cigarettes); 10. **Cancer or history of cancer (other than lung cancer):** subject with active cancer or a history of cancer with less than 5 years disease-free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g. basal cell carcinoma, in situ carcinoma of the cervix adequately treated) is acceptable; 11. **Cardiovascular diseases:** subjects who have known and clinically significant (CS) cardiovascular conditions such as, but not limited to, unstable or acute ischemic heart disease experienced within one year prior to study entry, class III/IV heart failure (according to the classification by the New York Heart Association [NYHA]), history of atrial fibrillation, uncontrolled hypertension, history of sustained or non-sustained cardiac arrhythmias diagnosed within 6 months prior to study entry and not controlled with therapy according to the Investigator's opinion; 12. **Electrocardiogram (ECG) criteria:** any CS abnormal 12-lead ECG that, in the Investigator's opinion, would affect safety evaluations or place the subject at risk; *Note: In case the criterion is not met at screening, the test can be repeated once before randomisation in an unscheduled visit* 13. **Central nervous system disorders:** subjects with a history of symptoms or significant neurological disease such as but not limited to transient ischemic attack, stroke, seizure disorder or behavioural disturbances, according to the Investigator's opinion; 14. **Other concurrent diseases:** subjects with historical or current evidence of uncontrolled concurrent disease such as, but not limited to, hyperthyroidism, diabetes mellitus or other endocrine disease, haematological disease, autoimmune disorders (e.g. rheumatoid arthritis), gastrointestinal disorders (e.g. poorly controlled peptic ulcer, gastroesophageal reflux disease), significant renal impairment or other disease or condition that might, in the judgement of the Investigator, place the subject at undue risk or potentially compromise the results or interpretations of the study; 15. **Laboratory abnormalities:** subjects with CS laboratory abnormalities indicating a significant or unstable concomitant disease that might, in the judgement of the Investigator, place the subject at undue risk or potentially compromise the results or interpretations of the study; *Note: In case the criterion is not met at screening, the test can be repeated once before randomisation in an unscheduled visit*

	16. **Alcohol/drug abuse:** subjects with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening; 17. **Participation to investigational trial:** subjects who have received any investigational drug within the 30 days (60 days for biologics) prior to screening, or a more appropriate time as determined by the Investigator (e.g. approximately 5 half-lives of the investigational drug whatever is longer); 18. **Hypersensitivity:** history of hypersensitivity to any of the study medications components or a history of other allergy that, in the opinion of the Investigator, contraindicates the subject's participation; 19. Subjects **mentally or legally incapacitated** or subjects accommodated in an establishment as a result of an official or judicial order; 20. Recent **eye surgery** or any condition where **raised intracranial pressure** (caused by forceful exhalation) would be harmful; 21. **For female subjects only:** pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive serum human chorionic gonadotropin laboratory test. *Note: Serum pregnancy test to be performed at screening, and urine pregnancy test to be performed prior to randomisation to women of childbearing potential.* The following criteria will be re-checked at randomisation: #2, #7, #21.
Study plan	A total of 4 ambulatory study visits and a follow-up call will be performed during the trial, as follows: • A **pre-screening visit** (Visit 0) will be carried out 2 to 7 days before screening, to explain the study, obtain the written informed consent and to instruct the subject on screening visit procedures (e.g. wash-out from medication and restrictions). • A **screening visit** (Visit 1) will be carried out 2 to 21 days before Treatment period 1 (TP1), to help establishing the eligibility of subjects for inclusion in the study. Eligible subjects will continue using their medications (including asthma medications) as needed, ensuring the required wash-out before TP1. *Note: Visit 0 and Visit 1 can be combined if the study restrictions and wash-out requirements are respected at Visit 0.* • The **investigational phase** comprises two one-day treatment periods, separated by a minimum of 2 days and up to 7 days of wash-out from the study treatment. Each treatment period consists of one ambulatory visit at the investigational site: o **Treatment period 1** (TP1) including randomisation, followed by a single-dose administration of one of the two study treatments (HFA-152a or HFA-134a; according to each subject's randomisation arm) and the assessment of its effects;

	○ **Treatment period 2** (TP2) single-dose administration of the other study treatment and the assessment of its effects. *Note: for each subject, the study treatment administrations (at TP1 and TP2) will start at approximately the same time of the day.* During the period of wash-out from the propellant (between TP1 and TP2), subjects will take the asthma medications that were taken before the study start, and will ensure the required wash-out period before the administration of the second treatment (at TP2). • A **follow-up call** (or visit, if deemed necessary by the Investigator) will be performed between 7 and 10 days from TP2. The expected duration of the clinical trial for the subjects is around 6 weeks. **Measures** The following safety measures will be evaluated at each treatment period (at TP1 and TP2): • Spirometry: Serial spirometries will be performed. Spirometry assessments (FEV_1 and peak expiratory flow [PEF]) will be performed at the following timepoints (starting at approximately the same time of the day for each subject): ○ Pre-dose: 45 min and 15 min before the first inhalation of the propellant (T0*) ○ Post-dose: 5 min, 15 min, 30 min, 1 hour (h), 1 h 30 min and 3 h after the last [redacted] inhalation of the propellant (T1**). • Vital Signs (duplicate systolic blood pressure [SBP] and diastolic blood pressure [DBP], assessed after 5 min in supine position) and single local 12-lead safety ECG (heart rate [HR], QRS interval [QRS], PR interval [PR] and QT interval corrected using Fridericia's formula [QTcF]) will be evaluated at the following timepoints at each treatment period: ○ Pre-dose: within 1 h before T0* (to be performed before the first pre-dose spirometry); ○ Post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1**. *T0 is the time of the first inhalation of the study treatment, and must be used to calculate the pre-dose timepoints. **T1 is the time of the last [redacted] inhalation of the study treatment, and must be used to calculate the post-dose timepoints. Subjects must perform the [redacted] inhalations within 12 min.
Most relevant allowed concomitant treatments	• Asthma treatment as needed (see Inclusion criterion #6 for the allowed treatments), with an appropriate wash-out before the spirometric assessments (the required wash-out periods are provided in the section below); • Systemic corticosteroid and/or nebulised treatment containing β2-agonists and/or corticosteroids, and/or antibiotics therapy for severe asthma exacerbation. In case of asthma exacerbation requiring treatment, the visit must be postponed (4 weeks after recovery and stopping the treatment);

	• Antihistamines (oral, ocular, intranasal) and intranasal corticosteroids for the treatment of allergy or rhinoconjunctivitis symptoms; • Allergen immunotherapy for the treatment of respiratory allergy, if already started before inclusion in the study; • Appropriate treatment for concomitant diseases, seasonal influenza and SARS-CoV-2 vaccination (1 week should elapse from vaccination to the treatment period) will be permitted if they do not interfere with the study treatment or the study evaluations, and if they are not listed among the "Non-permitted concomitant medications" (provided in the section below); • Hormonal contraceptives; • Hormonal replacement treatment for postmenopausal women.
Most relevant forbidden concomitant treatments	• Regular daily maintenance treatment with ICS, ICS/long-acting β2-agonist (LABA), leukotriene receptor antagonists (LTRA), or long-acting anti-muscarinic (LAMA), administered alone or in combination; • Systemic corticosteroids (see exceptions in the section above); • Monoclonal antibodies (e.g. anti-IgE or anti-immunoglobulin G [IgG] antibodies) or biological drugs used for the treatment of respiratory conditions, and for any other condition if impact on respiratory outcomes cannot be excluded; • Any medication that could interact with the asthma treatments administered as needed, according to Investigator's judgement. **Prior to any spirometric study assessments**, the following wash-out periods apply: • Inhaled/nebulised SABA: 6 h; • ICS (in combination with SABA): 24 h; • ICS-formoterol: 24 h.
Safety variables	Safety variable evaluating the potential for bronchoconstriction of each propellant: • Relative change from baseline* in FEV_1 at the 15 min post-dose timepoint. Safety variables completing the evaluation of the potential for bronchoconstriction of each propellant: • Relative change from baseline* in FEV_1 at all the other post-dose timepoints (5 min, 30 min, 1 h, 1 h 30 min and 3 h after T1); • Absolute change from baseline* in FEV_1 at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1); • Number and percentage of subjects with a relative change from baseline* in FEV_1 at each post-dose timepoint <-15%; • Number and percentage of subjects with a relative change from baseline* in FEV_1 at any post-dose timepoint <-15%;

	• Change from baseline* in FEV_1 area under the concentration-time curve from time zero to 3 hours (AUC_{0-3h}); • Relative change from baseline* in PEF at all post-dose timepoints; • Absolute change from baseline* in PEF at all post-dose timepoints; • Number and percentage of subjects with use of rescue medication in the 3 h after T1; • Mean use (puffs) of rescue medication in the 3 h after T1. * The baseline FEV_1 and PEF values are the mean of the 2 pre-dose assessments (i.e. performed 45 min and 15 min before T0). Safety variables evaluating the general safety and tolerability of the two propellants: • Adverse Events (AEs) and AEs of particular interest (bronchospasm, cough, dysphonia, hoarseness); • Vital signs (SBP and DBP); • 12-lead ECG parameters: HR, QTcF, PR and QRS.
[redacted]	• [redacted]
Sample size calculation	The sample size has been calculated to verify equivalence between the test treatment (HFA-152a) and the reference treatment (HFA-134a) for the relative change from baseline in FEV_1 at the 15 min post-dose timepoint, with equivalence defined as a difference between the two treatments within the ±10%. A total of 20 evaluable subjects will ensure a 95% power to provide a 95% confidence interval (CI) of the mean difference of the relative change from baseline in FEV_1 at 15 min post-dose within the above-mentioned equivalence limits (i.e. [-10%; +10%]) assuming a within-subject standard deviation (SD) of 8%. Estimating a non-evaluable rate of 16%, a total of 24 subjects will be randomised.
Statistical methods	**Safety variables** Variable assessing the **primary objective** of the study (potential for bronchoconstriction of each propellant): • The relative change from baseline in FEV_1 at the 15 min post-dose timepoint will be analysed using an analysis of covariance (ANCOVA) model, including treatment group, subject and period as fixed effects, and FEV_1 baseline (mean of the two measurements at 45 min and 15 min pre-dose in each treatment period) as a covariate. The adjusted mean relative change from baseline obtained with each treatment and the adjusted mean difference between HFA-152a and HFA-134a with their 95% CIs and p-values will be estimated by the model. Variables completing the evaluation of the potential for bronchoconstriction of each propellant: • The relative changes from baseline in FEV_1 at all the other post-dose timepoints (5 min and 30 min, 1 h, 1 h 30 min and 3 h after T1) will

	be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose; • The absolute changes from baseline in FEV_1 at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) will be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose; • The number and percentage of subjects with a relative change from baseline in FEV_1 at each post-dose timepoint (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) and at any post-dose timepoint <-15% will be summarised for each treatment; • The change from baseline in FEV_1 AUC_{0-3h} will be summarised using descriptive statistics; • The relative and absolute changes from baseline in PEF at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) will be summarised for each treatment, using descriptive statistics; • The number and percentage of subjects with use of rescue medication in the 3 h post-dose will be summarised for each treatment; • The mean use (puffs) of rescue medication in the 3 h post-dose will be summarised for each treatment, using descriptive statistics. Variables assessing the **secondary objective** of the study (general safety and tolerability of the two different propellants): • The number of subjects who experienced at least one treatment-emergent adverse event (TEAE), adverse drug reaction (ADR), serious TEAE, serious ADR, TEAE leading to study discontinuation, and TEAE leading to death will be summarised for each treatment. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events) and by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Specific summary tables will be provided for the AEs of particular interest. All AEs will be listed. Pre-treatment AEs will be listed only; • The mean absolute values and mean changes from baseline in each 12-lead ECG parameter (HR, QRS, PR, and QTcF) will summarised for each treatment, using descriptive statistics. For QTcF, the following categories will also be analysed for each study treatment, by means of descriptive statistics: o For male subjects: QTcF interval >450 ms, >480 ms and >500 ms; o For female subjects: QTcF interval >470 ms and >500 ms; o For both male and female subjects: Change from baseline >30 ms and >60 ms. The analysis will be presented at each and any post-dose timepoint. All data will be listed.

	• Vital signs (SBP and DBP) mean absolute values at each pre-dose and post-dose timepoint and change from baseline will be summarised for each study treatment, by means of descriptive statistics. All vital signs will be listed. [redacted] • [redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5	Asthma Control Questionnaire©
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area Under the Concentration-Time Curve
AUC_{0-3h}	Area Under the Concentration-Time Curve from Time Zero to 3 Hours
BTPS	Body Temperature and Pressure Saturation
Ca	Calcium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
Cl	Chloride Electrolyte
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CS	Clinically Significant
DALY	Disability Adjusted Life Year
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 Second
FSH	Follicle-Stimulating Hormone
FVC	Forced Vital Capacity
γ-GT	Gamma-Glutamyl Transpeptidase
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice

GOLD	Global Initiative for Chronic Obstructive Lung Disease
GWP	Global Warming Potential
h	Hour
Hb	Haemoglobin
Hct	Haematocrit
HFA	Hydrofluoroalkane
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroid
ICSR	Individual Case Study Report
IgE	Immunoglobulin E
IgG	Immunoglobulin G
K	Potassium
LABA	Long-Acting β2-Agonist
LAMA	Long-acting anti-muscarinic
LTRA	Leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
min	Minute
Na	Sodium
No.	Number
NYHA	New York Heart Association
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PLT	Platelet
pMDI	Pressurised Metered Dose Inhaler
PP	Per-Protocol
PR	PR Interval
PT	Preferred Term
QRS	QRS Interval
QTcF	QT Interval Corrected Using Fridericia's Formula
RBC	Red Blood Cell
R&D	Research and Development
SABA	Short-Acting β2-Agonists
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
T0	Time of First Inhalation of the Study treatment
T1	Time of Last Inhalation of the Study treatment
TEAE	Treatment-Emergent Adverse Event
TP	Treatment Period
UK	United Kingdom
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
WONCBP	Women of Non-Childbearing Potential

CONTENT

1. INTRODUCTION

1.1 Background Information

Chronic respiratory diseases

Chronic respiratory diseases are among the leading causes of morbidity and mortality worldwide [1]. Among these, common chronic respiratory diseases include chronic obstructive pulmonary disease (COPD) with a global prevalence of 3.9% in 2017, and asthma with a global prevalence of 3.6% in 2017 [2].

COPD is an inflammatory disease of the airways characterised by persistent respiratory symptoms (e.g. cough, breathlessness, excess sputum production) and airway limitation, with a progressive decline in lung function. COPD has seen a recent increase in prevalence, and represents a substantial and increasing economic and social burden [3], [4].

Asthma is a serious, sometimes fatal disease affecting people of all ages. Asthma is characterised by chronic airway inflammation, respiratory symptoms (e.g. wheeze, shortness of breath, cough, chest tightness), and variable expiratory flow limitation. The number of disability adjusted life years (DALYs) lost due to asthma amounts to 26.2 million, representing about 1% of DALYs lost due to any disease, and is comparable to those lost due to diabetes or Alzheimer's disease [5].

COPD and asthma treatments help dilate major air passages, improve shortness of breath and quality of life, and prevent disease escalation [2].

Use of propellants in inhaler devices

Pressurised metered dose inhalers (pMDIs) represent one of the most commonly used devices for inhaled drug delivery in the treatment of COPD and asthma. The propellant, a liquified gas, provides the force required to generate the aerosol cloud.

More than 630 million pMDIs are estimated to be manufactured annually worldwide using up-to 10,000 tons of propellants [6]. The adoption of the Montreal Protocol in 1989 initiated the development of the hydrofluoroalkane (HFA) propellants currently used in pMDIs (HFA-134a and HFA-227ea), which replaced ozone depleting substances [7]. However, there is growing concern regarding the global warming potential (GWP) of many hydrofluorocarbons, including HFA-134a. This led to the introduction of regulations in many parts of the world that place controls on the usage of these substances. Accordingly, manufacturers of aerosolised products have been looking for potential alternatives to these HFAs in both industrial and medical application sectors. The transition towards a low GWP propellant is also in line with Chiesi's sustainability commitment.

A potential alternative to fluorocarbons with high ozone depleting potential and/or GWP in the pMDI application is HFA-152a (1,1 difluoroethane), designated by the United States Environmental Protection Agency as an acceptable replacement in certain applications, including as an aerosol propellant. HFA-152a has an environmental GWP one order of magnitude lower than HFA-134a or HFA-227ea, and a carbon footprint that is 90% reduced compared to an equivalent HFA-134a pMDI [8], [9], [10].

The toxicological properties of HFA-152a are well known in industrial applications and indicate a relatively low risk profile. However, additional data proving its safety for use as an inhaled drug are required before it can be approved as a novel excipient.

In non-clinical studies, the dose limiting effects of HFA-152a are associated with concentrations far greater than that delivered by a pMDI formulation, and the effects appear to resolve quickly following cessation of exposure [11]. HFA-152a essentially caused no other toxicities.

The pharmacokinetics (PK) of HFA-152a has been studied in healthy volunteers exposed to 0, 200 or 1000 ppm of HFA-152a for 2 hours (h) during light exercise in an exposure chamber [12]. Symptom ratings and changes in inflammatory markers revealed no exposure-related effects.

This study aims to compare the potential for bronchoconstriction, the general safety and the tolerability of the new HFA-152a propellant administered alone (not in combination with active compounds) to those of the marketed HFA-134a propellant administered alone (not in combination with active compounds).

1.2 Study Rationale

This clinical study has been designed to investigate the potential for bronchoconstriction of the new HFA-152a propellant, in comparison with the marketed HFA-134a propellant.

This study was conceived following concerns from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) about the lack of data on the potential of the new HFA-152a propellant to cause bronchoconstriction in healthy subjects or asthma patients with hyperreactive airways. In fact, safety studies performed during the clinical development programme assessed the safety of the HFA-152a propellant when used for the administration of asthma treatments via pMDI. According to the CHMP, these studies were not capable of assessing the potential for bronchoconstriction of the new propellant, which may be clinically relevant but not detected, given that the HFA-152a propellant was administered in combination with bronchodilating agents.

As this residual risk was deemed not adequately covered by the clinical development program, and as it cannot be predicted by *in-vitro* data, this appropriately designed clinical trial will adequately address this residual risk.

This randomised, double-blind, controlled, 2-way cross-over study will be conducted in male and female subjects with mild asthma (Step 1 of the Global Initiative for Asthma [GINA] 2021 guidelines). Each subject will be administered a single-dose [redacted] of each of the two following treatments, according to an order pre-specified by the randomisation list:

- **Test treatment**: placebo HFA-152a propellant via pMDI;
- **Reference treatment**: placebo HFA-134a propellant via pMDI.

Subjects will be asked to wash-out from their asthma treatments before the administration of the study treatment and before the spirometry assessments, in order to suppress the bronchodilating effect of the asthma treatments. The following wash-out periods will apply:

- Inhaled/nebulised short-acting β2-agonists (SABA): 6 h;
- Inhaled corticosteroids (ICS) (in combination with SABA): 24 h;
- ICS-formoterol: 24 h.

The selected treatment dose ([redacted]) corresponds to the maximum total daily dose of propellant allowed for administration with the Clenil pMDI device.

Subjects will perform [redacted] inhalations, with a minimum of 40 seconds between two consecutive inhalations (see Section 6.2.3.1). Subjects will be given up to 12 minutes (min) to perform the [redacted] inhalations, which will give them enough time to breath during treatment administration. To harmonise subjects' pre-dose and post-dose timepoints, the time of the first inhalation (T0) will be used for the calculation of the pre-dose timepoints, and the time of the last [redacted] inhalation (T1) will be used for the calculation of the post-dose timepoints.

The potential for bronchoconstriction of the propellants will be evaluated throughout spirometry assessments, specifically by the change in the values of the forced expiratory volume in 1 second (FEV_1) from baseline (pre-dose timepoints) to the post-dose timepoints. The spirometry schedule was designed to accurately characterise lung function. In particular, frequent sampling was planned around the predicted maximum effect of the propellant to inform about any post-dose bronchoconstriction.

1.3 Risk/Benefit Assessment

The toxicological properties of HFA-152a are well known in industrial applications and indicate a relatively low risk profile. Short-term inhalation of HFA-152a with light exercise did not have exposure effects in human subjects [12]. A comprehensive package of toxicology studies was conducted for the HFA-152a propellant alone, in conformance with the International Council for Harmonisation (ICH) M3(R2) requirements; results were described in the Investigator's Brochure for CHF 5993 pMDI HFA-152a. The pre-clinical studies did not elicit any findings that could not be attributed to the expected pharmacological action of the test items, and were similar to those previously reported with the formulation of CHF 5993 HFA-134a propellant. It was therefore considered that the change of the propellant to HFA-152a had not produced any new effects. Of particular note, the results of bacterial mutagenicity, *in-vitro* micronucleus, and *in-vivo* micronucleus assays did not show HFA-152a to be mutagenic or genotoxic. However, the results of the embryofoetal toxicology study in rats were not available at the time of the study. Thus, considering the recommendations related to contraception and pregnancy testing in clinical trials from the Clinical Trial Facilitation and Coordination Group [13], the worst-case scenario was considered, i.e. "Demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy" and contraception measures were taken accordingly.

Subjects will be closely monitored throughout the study and evaluated by the Investigator. Therefore, the overall risk/benefit assessment for the proposed study is considered to be acceptable.

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

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare the potential for bronchoconstriction [redacted] of the HFA-152a propellant *versus* [redacted] the HFA-134a propellant when administered alone (not in combination with other active compounds).

2.2 Secondary Objective

- To evaluate the general safety and tolerability of the two different propellants.

[redacted]

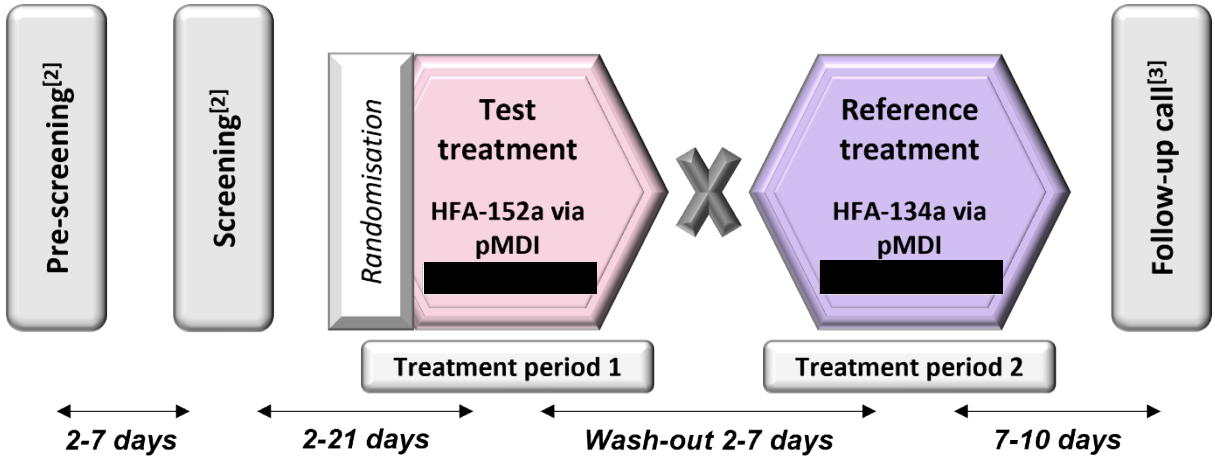
3. STUDY DESIGN

This is a Phase IIa, multicentre (approximately 4 centres in the United Kingdom [UK]), single-dose, randomised, double-blind, controlled, 2-way cross-over study to evaluate the potential for bronchoconstriction of the new HFA-152a propellant (single dose, [redacted]) *versus* the marketed HFA-134a propellant (single dose, [redacted]) in adult subjects with mild asthma (Step 1 of the GINA 2021 guidelines).

A double-blind design was chosen for this study to minimise the risk of bias in the study outcomes.

The study design is shown in Figure 1.

Figure 1. Study Design[1]



HFA = Hydrofluoroalkane; pMDI = Pressurised metered dose inhaler.

[1] The study design proposed in the figure is just an example of one of the possible sequences.

[2] The pre-screening and screening visits can be combined in one visit if the study restrictions and wash-out requirements are respected at pre-screening.

[3] A follow-up visit can be performed, if deemed necessary by the Investigator.

Study treatment

Approximately 24 adult subjects with mild asthma (Step 1 of the GINA 2021 guidelines) will be randomised to receive a single dose ([redacted]) of each of the following treatments, in an order determined by the randomisation list:

- **HFA-152a propellant** (also referred to as "test treatment"): placebo HFA-152a propellant alone (not in combination with other active compounds) via pMDI;
- **HFA-134a propellant** (also referred to as "reference treatment"): placebo HFA-134a propellant alone (not in combination with other active compounds) via pMDI.

Study visits

A total of 4 ambulatory study visits and a follow-up call will be performed during the study, as follows:

- A **pre-screening visit** (Visit 0) will be carried out 2 to 7 days before screening, to explain the study, obtain the written informed consent and to instruct the subject on screening visit procedures (e.g. wash-out from medication and restrictions).
- A **screening visit** (Visit 1) will be carried out 2 to 21 days before Treatment period 1 (TP1), to help establishing the eligibility of a subject for inclusion in the study (including routine haematology and blood chemistry, medical history, physical examination, 12-lead electrocardiogram [ECG], lung function, vital signs and training for the use of inhalers). Eligible subjects will continue using their medications (including asthma medications) as needed, ensuring the required wash-out before TP1.

  Note: Visit 0 and Visit 1 can be combined if the study restrictions and wash-out requirements are respected at Visit 0.

- The **investigational phase** comprises two one-day treatment periods, separated by a minimum of 2 days and up to 7 days of wash-out from the study treatment. Each treatment period consists of one ambulatory visit at the investigational centre:
    - **Treatment period 1** (TP1) including randomisation, followed by a single-dose administration of one of the study treatments (HFA-152a or HFA-134a; according to each subject's randomisation arm) and the assessment of its effects;
    - **Treatment period 2** (TP2) single-dose administration of the other study treatment and the assessment of its effects.

      Note: For each subject, the study treatment administrations (at TP1 and TP2) will start at approximately the same time of the day.

  During the period of wash-out from the propellant (between TP1 and TP2), subjects will take the asthma medications that were taken before the study start and will ensure the required wash-out period before the administration of the second propellant (at TP2).
- A **follow-up call** (or visit, if deemed necessary by the Investigator) will be performed between 7 and 10 days from TP2.

A subject's participation in the study will end with the follow-up call (or visit, if deemed necessary by the Investigator).

The end of the trial is defined as the last follow-up contact of the last subject in the trial.

The expected duration of the clinical trial for the subjects is around 6 weeks

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

Subjects attending the hospital clinics/study centres will be recruited. Adult male and female subjects with mild asthma (Step 1 of the GINA 2021 guidelines), aged from 18 to 75 years old (inclusive) will be selected.

A total of 24 subjects will be randomised in accordance with the inclusion and exclusion criteria, in order to reach a total of 20 completed and evaluable subjects, considering a non-evaluable rate of approximately 16%.

4.2 Inclusion Criteria

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

1. **Subject's written informed consent** obtained prior to any study related procedure;
2. **Gender and age:** Male or female adults aged from 18 to 75 years old (inclusive);
3. **Diagnosis of asthma:** documented established diagnosis of mild asthma for at least 6 months according to Step 1 of the GINA 2021 guidelines;

4. **Lung function:** subjects with a pre-bronchodilator FEV_1 ≥60% of the predicted normal value and ≥1.5 L at screening and prior to randomisation, after appropriate wash-out from bronchodilators;

   Note: In case of FEV_1 values <60% at screening, measures can be repeated once before randomisation in an unscheduled visit.
5. **Documented excessive variability in lung function (one or more of the following):** positive bronchodilator reversibility test, defined as an increase in FEV_1 of >12% and/or >200 mL from baseline within 30 min after inhalation of 200-400 µg salbutamol (albuterol) according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) (ATS/ERS) standards; or positive bronchial challenge test, defined as a decrease from baseline in FEV_1 of ≥20% with standard doses of methacholine, or a decrease of ≥15% with standardised hyperventilation, hypertonic saline or mannitol challenge. Excessive variability in lung function must be documented within the past 2 years (*a copy of the original spirometry report must be included as source documentation*). In case evidence of documented excessive variability in lung function is not available, the test (bronchodilator reversibility or bronchial challenge) should be performed at screening;

   In case the criterion of excessive variability in lung function is not met at screening, the test can be repeated once before randomisation in an unscheduled visit. A bronchial challenge test can be performed, if a bronchodilator reversibility test was unsuccessful and vice versa.
6. **Current asthma therapy:** as needed low-dose ICS-formoterol, as needed SABA, or low-dose ICS whenever SABA is taken; taken not more than twice a week (2 events) in the 4 weeks prior to screening or in the 6 weeks prior to randomisation. For subjects using pMDI, spacer is allowed (as it improves delivery and reduces the risk of ICS local side-effects);

   Low-dose ICS is defined by GINA 2021 (box 3-6) as follows:

Inhaled corticosteroid	Adults daily low dose
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500 µg
Beclometasone dipropionate (DPI or pMDI, extrafine, HFA)	100-200 µg
Budesonide (DPI or pMDI, standard particle, HFA)	200-400 µg
Ciclesonide (pMDI, extrafine, HFA)	80-160 µg
Fluticasone furoate (DPI)	100 µg
Fluticasone propionate (DPI)	100-250 µg
Fluticasone propionate (pMDI, standard particle, HFA)	100-250 µg
Mometasone furoate (DPI)	See product information
Mometasone furoate (pMDI, standard particle, HFA)	200-400 µg

7. **Asthma control:** controlled or partly controlled based on an Asthma Control Questionnaire© (ACQ-5) score <1.5 at screening (or pre-screening) and prior to randomisation;
8. **Ability to use the inhalers:** subjects must have a cooperative attitude and the ability to be trained to use correctly the pMDI inhalers at screening;
9. **Ability to comply with the protocol:** subjects must have a cooperative attitude, the ability to perform the required outcome measurements, and the ability to understand the risks involved at screening and prior to randomisation;
10. **Female subjects** fulfilling one of the following criteria:
    a) **Women of non-childbearing potential** (WONCBP) defined as physiologically incapable of becoming pregnant (i.e. postmenopausal or permanently sterile, as per definitions given in Appendix 3 or Section 4.1 of the Clinical Trials Facilitation and Coordination Group guidance). 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 (FSH) levels (according to local laboratory ranges);
    b) **Women of childbearing potential** (WOCBP) fulfilling one of the following criteria:
        i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method preferably with low user dependency, from the signature of the informed consent form (ICF) and until the follow-up call/visit or;
        ii. WOCBP with non-fertile male partners (contraception is not required in this case).

    Note: In case of hormonal contraception, an additional non-hormonal method (barrier method, preferably male condom) is required.
11. **Male subjects** fulfilling one of the following criteria:
    a) Fertile male subjects with pregnant or non-pregnant WOCBP partners: they must be willing to use male condom from the signature of the ICF and until the follow-up call/visit, or;
    b) Non-fertile male subjects (contraception is not required in this case), or;
    c) Fertile male subjects with WONCBP partner (contraception is not required in this case).

    For the definition of WOCBP, fertile men and the list of highly effective birth control methods, refer to Appendix 3 (or Section 4.1 of the Clinical Trials Facilitation and Coordination Group guidance).

The following criteria will be re-checked at randomisation: #4, #6, #7, #9.

4.3 Exclusion Criteria

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

1. **History of "at risk" asthma:** history of near fatal asthma, hospitalisation for asthma in intensive care unit which, in the judgement of the Investigator, may place the subject at undue risk;
2. **Recent exacerbation:** asthma exacerbation requiring systemic corticosteroids or emergency room admission or hospitalisation within 4 weeks prior to screening and prior to randomisation;

3. **Asthma requiring use of biologics:** asthma subjects treated with chronic systemic corticosteroids or anti-immunoglobulin E (IgE) or other monoclonal or polyclonal antibodies;
4. **Respiratory disorders other than asthma:** subjects with known respiratory disorders other than asthma. This can include, but is not limited to, diagnosis of COPD as defined by the current guidelines (e.g. Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
5. **Lung cancer or history of lung cancer:** subject with a diagnosis of lung cancer or a history of lung cancer;
6. **Lung resection:** subject with a history of lung volume resection;
7. **Lower respiratory tract infection:** subject with lower respiratory tract infection that required use of antibiotics within 4 weeks prior to screening and prior to randomisation;
8. **Documented coronavirus disease 2019 (COVID-19) diagnosis** within 2 weeks prior to screening, or associated complications/symptoms which have not resolved within 2 weeks prior to screening;
9. **Smoking status:** current smoker, or ex-smoker with a smoking history of ≥10 pack-years (packyears = the number of cigarette packs per day times the number of years).

   To be eligible for the study, ex-smokers with a smoking history of <10 pack-years must have stopped smoking for ≥1 year (≥6 months for e-cigarettes);
10. **Cancer or history of cancer (other than lung cancer):** subject with active cancer or a history of cancer with less than 5 years disease-free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g. basal cell carcinoma, in situ carcinoma of the cervix adequately treated) is acceptable;
11. **Cardiovascular diseases:** subjects who have known and clinically significant (CS) cardiovascular conditions such as, but not limited to, unstable or acute ischemic heart disease experienced within one year prior to study entry, class III/IV heart failure (according to the classification by the New York Heart Association [NYHA]), history of atrial fibrillation, uncontrolled hypertension, history of sustained or non-sustained cardiac arrhythmias diagnosed within 6 months prior to study entry and not controlled with therapy according to the Investigator's opinion;
12. **ECG criteria:** any CS abnormal 12-lead ECG that, in the Investigator's opinion, would affect safety evaluations or place the subject at risk;

    Note: In case the criterion is not met at screening, the test can be repeated once before randomisation in an unscheduled visit
13. **Central nervous system disorders:** subjects with a history of symptoms or significant neurological disease such as, but not limited to transient ischemic attack, stroke, seizure disorder or behavioural disturbances, according to the Investigator's opinion;
14. **Other concurrent diseases:** subjects with historical or current evidence of uncontrolled concurrent disease such as, but not limited to, hyperthyroidism, diabetes mellitus or other endocrine disease, haematological disease, autoimmune disorders (e.g. rheumatoid arthritis), gastrointestinal disorders (e.g. poorly controlled peptic ulcer, gastroesophageal reflux disease), significant renal impairment or other disease or condition that might, in

the judgement of the Investigator, place the subject at undue risk or potentially compromise the results or interpretations of the study;

15. **Laboratory abnormalities:** subjects with CS laboratory abnormalities indicating a significant or unstable concomitant disease that might, in the judgement of the Investigator, place the subject at undue risk or potentially compromise the results or interpretations of the study;

    Note: In case the criterion is not met at screening, the test can be repeated once before randomisation in an unscheduled visit
16. **Alcohol/drug abuse:** subjects with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening;
17. **Participation to investigational trial:** subjects who have received any investigational drug within the 30 days (60 days for biologics) prior to screening, or a more appropriate time as determined by the Investigator (e.g. approximately 5 half-lives of the investigational drug whatever is longer);
18. **Hypersensitivity:** history of hypersensitivity to any of the study medications components or a history of other allergy that, in the opinion of the Investigator, contraindicates the subject's participation;
19. Subjects **mentally or legally incapacitated** or subjects accommodated in an establishment as a result of an official or judicial order;
20. Recent **eye surgery** or any condition where **raised intracranial pressure** (caused by forceful exhalation) would be harmful;
21. **For female subjects only:** pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive serum human chorionic gonadotropin laboratory test.

    Note: Serum pregnancy test to be performed at screening, and urine pregnancy test to be performed prior to randomisation to women of childbearing potential.

The following criteria will be re-checked at randomisation: #2, #7, #21.

4.4 Subject Withdrawals

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

- An adverse event (AE) occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the study. In this case, the appropriate measures will be taken;
- Occurrence of pregnancy;
- The subject is lost to follow-up;
- The subject withdraws consent;
- The subject's safety is affected by violation of inclusion or exclusion criteria or use of non-permitted concomitant medication;
- The subject is unwilling or unable to adhere to the study requirements, i.e. non-compliance;

- The Sponsor or the regulatory authorities or the Ethics Committee(s) (EC), for any reason, terminates the entire study, or terminates the study for this investigational site or this particular subject.

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

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

In the event of early termination, if the subject has not withdrawn his/her consent, an Early Termination visit should be scheduled to perform the following safety assessments, as described in Table 1 and in section 7.1.6:

Note: No follow-up call will be performed after the Early Termination visit.

In case of early withdrawal, the Investigator will have to fill in the "Study Termination" page in the electronic case report form (eCRF), reporting the main reason for withdrawal.

If a subject is withdrawn/drops-out of the study after randomisation, the subject's study number and corresponding study treatments should not be reassigned to another subject.

Individuals who do not meet the criteria for participation in the study (screen failures) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5. CONCOMITANT MEDICATIONS

5.1 Permitted Concomitant Medications

1. Asthma treatment as needed, (see Inclusion criterion # 6, Section 4.2 for the allowed treatments), with an appropriate wash-out before the spirometric assessments (see Section 5.2 for the wash-out periods, and Table 1 for the timepoints of spirometry assessments);
2. Systemic corticosteroid and/or nebulised treatment containing β2-agonists and/or corticosteroids, and/or antibiotics therapy for severe asthma exacerbation. In case of asthma exacerbation requiring treatment, the visit must be postponed (4 weeks after recovery and stopping the treatment);
3. Antihistamines (oral, ocular, intranasal) and intranasal corticosteroids for the treatment of allergy or rhinoconjunctivitis symptoms;
4. Allergen immunotherapy for the treatment of respiratory allergy, if already started before inclusion in the study;
5. Appropriate treatment for concomitant diseases, seasonal influenza and SARS-CoV-2 vaccination (1 week should elapse from vaccination to the treatment period) will be permitted if they do not interfere with the study treatment or the study evaluations, and if they are not listed among the "Non-permitted concomitant medications" (see Section 5.2 below);
6. Hormonal contraceptives;
7. Hormonal replacement treatment for postmenopausal women.

5.2 Non-Permitted Concomitant Medications

1. Regular daily maintenance treatment with ICS, ICS/long-acting β2-agonists (LABA), leukotriene receptor antagonists (LTRA), or long-acting anti-muscarinic (LAMA), administered alone or in combination;
2. Systemic corticosteroids (see exceptions in Section 5.1 above);
3. Monoclonal antibodies (e.g. anti-IgE or anti-immunoglobulin G [IgG] antibodies) or biological drugs used for the treatment of respiratory conditions, and for any other condition if impact on respiratory outcomes cannot be excluded;
4. Any medication that could interact with the asthma treatments administered as needed, according to Investigator's judgement.

Prior to any spirometric study assessments, the following wash-out periods must be respected:

- Inhaled/nebulised SABA: 6 h;
- ICS (in combination with SABA): 24 h;
- ICS-formoterol: 24 h.

6. TREATMENTS

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

Any rescue medications used during the study will be purchased locally, by the investigational centres. The investigational centres will then be reimbursed by the Sponsor.

6.1 Appearance and Content

Test treatment: placebo HFA-152a propellant pMDI, presented as:

- Active ingredients: none;
- Excipients: HFA-152a propellant, [redacted];
- Presentation: each canister contains 120 doses;
- Appearance: aluminium canister + grey dose counter actuator.

Reference treatment and training kit: CHF1535 placebo HFA-134a propellant pMDI, presented as:

- Active ingredients: none;
- Excipients: HFA-134a propellant, [redacted];
- Presentation: each canister contains 120 doses;
- Appearance: aluminium canister + grey dose counter actuator.

6.2 Dosage and Administration

6.2.1 Selection of Doses in the Study

The dose of test treatment and reference treatments administered in this study [redacted] corresponds to the maximum total daily dose of propellant allowed for

administration with the Clenil pMDI device at 200 mg/inhalation [redacted].

6.2.2 Dosage

Subjects will receive a single dose [redacted] of each of the following products:

- **Test treatment**: placebo HFA-152a propellant pMDI;
- **Reference treatment:** placebo HFA-134a propellant pMDI.

The administration of the study treatment will occur using two pMDI canisters and two actuators (one for each of the two treatment periods) for each subject. For each treatment period, each subject will take [redacted] (single-dose administration) from one of the pMDIs.

6.2.2.1 Concomitant Medication for Asthma

Subjects will preserve their current asthma therapy, which may include low-dose ICS-formoterol, SABA or low-dose ICS whenever SABA is taken (low-dose SABA is defined in Inclusion criterion #6, Section 4.2). Subjects can take their asthma therapy as needed, but no more than twice a week in the 4 weeks prior to screening and randomisation or between TP1 and TP2.

Prior to the spirometry assessments (see Table 1), subjects will be asked to wash-out from inhaled/nebulised SABA (6 h), ICS (in combination with SABA; 24 h) and ICS-formoterol (24 h).

6.2.2.2 Investigational Phase

According to the allocation based on the randomisation list, eligible subjects will be administered one single dose [redacted] of each of the following study treatments in a cross-over design:

- **Test treatment**: placebo HFA-152a propellant via pMDI;
- **Reference treatment**: placebo HFA-134a propellant via pMDI.

6.2.3 Administration

Treatment administration will take place at the investigational sites, during TP1 and TP2 (see Table 1). The two treatment administrations will be separated by a 2- to 7-day wash-out period, and must be performed at approximately the same time of the day. The treatment will be administered according to the instructions for use (provided in a separate document) and under the supervision of the Investigator or his/her designee.

Before study treatment administration, restrictions related to treatment administration and study assessments will be checked (see Section 7.2), and the pre-dose assessments will be performed (see Table 1).

6.2.3.1 Administration with Pressurised Metered Dose Inhaler

The study treatment will be administered by inhalation using the pMDI device, according to the following instructions:

- **Position**: subjects must be in an upright position;
- **Duration of treatment administration**: the [redacted] inhalations should be performed within 12 min;

- **T0** is defined as the moment when the first inhalation takes place, and will be used to calculate the pre-dose timepoints;
- **T1** is defined as the moment when the last [redacted] inhalation takes place, and will be used to calculate the post-dose timepoints.

Subjects performing the [redacted] inhalations in more than 12 min will be considered as protocol deviations;

- **Time between two consecutive inhalations**: two consecutive inhalations must be separated by 40 seconds minimum, during which subjects must:
  - Hold their breath for the 10 seconds following the inhalation;
  - Wait approximately 30 seconds before taking the next inhalation.

If a subject coughs during the [redacted] inhalations, the Investigator must wait until the cough is resolved and then resume treatment administration. If the cough is severe and does not resolve spontaneously, the subject must stop treatment intake in the interest of his/her safety. The appropriate measures should be taken.

An incorrect inhalation is defined as "a significant reduction of delivered dose that reaches the lungs based on Investigator or designee judgement". Even if this is the case, no extra inhalations (i.e. more than the [redacted] inhalations required) will be administered.

Treatment administration will be recorded in the eCRF by the Investigator or designee. Any issues occurring during the inhalations as evaluated by the Investigator or designee will be reported in the eCRF.

6.2.4 Subject Training

6.2.4.1 Training with Pressurised Metered Dose Inhaler Placebo

At screening, the correct use of the pMDI device will be explained to the subjects according to the instructions for use (provided in separate documents).

Subjects will be trained by using a placebo HFA-134a inhaler, which is identical from a functional point of view to the device used for the administration of the study treatment (see Section 6.3.1). Therefore, the training will be done with the pMDI device, with the inhalation repeated four times or as many times as necessary until the subject is properly trained.

The training kits will be kept at the investigational site by the Investigator and will not be dispensed to the subjects. The training kit will be assigned to the subject at screening.

The subject will not be included in the study if the training is not completed successfully. Training evidence will be recorded in the eCRF by the Investigator or designee.

6.3 Packaging

All investigational products will be prepared in accordance with Good Manufacturing Practices (GMP) as required by the current GCP. Chiesi will supply the material described in the following sections.

6.3.1 Training Kit

The training kits will be supplied to the investigational sites. Each kit will consist of one box containing placebo HFA-134a propellant pMDI. The training kits will be used at screening only (see Table 1) and must be stored as specified in Section 6.8.

Training kits will be supplied in the following packages:

- **Primary packaging**: one labelled canister containing CHF1535 placebo HFA-134a propellant pMDI, plus one labelled dose counter actuator;
- **Secondary packaging** (subject box): labelled box containing one labelled canister and one labelled dose counter actuator.

6.3.2 Study Treatment Kits

Treatment kits will be supplied to the Investigator as subject boxes containing two period boxes, each containing one pMDI device. For each treatment kit, "Reserve" kits will be prepared in case of drop-out or device malfunctioning; they will be exactly the same as the treatment kit, but will be identified with a specific printed label "Reserve" (this will allow an easier management of the reserve kits, avoiding any mistakes by the Investigator).

Treatment kits will be supplied in the following packages:

- **Primary packaging**: one labelled canister containing placebo HFA-152a propellant or placebo HFA-134a propellant for inhalation, plus one labelled dose counter actuator;
- **Secondary packaging** (period box): labelled box containing one canister and one actuator to be used at one treatment period;
- **Tertiary packaging** (subject box): one labelled box containing two period boxes.

6.4 Labelling

All labelling of primary/secondary/tertiary for training, treatment and reserve kits will be in English and will be compliant with Annex 13 of Volume 4 in the GMP [14] and according to local law and regulatory requirements.

6.5 Treatment Allocation

A balanced block randomisation list will be prepared using a computerised system. Each subject will be assigned to one of the two possible treatment sequences arranged in a 2x2 William design.

Each subject will be identified by a unique five-digit code (two digits specific to the investigational centre and three digits specific to each subject [XXYYY]) assigned at screening.

At randomisation (TP1), each eligible subject will be assigned the lowest randomisation number available at the investigational centre according to a pre-established randomisation list:

- Subjects who do not meet inclusion and/or exclusion criteria at screening or prior to randomisation will not be eligible to enter the study. They will be considered as "screen failure subjects";
- Subjects who fully meet inclusion and/or exclusion criteria at screening or before randomisation will be eligible to enter the study;
- Subjects who prematurely terminate the study will be considered as "drop-out subjects". These subjects cannot be screened again.

Note: If a subject is withdrawn or discontinued from the study after randomisation, the subject code and randomisation number will not be reassigned to another subject.

6.6 Treatment Code

The randomisation list will be provided to the labelling facility but will not be available to subjects, Investigators, monitors or employees of the investigational centre involved in the management of the trial before unblinding of the data, unless in case of emergency.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomisation list.

An individual disclosure envelope will be supplied to the Investigator for each subject and will contain the medication assignment for that subject.

The Investigator will keep the treatment code envelopes in a locked, secure storage facility. A treatment code envelope can only be opened in an emergency situation, where the Investigator considers it essential to know what treatment the subject was taking. The Sponsor and the clinical monitor shall be notified promptly if a treatment code envelope is opened.

The Investigator shall provide a signed explanation in the eCRF, explaining the reasons for which the treatment code was opened.

All treatment code envelopes, either unopened or opened, will be returned to the contract research organisation (CRO) upon termination of the study or will be destroyed at site after a full reconciliation.

A second set of code break envelopes will be supplied to the Chiesi Global Pharmacovigilance, to be opened before reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR) to the Regulatory Authorities and the EC.

Subjects will receive a card on which the investigator name, the site address and the phone numbers of the investigational site are reported. These can be contacted in case of emergency.

6.7 Treatment Compliance

For each subject, the number of correct and incorrect inhalations taken in each treatment period will be recorded in the eCRF.

6.8 Drug Storage

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

The following storage conditions must be respected:

- **Training kit** (placebo HFA-134a propellant pMDI): before the use, kits must be stored in a refrigerator at a temperature between 2°C and 8°C;
- **Treatment kits (and Reserve kits)** (placebo HFA-152a propellant pMDI and placebo HFA-134a propellant pMDI): the subject box must be stored in a refrigerator at a temperature between 2˚C and 8˚C. At study visits, only the period box must be removed from the refrigerator on the day of usage, while the subject box must be maintained in the refrigerator until the next treatment administration period.

  Note: the product administered to the subjects should be at room temperature (not cold).

Any deviation from the required storage conditions must be reported promptly, and the Sponsor will assess whether the affected kits can still be used.

6.9 Drug Accountability

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

An inventory will be maintained by the Investigator or Pharmacist (or other designated individual), to include a signed account of all the study treatments received 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 treatments, supplied, used or unused, will be destroyed by the Investigator, directly at the investigational site. In this case, a destruction certificate must be requested from the investigational site and must be filed, both at the investigational site and by the Sponsor. Destruction will not occur until authorised by Chiesi.

6.10 Provision of Additional Care

At study completion or early termination, it is under the Investigator's responsibility to recommend subjects to continue using their usual asthma therapy or to refer them to the General Practitioner.

7. STUDY PLAN

7.1 Study Schedule

The study will be conducted as described in Section 3 and Table 1.

Current UK national laws and site-specific recommendations for the prevention of the coronavirus disease 2019 (COVID-19) pandemic will be strictly adhered to. These include subjects' monitoring for COVID-19 symptoms and the adherence to the appropriate measures to control the transmission of the virus in the hospital setting [15].The study plan and scheduled tests are summarised in Table 1.

Table 1. Schedule of Assessments

	Pre-screening visit (Visit 0)[1]	Screening visit (Visit 1)[1]	Investigational Phase		Follow-up call[2]	Early Termination visit
			TP1	TP2		
Date	2-7 days before screening	2-21 days before TP1	Day 1	2-7 days after TP1	7-10 days after TP2	
Informed consent	X					
Randomisation			X			
Ambulatory visit	X	X	X	X	X[2]	X
Treatment intake						
Treatment administration[3]			X	X		
Training						
Placebo training		X				
Subject Health Evaluation						
Inclusion/Exclusion criteria		X	X			
Medical history, concomitant diseases and previous medications		X				
Demographic data		X				
Height and weight		X				
Physical examination		X	X	X		X
ACQ-5	X*	X	X			
Adverse events recording		X	X	X	X	X
Restrictions		X	X	X		
Concomitant medications	X	X	X	X	X	X
Safety assessment in blood						
Clinical chemistry		X				
Haematology		X				
FSH or pregnancy test		X				
Generic assessments in urine						
Urinalysis		X				
Pregnancy test			X	X		X
Cardiac assessments[4]						
12-lead ECG		X	X	X		X
Vital signs - Blood pressure		X	X	X		X
Pulmonary Assessments						
Bronchodilator reversibility or bronchial challenge test[5]		X				
Lung function[6]		X	X	X		
Other Assessments						
[redacted]			X	X		

ACQ-5 = Asthma Control Questionnaire©; DBP = Diastolic blood pressure; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in 1 second; FSH = Follicle-stimulating hormone; h = hour; min = minute; PEF = Peak expiratory flow;

SBP = Systolic blood pressure; T0 = Time of the first inhalation of the study treatment; T1 = Time of the last [redacted] inhalation of the study treatment; TP = Treatment period.

[1] Visit 0 and Visit 1 can be combined in a single visit if the study restrictions and wash-out requirements are respected at Visit 0.

[2] A follow-up visit can be performed, if deemed necessary by the Investigator. A follow-up call (or visit) is not required in case of early withdrawal.

[3] A single dose [redacted] will be administered. Subjects must perform the [redacted] inhalations within 12 min. For each subject, the two treatment administrations (at TP1 and TP2) must start at approximately the same time of the day.

[4] Cardiac assessments will be performed as follows:

- Vital signs: duplicate SBP and DBP will be evaluated after 5 min in supine position and before the spirometry assessments and blood tests, at screening (Visit 1), and at the following timepoints on TP1 and TP2:
  - Pre-dose: within 1 h before T0;
  - Post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1.
- Local 12-lead safety ECG: a triplicate ECG will be performed to assess eligibility at screening (Visit 1), before the spirometry assessments and blood tests and a single ECG will be evaluated on TP1 and TP2, at the same timepoints as the vital signs.

[5] The bronchodilator reversibility or bronchial challenge test will be performed to assess a subject's eligibility, in case documented evidence of excessive variability in lung function is not available or in case the documentation is older than 2 years. In case the criterion of excessive lung function variability is not met at screening, the test (bronchodilator reversibility or bronchial challenge) can be repeated once before randomisation (performed at TP1).

[6] Lung function assessments (spirometry [FEV_1 and PEF]) will be performed as follows:

- Screening (Visit 1): single spirometry to assess the subject's eligibility;
- TP1 and TP2:
  - Pre-dose: 45 min and 15 min before T0;
  - Post-dose: 5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1.

[redacted]

* ACQ-5 questionnaire can be administered at pre-screening or at screening visit.

7.1.1 Pre-screening (Visit 0)

A pre-screening visit will be carried out 2 to 7 days before screening, in order to fully explain the study to the subject by the Investigator or his/her designee. The Investigator or his/her designee should provide subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
If subject agrees to participate, the signed and dated informed consent must be obtained before any study related procedures.

The following procedures will take place at pre-screening:

- Concomitant medications: any medication taken regularly at the time of the ICF signature will be recorded.
- The subject will be informed about the study restrictions and the wash outs to be respected prior to screening visit.
- ACQ5 questionnaire can be performed at this visit or at the following one.

If the study restrictions and wash-out requirements (see Section 7.2) are respected at Visit 0, Visit 0 and Visit 1 can be combined in one visit.

7.1.2 Screening (Visit 1)

A screening visit will be carried out in order to confirm a subject's eligibility for the study.

The visit will take place 2 to 7 days after the pre-screening visit, and 2 to 21 days before TP1 (i.e. randomisation and administration of the first study treatment). In case the restrictions are not respected the visit can be rescheduled once

The following procedures will take place at screening:

- Demographic data collection: demographic data including age, gender and race will be recorded;
- Physical examination: a comprehensive physical examination will be performed;
- Medical/surgical history, concomitant diseases and previous medications: subject's medical and surgical history, as well as concomitant diseases (i.e. diseases pre-existing at the time of the ICF signature) will be recorded. Any medications taken in the month preceding the pre-screening visit will be recorded;
- Study restrictions: study restriction criteria will be checked according to Section 7.2;
- Concomitant medications: any medication taken regularly at the time of this visit will be recorded;
- AE recording: the occurrence of any AEs since the pre-screening visit (ICF signature) will be checked, AEs will be recorded in the eCRF, along with the related concomitant medications.
  In cases where CS abnormalities are revealed during the physical examination or screening procedures, these will be recorded in the subject's eCRF as medical history, unless the start date/time is after the ICF signature date/time and it is not due to a pre-existing condition. In the latter case, it will be recorded in the eCRF as an AE;
- Local safety ECG: triplicate 12-lead ECG will be used to measure heart rate (HR), QRS interval (QRS), PR interval (PR) and QT interval corrected using Fridericia's formula (QTcF). The assessment will be performed according to Section 7.3.3;
- Blood pressure: SBP and DBP will be measured according to Section 7.3.2;
- Blood test: blood samples will be collected for safety evaluations (clinical chemistry and haematology), after the 12-lead ECG and blood pressure assessments, according to Section 7.3.4;
- FSH or pregnancy tests: blood samples will be collected from female subjects for FSH (for not childbearing potential women) and serum pregnancy tests (for childbearing potential women), according to Section 7.3.4;
- Urine test: urine samples will be collected for urinalysis, according to Section 7.3.5;
- Height and weight: will be recorded;
- Lung function: single spirometry will be performed (after the ECG records and the assessment of the Vital signs) according to Section 7.3.1;
- Bronchodilator reversibility or bronchial challenge test: will be performed in case documented evidence of excessive variability in lung function is not provided, or in case the documentation is older than 2 years;
- Asthma Control Questionnaire© (ACQ-5): asthma control level will be assessed using the ACQ-5 questionnaire, according to Section 7.3.6.1;
- Training: subjects will receive training on the proper use of the inhaler with a pMDI placebo, according to Section 6.2.4.1;
- Subject selection: inclusion/exclusion criteria will be checked (see Section 4.2 and Section 4.3, respectively).

7.1.3 Treatment Period 1 (TP1)

TP1 is the first visit of the investigational phase and takes place 2 to 21 days after screening.

The following procedures and assessments will take place during this ambulatory visit:

- Subject selection: inclusion and exclusion criteria will be re-checked (see Section 4.2 and Section 4.3, respectively). Subjects not fulfilling the inclusion criteria or meeting any of the exclusion criteria will be recorded as screening failures;
- Study restrictions: study restriction criteria will be checked, according to Section 7.2;
- ACQ-5: asthma control level will be re-assessed using the ACQ-5, according to Section 7.3.6.1;
- Randomisation: subjects will be randomised according to Section 6.5.
- Concomitant medications: concomitant medications taken by the subject since the screening visit and during TP1 will be checked and recorded;
- AE recording: the status of AEs ongoing at the screening visit will be checked and updated in the eCRF when applicable. Any new AE occurring since the previous visit will be checked and recorded in the eCRF, as well as the related concomitant medications. Any AE occurring during the study visit must also be monitored and recorded in the eCRF;
- Pregnancy test: urine samples will be collected from childbearing potential female subjects for pregnancy testing, according to Section 7.3.5;
- Physical examination: a full physical examination will be performed, and any new CS abnormality revealed since the screening visit will be recorded as an AE;
- 12-lead ECG: a single ECG will be recorded to assess ECG parameters (HR, PR, QRS and QTcF), according to Section 7.3.3. The assessment will be performed in pre-dose: within 1 h before T0; and in post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1;
- Blood pressure: SBP and DBP will be measured after 5 min in supine position, as described in Section 7.3.2. The assessment will be performed before or after the 12-lead ECG assessment, in pre-dose: within 1 h before T0; and in post-dose: 45 min, 1 h 45 min and 2 h 45 mins after T1;
- Lung function: serial spirometries will be performed according to Section 7.3.1. Spirometry assessments will be collected in pre-dose: 45 min and 15 min before T0; and in post-dose: 5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1;
- Study treatment administration: single-dose ([redacted]) treatment administration according to Section 6.2.3, based on each subject's randomisation arm;
- [redacted]

TP1 will be followed by a 2- to 7-day wash-out period from the propellant.

7.1.4 Treatment Period 2 (TP2)

TP2 is the second visit of the investigational phase. It takes place 2 to 7 days after TP1.

The following procedures and assessments will take place during this ambulatory visit:

- Study restrictions: study restriction criteria will be checked, according to Section 7.2;
- Concomitant medications: concomitant medications taken by the subject since TP1 and during TP2 will be checked and recorded;
- AE recording: the status of AEs ongoing at TP1 will be checked and updated in the eCRF when applicable. Any new AE occurring since the previous visit will be checked and recorded in the eCRF, as well as the related concomitant medications. Any AE occurring during the study visit must also be monitored and recorded in the eCRF;
- Pregnancy test: urine samples will be collected from childbearing potential female subjects for pregnancy testing, according to Section 7.3.5;
- Physical examination: a full physical examination will be performed and any new CS abnormality revealed since TP1 will be recorded as an AE;
- 12-lead ECG: a single ECG will be recorded to assess ECG parameters (HR, PR, QRS and QTcF), according to Section 7.3.3. The assessment will be performed in pre-dose: within 1 h before T0; and in post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1;
- Blood pressure: SBP and DBP will be measured after 5 min in supine position, as described in Section 7.3.2. The assessment will be performed before or after the 12-lead ECG assessment, in pre-dose: within 1 h before T0; and in post-dose: 45 min, 1 h 45 min and 2 h 45 min after T1;
- Lung function: serial spirometries will be performed according to Section 7.3.1. For each subject, the assessments will start at approximately the same time of the day as at TP1. Spirometry assessments will be collected in pre-dose: 45 min and 15 min before T0; and in post-dose: 5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1;
- Study treatment administration: single-dose ([redacted]) administration of the second propellant (based on each subject's randomisation arm, following a cross-over design), according to Section 6.2.3. For each subject, treatment administration will start at approximately the same time of the day as at TP1;
- [redacted]

A follow-up call (or visit, if deemed necessary by the Investigator) will be performed 7 to 10 days after TP2.

7.1.5 Follow-up Call

A follow-up call (or visit, if deemed necessary by the Investigator) will be performed 7 to 10 days after TP2, for a safety follow-up.

The following assessments will be performed during this call:

- AE recording: the status of any AEs ongoing at TP2 will be checked and updated in the eCRF, along with the related concomitant medications. Any new AE occurring since TP2 will be checked and recorded in the eCRF, as well as the related concomitant medications;

- Concomitant medications: concomitant medications taken by the subject since TP2 will be checked and recorded.

7.1.6 Early Termination Visit

In the case of early discontinuation, an Early Termination visit will be performed in order to assess the subject's safety.

The following assessments will be performed:

- Concomitant medications: concomitant medications taken by the subject since the last study visit and during the Early Termination visit will be checked and recorded;
- AE recording: the status of any AEs ongoing at the previous visit will be checked and updated in the eCRF, along with the related concomitant medications. Any new AE occurring since the previous visit will be checked and recorded in the eCRF, as well as the related concomitant medications. Any AE occurring during the study visit must also be monitored and recorded in the eCRF;
- Pregnancy test: urine samples will be collected from childbearing potential female subjects for pregnancy testing, according to Section 7.3.5;
- Physical examination: a full physical examination will be performed and any new CS abnormality revealed since the previous visit will be recorded as an AE;
- 12-lead ECG: a single ECG will be recorded to assess ECG parameters (HR, PR, QRS and QTcF), according to Section 7.3.3;
- Blood pressure: SBP and DBP will be measured after 5 min in supine position, as described in Section 7.3.2.

7.2 Study Restrictions and Standardisation

The following restrictions should be applied and should be checked at each visit at the investigational site:

- No smoking or intake of substances containing nicotine: up to the end of the investigational phase (for the eligibility of ex-smokers, see Exclusion criterion #9, Section 4.3);
- Current asthma therapy: low-dose ICS-formoterol, SABA, or low-dose ICS (whenever SABA is taken) should be taken as needed, but not more than twice a week (2 events) in the 4 weeks prior to screening or in the 6 weeks prior to randomisation, and between the treatment periods.

  A definition of low-dose ICS is provided in Inclusion criterion #6, Section 4.2.

The following restrictions should be applied before spirometry assessments (i.e. before screening, TP1 and TP2) [16]:

- Wash-out period:
  - Inhaled/nebulised SABA: 6 h;
  - ICS (in combination with SABA): 24 h;
  - ICS-formoterol: 24 h.

- No intake of intoxicants such as alcohol, caffeine/xanthine containing beverages or food (coffee, tea, chocolate, cola) within 8 h. Decaffeinated products are permitted;
- No strenuous activities within 1 h;
- Avoiding wearing clothes that substantially restrict full chest and abdominal expansion.

7.3 Investigations

7.3.1 Lung Function Assessment

Lung function will be evaluated at the timepoints specified in Table 1.

Centralised spirometry will be used for the assessment performed during TP1 and TP2 for this trial while the local spirometer is used for the eligibility lung function assessments. The specific procedures for centralised spirometry will be provided to the Investigator by the centralised spirometry company.

Calibration of the local spirometer must be performed at each screening visit prior to spirometry manoeuvres and the reports must be kept at the investigational sites and be accessible to the clinical research associate and the Sponsor. Personnel using the spirometer will be adequately trained to follow the commonly accepted procedures. The predicted values will be calculated according to the formulas reported by Quanjer et al. [17].

The same brand and model of spirometer will be provided by the centralised spirometry company for all measurements during TP1 and TP2and adjusted for the ATS/ERS standards [16]. The predicted values will be calculated according to the formulas reported by Quanjer et al. [17]. Personnel using the spirometer will be adequately trained to follow the commonly accepted procedures. The spirometer provided by the centralized spirometry company do not need the calibration procedure.

Subjects should be at rest before each lung function test. All measurements are to be made with the subjects in sitting or standing position (for the same subject, the position must be consistent throughout the study) with the nose clipped. Values will be corrected for body temperature and pressure saturation (BTPS) conditions [18].

At each timepoint specified in Table 1, subjects will perform three attempts for the measurement of FEV_1 and peak expiratory flow (PEF). In order to be considered as technically satisfactory attempts, measurements should be free from cough and false-start. The highest value (in L) of FEV_1 and PEF from three technically satisfactory attempts (not necessarily coming from the same curve) will be recorded. The two largest FEV_1 measurements must be within 150 mL of each other (or 100 mL, if the forced vital capacity [FVC] value is ≤1L). If the difference is larger, additional spirometry assessments (up to 8) will be made until the above criterion is met. If, at the end, the tests are not within 150 mL, the highest value of FEV_1 and PEF will be recorded and used for eligibility or continuation criteria.

In case lung function measurements obtained at screening were below the expected value, (see Inclusion criterion #4 in Section 4.2), the subject will be asked to return to the investigational site once before randomisation to repeat the test. If, at that time, FEV_1 ≥60% of the predicted normal value and ≥1.5 L, the subject can be included in the study. Otherwise, the subject will be discharged and recorded as a screening failure.

If a subject shows a progressive reduction in FEV_1 with each subsequent blow, with cumulative drop above 15% of the starting value, the test procedure may be terminated in the interest of the subject's safety. During the 3 h post-dose serial spirometry, the use of rescue medication should

be as limited as possible and rescue medication intake must be under medical control. The serial spirometries can be discontinued after the intake of rescue medication, based on the Investigator's judgement. In this case and if deemed necessary, a safety spirometry can be performed by the site. Details on intake of rescue medication during the treatment periods will be recorded in the eCRF.

The restrictions to be applied before spirometry assessments are described in Section 7.2, [16].

In case any of the restrictions is not respected, the study visit should be rescheduled once, to be performed within the allowed time window between the previous and the current visit.

For the post-dose lung function assessments, the following time deviations from the theoretical post-T1 times will be allowed (actual time to be recorded is the time when the first lung function manoeuvre starts):

- 5 min and 15 min post-dose: ± 2 min;
- 30 min and 1 h post-dose: ± 5 min;
- 1h 30 min and 3 h post-dose: ± 15 min.

Longer time deviations will be evaluated on a case-by-case basis during the Blind Data Review meeting.

7.3.2 Vital Signs (blood pressure)

SBP and DBP will be evaluated at the timepoints specified in Table 1.

All measurements will be made in duplicate within a 5-min interval. Subjects should be resting in a quiet, supervised setting with minimal stimulation (e.g. no television, loud music, computer games) and lay in a supine position for 5 min (whenever possible) before each measurement. Blood pressure measurements must be performed before the lung function assessments and the blood tests, as specified in Table 1.

Acceptable time deviations from theoretical post-dose timepoints are ± 10 min.

7.3.3 Electrocardiogram Assessments

ECG assessments will be performed at the timepoints specified in Table 1.

Subjects should be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games). ECG recordings will be performed either before or after blood pressure measurements, and must be performed before the lung function assessments and the blood tests, as specified in Table 1.

At screening, a triplicate 12-lead digitised ECG recording will be performed. The values of all ECG parameters and the overall ECG evaluation will be reported in the eCRF. The average of the triplicate recordings will be used to assess the subjects' eligibility (see Exclusion criterion #12 in Section 4.3). In case abnormal CS ECG results are obtained at screening, the subject will be asked to return to the investigational site once before randomisation to repeat the ECG measurement. If, at that time, ECG interpretation is not considered abnormal clinically significant, the subject can be included in the study. Otherwise, the subject will be discharged and recorded as a screening failure.

During the Investigational Phase (TP1 and TP2) and the Early Termination visit, single ECGs will be performed for safety assessments. Acceptable time deviations from theoretical post-dose timepoints are ± 10 min.

7.3.4 Blood Sample Collection

Blood samples will be collected at screening, as specified in Table 1.

Laboratory tests can be repeated, if deemed necessary by the Investigator, to assess the subject's safety or to confirm his/her eligibility.

Approximately 20 mL of blood will be collected according to the local procedures, to assess the following parameters:

- Routine blood haematology: red blood cells (RBC) count, white blood cells (WBC) count and differential count (absolute value and %), total haemoglobin (Hb), haematocrit (Hct), platelets (PLT) count;
- Serum clinical chemistry: creatinine, urea, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, total cholesterol, triglycerides, sodium (Na), potassium (K), calcium (Ca), chloride electrolytes (Cl);
- Serum pregnancy test (in case of WOCBP) and FSH test (in case of post-menopausal women, if the FSH value is deemed necessary by the investigator).

In case clinically significant abnormal laboratory values are obtained at screening that could indicate a temporary condition (see Exclusion criteria #13, #14 and #15 in Section 4.3 for details), the subject will be asked to return to the centre once before randomisation, to repeat the test. If, at that time, no clinically significative abnormalities are observed, the subject can be included in the study. Otherwise, the subject will be discharged and recorded as a screening failure.

Blood collection and sample preparation will be performed according to the procedures provided by the local laboratory, which will be in charge of transmitting the results to the Investigator for evaluation. Only CS abnormal values of laboratory results will be entered in the eCRF by the Investigator, and AEs/serious adverse events (SAEs) will be reported. The normal ranges will be provided by the local laboratory and included in the eCRF

7.3.5 Urine Sample Collection

A urine sample will be collected from all subjects at screening for the urinalysis (quantitative [proteins] and qualitative [ketones, microscopic examination of the sediment]).

During the investigational phase (TP1 and TP2) and the Early Termination visit (if relevant), urine will be collected from childbearing potential female subjects for laboratory pregnancy tests.

7.3.6 Administered Questionnaires

7.3.6.1 Asthma Control Questionnaire

The five-item ACQ-5 questionnaire will be used for the evaluation of each subject's asthma control level [19]. The questionnaire will be administered at pre-screening or screening to assess eligibility, and at TP1 (before randomisation) to confirm eligibility.

The ACQ-5 is a self-administered questionnaire which includes five questions on asthma symptoms experienced during the past week. Subjects must score each of the questions on a scale of 0 to 6, where 0 represents excellent control of the symptom and 6 represents extremely poor control. The overall score of the ACQ-5 is the mean of the five responses [19].

Subjects must have an overall score of <1.5 to be eligible for inclusion in this study (see Inclusion criterion #7, Section 4.2).

[redacted]

8. EFFICACY ASSESSMENTS

No efficacy assessments are planned in this study.

9. SAFETY ASSESSMENTS

The **primary objective** of this study is to compare the potential for bronchoconstriction [redacted] of the HFA-152a propellant *versus* [redacted] the HFA-134a propellant when administered alone (not in combination with other active compounds).

The potential for bronchoconstriction will be assessed through centralised spirometry assessments performed at TP1 and TP2, as described in Section 7.3.1. At each treatment period, FEV_1 and PEF will be assessed in pre-dose: 45 min and 15 min before T0; and in post-dose: 5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1.

The following safety variable will be considered for the evaluation of the potential for bronchoconstriction of each propellant:

- Relative change from baseline* in FEV_1 at the 15 min post-dose timepoint.

In addition, the following safety variables will be considered to complete the evaluation of the potential for bronchoconstriction of each propellant:

- Relative change from baseline* in FEV_1 at all the other post-dose timepoints (5 min and 30 min, 1 h, 1 h 30 min and 3 h after T1);
- Absolute change from baseline* in FEV_1 at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1);
- Number and percentage of subjects with a relative change from baseline* in FEV_1 at each post-dose timepoint <-15%;
- Number and percentage of subjects with a relative change from baseline* in FEV_1 at any post-dose timepoint <-15%;
- Change from baseline* in FEV_1 area under the concentration-time curve from time zero to 3 hours (AUC_{0-3h});
- Relative change from baseline* in PEF at all post-dose timepoints;
- Absolute change from baseline* in PEF at all post-dose timepoints;
- Number and percentage of subjects with use of rescue medication in the 3 h after T1;
- Mean use (puffs) of rescue medication in the 3 h after T1.

  * The baseline FEV_1 and PEF values are the mean of the 2 pre-dose assessments (i.e. performed 45 min and 15 min before T0).

The **secondary objective** of the study is to evaluate the general safety and tolerability of the two propellants.

The general safety of the propellants will be assessed at TP1 and TP2, throughout local safety ECGs (as described in Section 7.3.3), vital signs (as described in Section 7.3.2), and recording of AEs and concomitant medications.

The following safety variables will be considered for the evaluation of the general safety and tolerability of each propellant:

- AEs and AEs of particular interest (bronchospasm, cough, dysphonia, hoarseness);
- Vital signs (SBP and DBP);
- 12-lead ECG parameters: HR, QTcF, PR and QRS.

[redacted]

- [redacted]

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** (AE) 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 AE 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 (ADR)** is an "untoward and unintended response to an investigational medicinal product related to any dose administered".

Within this trial the causality of an AE has to be considered with regards to the placebo and its excipients.

All AEs 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 ADR** 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 AE but an outcome. It is the cause of death that should be regarded as the AE. 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 AE and "fatal" as its reason for being serious;

- **Is life-threatening**

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

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

  Hospitalisation 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. Hospitalisation for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g. life-threatening; persistent or significant disability or incapacity; medically significant);

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

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

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

- **Is a medically significant AE**

  This criterion allows for any situations in which important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the subject's health or may require intervention to prevent one of the above outcomes. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

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

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

A **Non-Serious Adverse Event/Non-Serious ADR** is an AE or ADR that does not meet the criteria listed above for an SAE/serious ADR.

10.2 Expectedness

Since no active ingredient will be included in the study treatment but only pMDI containing placebo propellant and excipients will be administered, there is no reference document for the assessment of the expectedness of AEs in this study. All AEs assessed as related to the study treatments and/or their excipients will be considered as unexpected AEs for safety reporting purposes.

10.3 Intensity of Adverse Event

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

- **Mild:** the event causes a minor discomfort or does not interfere with the daily activities 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 patient 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 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 treatment intake and event's onset;
- Dechallenge (did the event abate after stopping the study treatment?);
- Rechallenge (did the event reappear after reintroduction of the study treatment?);
- Medical history;
- Study treatment(s);
- Mechanism of action of the study treatment;
- 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 Treatment Due to an Adverse Event

- Dose not changed;
- Treatment permanently withdrawn;
- Unknown;
- Not applicable.

10.6 Other Actions Taken

- Specific therapy/medication;
- Concomitant procedure.

10.7 Outcome

Each AE 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 AEs occurring during the course of the study must be documented in the AE page of the eCRF. Moreover, if the AE is serious, the SAE Form must also be completed.

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

The recording period for AEs is the period starting from the signature of the ICF until the subject's study participation ends.

Any CS abnormalities detected at screening (Visit 1) not due to a pre-existing condition or CS changes at the following visits in the medical opinion of the Investigator must be reported as AEs in the eCRF.

If a CS abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE page of the eCRF must be completed, as appropriate. A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the CS abnormal laboratory finding, should be reported on the AE page of the eCRF. 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 SAEs to the [redacted] Safety Contact listed below within 24 h of awareness. The information must be sent by providing the completed Serious Adverse Event

paper form. At a later date, the [redacted] Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager and the Clinical Research Physician.

Safety Contact	Fax no.	E-mail
[redacted] Safety Contact	[redacted]	[redacted]
Chiesi Safety Contact	[redacted]	[redacted]

Reporting of SAEs from the investigational site is from the time of a subject's signature of the ICF and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be reported if the Investigator becomes aware of them.

Up to the closure of the investigational site, SAE reports should be reported to the [redacted] Safety Contact. New SAEs occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committees

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported in compliance with the timelines and standards for reporting SUSARs according to local UK regulations. The Medicines and Healthcare products Regulatory Agency (MHRA) will be informed through MHRA Individual Case Study Report (ICSR) Submission portal, while the EC and the Investigators by Council for International Organizations of Medical Sciences (CIOMS) I form or by periodic line-listings produced by Chiesi Global Pharmacovigilance.

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

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 [redacted]/Chiesi Safety Contact together with the SAE 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 [redacted]/Chiesi Safety Contact as soon as available, retaining a copy on site.
- All documents provided by the Investigator or site staff to the [redacted] Safety Contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and till the age of one year of the child, to detect any congenital anomality or birth defect. The pregnancy must be reported by the Investigator within 24 h by fax/e-mail to the [redacted]/Chiesi Safety Contact using the paper

Pregnancy Report Form. The [redacted] 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 [redacted]/Chiesi 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 of study treatment, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.
- Any ADR occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority according to the applicable laws. The Investigator is also recommended to report all ADRs to the relevant Marketing Authorisation Holders of the involved medicinal products. Additionally, 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 eCRF will be filled-in by the Investigator and/or his/her representative designee.

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.

Questionnaires will be collected on paper and data will be entered in the database by trained and authorised site personnel.

Medical history, AEs and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); medications will be coded using the World Health Organization (WHO) Drug dictionary and Anatomical Therapeutic Chemical (ATC) classification.

External data for spirometry assessments will be processed centrally, sent to the designated CRO and reconciled with the corresponding information recorded in the eCRF.

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 randomisation codes will be opened, and the planned statistical analyses 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 authorised 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 verify equivalence between the test treatment (HFA-152a) and the reference treatment (HFA-134a) for the relative change from baseline in FEV_1 at the 15 min post-dose timepoint, with equivalence defined as a difference between the two treatments within the 10% (i.e. [-10%; +10%]).

A total of 20 evaluable subjects will ensure a 95% power to provide a 95% confidence interval (CI) of the mean difference of the relative change from baseline in FEV_1 at 15 min post-dose within the above-mentioned equivalence limits (i.e. [-10%; +10%]) assuming a within-subject standard deviation (SD) of 8%.

Estimating a non-evaluable rate of 16%, a total of 24 subjects will be randomised.

12.2 Populations for Analysis

- **Safety population:** all randomised subjects who receive at least one dose of any of the two study treatments (analysed as treated);
- **Per-protocol population (PP):** all subjects from the Safety population, except those subjects with important protocol deviations impacting the analysis population. Exact definition of important protocol deviations impacting the analysis population will be discussed by the study team during the blind review of the data and described in the Data Review Report.

Since a cross-over design will be used, the inclusion in the populations for analysis will be defined on a per-period basis.

The Safety population will be used for the analysis of all safety variables. The variables assessing the primary study objective will also be analysed considering the PP population, for sensitivity purposes.

12.3 Statistical Analysis

A detailed statistical analysis plan will be described in the Statistical Analysis Plan (SAP), which will be finalised before breaking the blind.

12.3.1 Descriptive Statistics

General descriptive statistics for numeric variables will be summarised using n (number of observed values), the mean, the 95% CI of the mean, the SD, the median and the minimum and

maximum values. Categorical variables will be summarised using the number and percent of subjects with a specific level of the variable.

12.3.2 Missing Data

As a general rule, missing data will not be imputed.

For serial spirometry-derived parameters, the following rules will apply:

- Pre-dose FEV_1 and PEF:
  - In case only one pre-dose measurement is available, it will be used as pre-dose FEV_1 and PEF;
  - In case no pre-dose measurements are available, the pre-dose FEV_1 and PEF will be considered missing.
- FEV_1 $AUC_{0\text{-}3h}$ calculation:
  - In case only one pre-dose measurement is available, it will be used as pre-dose value (corresponding to time 0 for the calculation of the area under the concentration-time curve [AUC]);
  - In case no pre-dose measurements are available, the entire curve will be considered missing;
  - Single, isolated missing values (different from pre-dose) will be replaced by linear interpolation using adjacent values;
  - In case of two or more consecutive missing timepoints, the entire curve will be considered missing;
  - In case of three or more missing timepoints, the entire curve will be considered missing.

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

12.3.3 Subject Demographics and Baseline Characteristics

Demographics and baseline variables will be summarised by sequence and overall, using descriptive statistics for the Safety population.

The following variables will be presented: age, gender, race, height, weight, asthma history, medical history, prior medications, physical examination, vital signs, 12-lead ECG, ACQ-5, lung function, urinalysis, and safety blood assessments (routine haematology and clinical chemistry parameters).

The following demographic and baseline variables will also be presented for the PP population: demographics (age, gender, race), asthma history and lung function.

12.3.4 Primary Efficacy Variables

No primary efficacy variables are considered in this study.

12.3.5 Secondary Efficacy Variables

No secondary efficacy variables are considered in this study.

12.3.6 Safety Variables

Safety analyses will be based on the Safety population. For sensitivity purposes, the safety variables assessing the primary objective of the study will also be analysed in the PP population (see Section 12.2).

The safety variables of the study are presented in Section 9.

The safety variable assessing the **primary objective** of the study (i.e. evaluation of the potential for bronchoconstriction of each propellant) will be analysed as follow:

- The relative change from baseline in FEV_1 at the 15 min post-dose timepoint will be analysed using an analysis of covariance (ANCOVA) model, including treatment group, subject and period as fixed effects, and FEV_1 baseline (mean of the two measurements at 45 min and 15 min pre-dose in each treatment period) as a covariate.
  The adjusted mean relative change from baseline obtained with each treatment and the adjusted mean difference between HFA-152a and HFA-134a with their 95% CIs and p-values will be estimated by the model.

The other safety variables completing the evaluation of the potential for bronchoconstriction of each propellant will be analysed as follows:

- The relative changes from baseline in FEV_1 at all the other post-dose timepoints (5 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) will be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose;
- The absolute changes from baseline in FEV_1 at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) will be analysed using the same model used for the relative change from baseline in FEV_1 at 15 min post-dose;
- The number and percentage of subjects with a relative change from baseline in FEV_1 at each post-dose timepoint (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) and at any post-dose timepoint <-15% will be summarised for each treatment;
- The change from baseline in FEV_1 $AUC_{0\text{-}3h}$ will be summarised using descriptive statistics;
- The relative and absolute changes from baseline in PEF at all post-dose timepoints (5 min, 15 min, 30 min, 1 h, 1 h 30 min and 3 h after T1) will be summarised for each treatment, using descriptive statistics;
- The number and percentage of subjects with use of rescue medication in the 3 h post-dose will be summarised for each treatment;
- The mean use (puffs) of rescue medication in the 3 h post-dose will be summarised for each treatment, using descriptive statistics.

The safety variables assessing the **secondary objective** of the study (i.e. general safety and tolerability of the two different propellants) will be analysed as follow:

- **Adverse events and adverse events of particular interest:**
  All AEs starting on or after the time of first study treatment intake will be classified as treatment-emergent adverse events (TEAE). Any AEs started after the informed consent signature and before the time of first study treatment intake will be classified as pre-treatment AEs.
  The number of subjects who experienced at least one TEAE, ADR, serious TEAE, serious ADR, TEAE leading to study discontinuation, and TEAE leading to death will

be summarised for each treatment. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events) and by system organ class (SOC) and preferred term (PT) (number and percentage of subjects having at least one occurrence of that event) using the MedDRA. Specific summary tables will be provided for the AEs of particular interest (bronchospasm, cough, dysphonia, hoarseness).
All AEs will be listed.
Pre-treatment AEs will be listed only.

- **ECG**
  For ECG parameters: HR, QRS, PR, and QTcF, mean absolute values and change from baseline will be summarised for each treatment using descriptive statistics. For QTcF, the following categories will also be analysed for each study treatment, by means of descriptive statistics:
    - For male subjects: QTcF interval >450 ms, >480 ms and >500 ms;
    - For female subjects: QTcF interval >470 ms and >500 ms;
    - For both, male and female subjects: Change from baseline >30 ms and >60 ms.

  The analysis will be presented at each post-dose timepoint and at any post-dose timepoint.
  All data will be listed.
- **Vital signs**
  Vital signs (SBP and DBP) mean absolute values at each pre-dose and post-dose timepoint and change from baseline will be summarised for each study treatment, by means of descriptive statistics.
  All vital signs will be listed.

[redacted]

- [redacted]

12.3.8 Interim Analysis

No interim analyses are planned.

13. ETHICS COMMITTEE

The study proposal will be submitted to the EC in accordance with the UK requirements.

The EC shall give its opinion in writing, clearly identifying the study number, study title and ICF approved; before the clinical trial commences.

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

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

14. REGULATORY REQUIREMENTS

The study will be notified to (or authorised by) the Health Authorities according to the legal requirements in the UK.

Selection of the subjects will not start before the approval of the EC has been obtained and the study has been notified to (or authorised by) the Health Authorities.

15. INFORMED CONSENT

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

Adequate time shall be given to the subject to enquiry the Investigator about any clarification needed and to consider his/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. Moreover, the Investigator must sign and date the informed consent form (ICF). A subject's inclusion in the study, as well as the processing of his/her data is based on subject's explicit consent, as pointed out within the informed consent.

In case of rescreening, the subject should sign a new informed consent and will be assigned with a new subject number. A link to prior subject number will be recorded in the eCRF.
Female subjects becoming pregnant during the study and partner of a subject participating to the study becoming pregnant will have to sign a specific informed consent form to provide permission to Chiesi to collect information about the pregnancy, its outcome and the birth and health of the newborn child.

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

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 the data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

16.2 Direct Access to Source Document/Data

The Investigators or designated personnel must permit trial-related monitoring, audits, EC review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by [redacted] who has been designated by Chiesi.

It is understood that the monitor(s) will contact and visit the Investigator/centre before the study, regularly throughout the study and after the study had been completed, and that they will

be permitted to inspect the various study records: eCRFs, 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 eCRFs for accuracy and completeness;
- To validate the contents of the eCRFs 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 eCRF. 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 Investigational sites 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 Research and Development (R&D) Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GCP 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 or damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the medication was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

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

20. CONFIDENTIALITY

All study documents will be 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 that 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 (optionally) his/her address and telephone number. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21. PREMATURE TERMINATION OF THE STUDY

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

The Sponsor should submit a written notification to the Regulatory Authority concerned and EC providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

The Clinical Study Report, including the statistical and clinical evaluations, shall be prepared and sent to the Investigator for agreement and signature.

At the end of the trial, a summary of the CSR will be provided to all the ECs, to the UK Competent Authority and to the Investigators.

23. RECORD RETENTION

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

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

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

24. PUBLICATION OF RESULTS

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

Chiesi furthermore reserves the right to use such data for industrial purposes.

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

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

25. REFERENCES

[1] GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691-706.

[2] GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020 8(6):585-596.

[3] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.

[4] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163-2196.

[5] Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol. 2014;795:17-29.

[6] UN Environment Programme (UNEP) Annual Report 2014. https://www.unenvironment.org/resources/annual-report/unep-2014-annual-report. Accessed April 2021.

[7] The Montreal Protocol on Substances that Deplete the Ozone Layer. https://ozone.unep.org/treaties/montreal-protocol-substances-deplete-ozone-layer/text. Accessed April 2021.

[8] Myhre G, Shindell G, Bréon F-M, Collins W, Fuglestvedt J, Huang J, Koch D, Lamarque JD, Lee D, Mendoza B, Nakajima T, Robock A, Stephens G, Takemura T, Zhang H. 2013: Anthropogenic and Natural Radiative Forcing. In: Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Stocker TF, Qin D, Plattner GK, Tignor M, Allen SK, Boschung J, Nauels A, Xia Y, Bex V, Midgley PM (eds.). Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA. Pp. 659-740.

[9] Jeswani H, Corr S, Azapagic A. Reducing carbon footprints of metered dose inhalers. Inhalation. 2017;11(6).

[10] Panigone S, Sandri F, Ferri R, Volpato A, Nudo E, Nicolini G. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. BMJ Open Respir Res. 2020 Mar;7(1):e000571.

[11] Avella J, Kunaparaju N, Kumar S, Lehrer M, Zito SW, Barletta M. Uptake and distribution of the abused inhalant 1,1-difluoroethane in the rat. J Anal Toxicol. 2010;34(7):381-388.

[12] Ernstgård L, Sjögren B, Dekant W, Schmidt T, Johanson G. Uptake and disposition of 1,1-difluoroethane (HFC-152a) in humans. Toxicol Lett. 2012 February 25;209(1):21-29.

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

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf. Accessed April 2021.

[14] EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4 - EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use. Annex 13 – Manufacture of Investigation Medicinal Products. 2010. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf. Accessed March 2021.

[15] COVID-19 Rapid guideline: arranging planned care in hospitals and diagnostic services. National Institute for Health and Care Excellence (NICE) guideline NG179. 2020 July 27. Overview | COVID-19 rapid guideline: arranging planned care in hospitals and diagnostic services | Guidance | NICE. Accessed February 2022.

[16] Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88.

[17] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-1343.

[18] Miller M.R., Hankinson J., Brusasco V., Burgos F., Casaburi R., Coates A., Crapo R., Enright P., van der Grinten C.P.M., Gustafsson P., Jensen R., Johnson D.C., MacIntyre N., McKay R., Navajas D., Pedersen O.F., Pellegrino R., Viegi G. and Wanger J. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005; 26: 319–338.

[19] Juniper E. Asthma Control Questionnaire (ACQ). ACQ-5 - United Kingdom/English Version. 22 Sep 2017.

Clinical Study Code No.: CLI-05993AB6-07	Version No.: 2.0
EUDRACT No.: 2022-000536-36	Date: 30 August 2022

APPENDIX 1
Approval of the protocol by the Coordinating Investigator

A SINGLE-DOSE, RANDOMISED, DOUBLE-BLIND, CONTROLLED, 2-WAY CROSS-OVER STUDY TO ASSESS THE POTENTIAL FOR BRONCHOCONSTRICTION OF THE NEW PROPELLANT HFA-152a VERSUS THE MARKETED HFA-134a PROPELLANT, IN ADULT SUBJECTS WITH MILD ASTHMA.

Product:
Test product: Placebo HFA-152a propellant
Reference product: Placebo HFA-134a propellant

Pharmaceutical Form:
Test product: pressurised metered dose inhaler (pMDI) with HFA-152a
Reference product: pressurised metered dose inhaler (pMDI) with HFA-134a

Approval of Clinical Study Protocol by the Investigator:

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

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

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

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Coordinating Investigator's Name: _____, MD

Centre No.: _____

_____ _____
Signature Date

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

Clinical Study Code No.: CLI-05993AB6-07	Version No.: 2.0
EUDRACT No.: 2022-000536-36	Date: 30 August 2022

APPENDIX 2
Approval of the protocol by the Principal Investigator

A SINGLE-DOSE, RANDOMISED, DOUBLE-BLIND, CONTROLLED, 2-WAY CROSS-OVER STUDY TO ASSESS THE POTENTIAL FOR BRONCHOCONSTRICTION OF THE NEW PROPELLANT HFA-152a VERSUS THE MARKETED HFA-134a PROPELLANT, IN ADULT SUBJECTS WITH MILD ASTHMA.

Product:
Test product: Placebo HFA-152a propellant
Reference product: Placebo HFA-134a propellant

Pharmaceutical Form:
Test product: pressurised metered dose inhaler (pMDI) with HFA-152a
Reference product: pressurised metered dose inhaler (pMDI) with HFA-134a

Approval of Clinical Study Protocol by the Investigator:

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

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

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

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Principal 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

Definition of women of childbearing potential, postmenopausal state 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 postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal 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.

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 (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral;
  - Intravaginal;
  - Transdermal;
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral;
  - Injectable;
  - Implantable [3];
- Intrauterine device (IUD) [3];
- Intrauterine hormone-releasing system (IUS) [3];
- Bilateral tubal occlusion [3];
- Vasectomised partner [1,3];
- Sexual abstinence [2].

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

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

[3] Methods with lower user dependency.

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