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Chiesi

CLINICAL STUDY PROTOCOL

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An exploratory, double-blind, randomised, multicenter, psychopharmacological study in adult patients with moderate to severe asthma to compare two pressurised Metered-Dose Inhalers (pMDIs) on patients' perception of asthma symptoms

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Chiesi Farmaceutici S.p.A.
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GENERAL INFORMATION

SPONSOR :	Chiesi Farmaceutici S.p.A.* Via Palermo 26/A 43122 Parma - Italy + 39 0521 2791 *also reported as Chiesi throughout the text
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MONITORING CRO	PPD

VERSION HISTORY

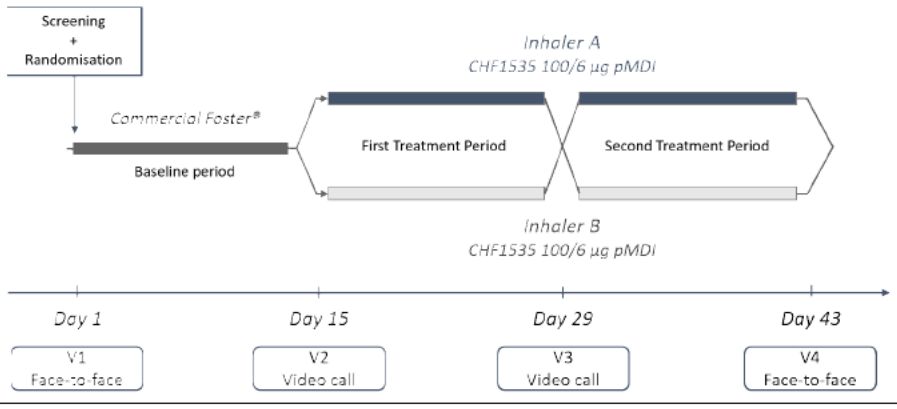
Version	Date	Change History
Version 1.0	14 APR 2021	First version
Version 2.0	14 OCT 2021	Non-substantial changes inserted Please refer to Summary of changes V1.0 14 OCT 2021 for the list of all changes

PROTOCOL OUTLINE

Study title	An exploratory, double-blind, randomised, multicenter, psychopharmacological study in adult patients with moderate to severe asthma to compare two pressurised Metered-Dose Inhalers (pMDIs) on patients' perception of asthma symptoms
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF1535 100/6 µg pMDI: Beclomethasone dipropionate plus formoterol fumarate
Centre(s)	Approx. 10 sites in Italy
Indication	Moderate to severe asthma
Study design	Exploratory, double-blind, randomised, multicenter, 2x2 cross-over study
Study phase	IIIb
Objectives	In subjects with moderate to severe asthma, the following objectives will be assessed and compared: - The perception of asthma symptoms; - The psychopharmacological aspects; - The subjects' preference and perception of the devices; - The use of reliever medication; - The quality of life, after the use of two inhalers of CHF1535 100/6 µg pMDI.
Treatment duration	1 baseline period of 14 days and 2 treatment periods of 14 days
Baseline product dose/route/regimen	Commercial Foster® (CHF1535 100/6 µg) pMDI: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg (BDP/FF). Dose regimen: BDP/FF, 100/6 µg per inhalation, 2 inhalations in the morning (preferably before 10.00 am) and 2 inhalations in the evening (preferably before 10.00 pm). Administration: pressurised metered dose inhaler (pMDI). Subjects already using a spacer for drug administration shall continue to use it throughout the duration of the study.
Test product dose/route/regimen	CHF1535 100/6 µg pMDI: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg (BDP/FF), named Inhaler A Dose regimen: BDP/FF, 100/6 µg per inhalation, 2 inhalations in the morning (preferably before 10.00 am) and 2 inhalations in the evening (preferably before 10.00 pm). Administration: pressurised metered dose inhaler (pMDI). Subjects already using a spacer for drug administration shall continue to use it throughout the duration of the study.
Reference product dose/route/regimen	CHF1535 100/6 µg pMDI: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg (BDP/FF), named Inhaler B Dose regimen: BDP/FF, 100/6 µg per inhalation, 2 inhalations in the morning (preferably before 10.00 am) and 2 inhalations in the evening (preferably before 10.00 pm). Administration: pressurised metered dose inhaler (pMDI).

	Subjects already using a spacer for drug administration shall continue to use it throughout the duration of the study.
Number of subjects	75 randomised subjects
Study population	Subjects with moderate to severe asthma
Inclusion/exclusion criteria	**Inclusion criteria** Subject must meet all the following inclusion criteria to be eligible for enrolment into the study: 1. Subject's and/or subject legal representative's **written informed consent** obtained prior to any study related procedure. 2. **Age**: ≥18 and ≤75 years of age. 3. **Diagnosis of asthma**: Established diagnosis of permanent asthma for at least 6 months prior to screening/randomisation visit, with documented history of variable respiratory symptoms and confirmed variable expiratory airflow limitation according to the description in the Box 1-2 of the 2020 GINA Report. 4. **Current asthma therapy:** Subject on maintenance therapy treated by Foster® (CHF1535 100/6 µg pMDI) for at least 6 months prior to screening/randomisation visit (A subject under Foster® MART indication is eligible). 5. **Asthma control**: Asthma Control Test (ACT) ≥ 20 at screening/randomisation visit. 6. **Ability to comply** with the protocol: Subject must have a cooperative attitude and the ability to be trained to use correctly the diary and answer the Visual Analogue Scale (VAS), to be able to perform the required outcomes measurements and the ability to understand the risks involved. **7.** Subject willing and able to use their electronic device to **download the application to fill in the study e-diary** and to enable **video communication.** 8. **Female subjects**: a. WOCBP fulfilling one of the following criteria: i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until Visit 4 *or* ii. WOCBP with non-fertile male partners (contraception is not required in this case). For the definition of WOCBP and of fertile men and the list of highly effective birth control methods, refer to Appendix 4. *or* b. Female subjects of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile, as per definitions given in Appendix 4). Tubal ligation or partial surgical interventions are not acceptable. If indicated, as per investigator's request, post-menopausal status may be confirmed by follicle-stimulating hormone levels (according to local laboratory ranges). **Exclusion criteria** The presence of any of the following will exclude a subject from study enrolment:

	1. **Pregnant or lactating woman** where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive urine pregnancy test. Urine pregnancy test will be performed at screening/randomisation visit and at the end of the study on all women of childbearing potential. 2. **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. 3. **Recent exacerbation**: Asthma exacerbation requiring systemic corticosteroids or emergency room admission or hospitalisation within 4 weeks prior to screening/randomisation visit. 4. **Non-permanent asthma**: exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine. 5. **Asthma requiring more than 1 inhaler** for **maintenance** treatment and **more than 1 inhaler** for **reliever** treatment. 6. **Asthma requiring use of biologics**: asthma subject treated with chronic systemic corticosteroids or anti-IgE or other monoclonal or polyclonal antibodies. 7. **Respiratory disorders** other than asthma: Subject with known respiratory disorders other than asthma. This can include but is not limited to diagnosis of COPD as defined by the current guidelines (e.g. GOLD guidelines), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease. 8. **Lower tract respiratory infection**: subject with lower respiratory tract infection that required use of antibiotics within 4 - 6 weeks prior to screening/randomisation. 9. **Smoking status**: current smoker or ex-smoker with a smoking current use/history of ≥ 10 pack-years (pack-years = the number of cigarette packs per day times the number of years). 10. **Cardiovascular diseases**: subject who has known clinically significant cardiovascular conditions such as but not limited to: unstable or acute ischemic heart disease within one year prior to study entry, NYHA class III/IV heart failure, history of atrial fibrillation, history of sustained and non-sustained cardiac arrhythmias diagnosed within 6 months prior to screening/randomisation visit not controlled with therapy according to the investigator's opinion. 11. **Other concurrent diseases**: subject 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, GERD), 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 interpretation of the study. 12. **Alcohol/drug abuse**: subject with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening/randomisation visit. 13. **Participation to investigational trial**: subject who has received any investigational drug within the last 30 days (60 days for biologics) or a more appropriate time as determined by the investigator (e.g. approximately 5 half-lives of the investigational drug whatever is longer).

	14. **Contra-indications**: contra-indications to Foster® constitute an exclusion criterion. For warnings, eligibility will be judged by the investigator. 15. **Hypersensitivity**: history of hypersensitivity to Foster® or any of its components or a history of other allergy that in the opinion of the investigator contraindicates the subject's participation. 16. **Subject mentally or legally incapacitated** or subjects accommodated in an establishment as a result of an official or judicial order. 17. **Blind, colour blind subject or any other dyschromatopsia**. 18. **Known psychiatric disorders** that may interfere with successful completion of this protocol according to the Investigator's judgment including schizophrenia, bipolar disorders and psychoses.
Study plan	Subjects who will have signed an informed consent for this study will be screened at the investigational site during the Screening/Randomisation Visit (V1). When all the inclusion and exclusion criteria have been checked, eligible subjects will be randomised on the same day, in one of the two treatment sequences (i.e. CHF1535 100/6 µg pMDI with Inhaler A then CHF1535 100/6 µg pMDI with Inhaler B, or CHF1535 100/6 µg pMDI with Inhaler B then CHF1535 100/6 µg pMDI with Inhaler A). The randomised subjects will then be provided with one Subject box corresponding to their randomisation number. The Subject box will contain: - One Foster® 100/6 µg pMDI inhaler - One CHF1535 100/6 µg pMDI, Inhaler A - One CHF1535 100/6 µg pMDI, Inhaler B The subject will follow the study treatment sequence as described below: - Subjects will be treated with Foster® 100/6 µg pMDI during the Baseline Period of 14 days; - Subjects will then be instructed to take CHF1535 100/6 µg pMDI inhalers A and B during 2 consecutive periods of 14 days each (First and Second Treatment Periods) in a sequential way dictated by the randomisation. The whole study will last approximately 6 weeks for each subject and a total of 2 face-to-face clinic visits (Screening/randomisation visit [V1] and Day 43 [V4]) and 2 remote video contact visits (Day 15 [V2] and Day 29 [V3]) are expected to be performed during the study. <u>Study design</u> 

Most relevant allowed concomitant treatments	○ Inhaled short-acting β2-agonists (SABA) or Foster® administered as reliever medication on as-needed basis. ○ In case of other concomitant diseases, any appropriate non-inhaled treatment that, according to the Investigator, does not interfere with the study evaluation parameters is allowed.
Most relevant forbidden concomitant treatments	○ ICS/LABA fixed combinations other than Foster®; ○ ICS/LABA/LAMA fixed combinations; ○ Inhaled ICS monotherapy; ○ Long-acting inhaled anticholinergics; ○ Long-acting inhaled β2-agonists; ○ Short-acting inhaled anticholinergics; ○ β-blocking drugs, including eye drops; ○ Any drug known to have a well-defined potential for hepatotoxicity (e.g. isoniazide, nimesulide, ketoconazole) within the previous 3 months before the screening/randomisation visit; ○ Enzyme-inducing or inhibiting drugs (e.g. glucocorticoids, ketoconazole) within the previous 3 months before the screening/randomisation visit; ○ Any drug that can cause significant Corrected by Heart Rate Q-T interval (QTc) prolongation.
Efficacy variables (and/or pharmacokinetics variables)	○ Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days and over the entire 14 days treatment period (questions #3-#6 of the Study specific subject's questionnaire, Appendix 3); ○ Summary measures for questions with continuous outcome covering subjects' psychopharmacological aspects (questions #7-#10 of the Study specific subject's questionnaire, Appendix 3); ○ Percentages of subjects to questions covering subjects' preference and perception of the devices (questions #11-#16 of the Study specific subject's questionnaire, Appendix 3); ○ Change from baseline in reliever medication use over the entire 14 days treatment period (questions #2 of the Study specific subject's questionnaire, Appendix 3); ○ Change from baseline in AQLQ(S) score after 14 days of treatment.
Safety variables	Adverse events (AEs) and Serious adverse events (SAEs).
Sample size calculation	The sample size calculation is not based on a formal statistical hypothesis, since this is an exploratory study. A total of 75 randomised subjects is deemed sufficient to assess the objectives of the study.
Statistical methods	**Analysis sets** The following analysis sets will be considered: ✓ Safety set: all randomised subjects who receive at least one dose of study treatment (analysed according to an *as-treated* approach). ✓ Intention-to-Treat (ITT) set: all randomised subjects who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline (analysed *as-randomised*).

- ✓ Per Protocol (PP) set: all subjects from the ITT set without any major protocol deviations (e.g. wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

Since the study has a cross-over design, the inclusion in each analysis set will be defined on a per-period basis.

Efficacy analysis

Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the entire 14 days treatment period will be analysed on the ITT using a linear mixed model for repeated measures including subject, period, treatment, timepoint (i.e. from Day 1 to Day 7 and from Day 8 to Day 14), period by timepoint interaction, and treatment by timepoint interaction as fixed effects. Baseline value is defined as the average of the VAS scores collected during the baseline period. Baseline value will not be included as covariate because it is common for the two periods and the inter-subject differences are already accounted for by the subject effect. An unstructured covariance matrix within period will be assumed, and the Kenward-Roger adjustment will be used for the degrees of freedom. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) will be estimated by the model (this analysis will assign equal weights to the two timepoints). Statistically significant difference between treatments is defined as $p<0.05$. Missing data will not be imputed. This analysis will be applied on questions collected daily using a VAS score (see Appendix 3 for the list of questions). Each question will be analysed separately.

Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days of treatment will be analysed on the ITT set and derived from the previous statistical model (specifications will be provided in the SAP).

Summary measures (descriptive statistics) for questions with continuous outcome covering subjects' psychopharmacological aspects will be reported on the ITT and PP set by treatment group. This analysis will be applied on questions not collected daily. Each question will be analysed separately. The list of all the questions is reported in Appendix 3.

Percentages of subjects to questions covering subjects' preference and perception of the devices will be reported on the ITT and PP set by treatment group. This analysis will be applied on questions not collected daily. Each question will be analysed separately. The list of all the questions is reported in Appendix 3.

Change from baseline in reliever medication use over the entire 14 days treatment period will be summarised on the ITT set by treatment group by descriptive statistics. Baseline value is defined as the average value (puffs/day) collected during the baseline period.

	Change from baseline in AQLQ(S) score after 14 days of treatment will be analysed on the ITT set by an analysis of variance model (ANOVA) including treatment, period and subject as fixed effect. Baseline value is defined as the AQLQ(S) score collected at the end of the baseline period. **Safety analysis** ***Occurrence of TEAEs, adverse drug reactions (ADRs), severe ADRs, serious ADRs, serious TEAEs (SAEs), non-serious TEAEs, severe TEAEs, TEAEs leading to discontinuation from study treatment and TEAEs leading to death*** will be summarised on the safety set by treatment group as the number of subjects, percentage of subjects, and number of events. TEAEs will also be summarised by System Organ Class and Preferred Term using the MedDRA dictionary. All adverse events starting on or after the time of first study drug intake will be classified as TEAE. Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. All adverse events will be listed. Pre-treatment adverse event will be listed only.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
ACT	Asthma Control Test
AE	Adverse Event
ANCOVA	Analysis of Covariance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ATC	Anatomical Therapeutic Chemical Classification
BDP/FF	Beclomethasone DiPropionate/Formoterol Fumarate
b.i.d.	Bis In Die
BYOD	Bring Your Own Device
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease appeared in 2019
CRA	Clinical Research Associate
(e)CRF	(Electronic) Case Report Form
CRO	Contract Research Organisation
DALY	Disability Adjusted Life Years
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
EC	Ethics Committee
ED	Early Discontinuation
EU	European Union
FEV1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GOLD	Global initiative for chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing System
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
MART	Maintenance and Reliever Therapy
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
NYHA	New York Heart Association
PIS	Participant Information Sheet
pMDI	Pressurised Metered Dose Inhaler
PR	Pulse Rate

PRO	Patient Reported Outcome
PP	Per-Protocol
QTc	Time interval between the Q and T wave in the ECF (corrected for Heart Rate)
SABA	Short-acting β2 agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Actue Respiratory Syndrome CoronaVirus 2
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WHO	World Health Organisation
WOCBP	Woman of Childbearing Potential

CONTENT

1. INTRODUCTION

1.1. Background information

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

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

The Global Initiative for Asthma (GINA) report [1] on the Global Strategy for Asthma Management and Prevention states that the long-term goals of asthma management are exacerbation risk reduction and symptom control, aiming to reduce the disease burden to the patient and minimise the "future risk" of exacerbation, airway damage leading to decline in lung function, and asthma-related death, all while balancing the potential for adverse drug reactions (ADRs) and the treatment cost required to achieve these goals.
A 5-step approach to the pharmacological treatment of asthma has been established by GINA and is widely accepted.
Treatment with regular daily low-dose inhaled corticosteroids (ICS) is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalisation and death.
For many patients, addition of a long-acting β2-agonist (LABA) to ICS has been shown to improve symptom control, lung function and quality of life. A long-term, daily treatment with ICS, e.g. beclomethasone dipropionate (BDP) in combination with LABA, e.g. formoterol is the preferred maintenance option recommended in GINA step 3-5.

Foster® (CHF 1535) is an extrafine fixed combination of the ICS beclomethasone dipropionate (BDP) and the LABA formoterol fumarate (FF). Foster® 100/6 µg pMDI has been approved in Europe since 2006 for the following indications:

- Asthma (maintenance treatment): regular treatment of asthma where use of a combination product (ICS and LABA) is appropriate, i.e. patients not adequately controlled with ICS and 'as needed' inhaled rapid-acting beta2-agonist, or patients already adequately controlled on both ICS and LABA.
- Asthma (Maintenance And Reliever Therapy - MART): for use in asthmatic patients already taking it as maintenance treatment and in need of a reliever medication
- Extension of indication, Chronic Obstructive Pulmonary Disease (COPD): symptomatic treatment of patients with severe COPD (forced expiratory volume in 1 second [FEV1] <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

In 2015, a line extension application led to the approval of a higher ICS strength, namely Foster® 200/6 µg pMDI, for the maintenance treatment of asthma only.
Foster® formulated with inhalation powder has also been developed by Chiesi, containing the same fixed dose of 100 or 200 µg BDP and 6 µg FF per inhalation, delivered via a multi-dose breath-actuated dry powder inhaler (DPI) device (NEXThaler®) and authorised for the same indications as the corresponding pMDI strengths.

Both strengths and formulations have been marketed in most European Union (EU) countries since their first authorisation.

1.2. Study rationale

The GINA report emphasises that implementation of an appropriate therapy has the potential to significantly reduce exacerbations, the main socio-economic burden of asthma, as well as to enhance patients' quality of life. Several studies have shown that guideline-defined asthma control is achievable in most patients, and that achievement of good control is associated with improved health status [4]. However, an appropriate pharmacological treatment is not enough to guarantee asthma control.

Poor adherence is defined as "the failure of treatment to be taken as agreed upon by the patient and the health care provider" [1], and it has been reported as a risk factor for exacerbations and mortality [5] [6], affecting approximately 50% of asthmatic patients [7] [8] [9]. This is the reason why, according to GINA, all the factors related to poor adherence must be identified and managed over all the steps of the asthma management cycle for personalised asthma care (i.e. initial diagnosis and review assessments). Poor adherence must be excluded before a diagnosis of severe asthma can be made and before any step-up in treatment, to avoid unnecessary overmedication [7].

The increasing awareness of the importance of adherence and of developing strategies to improve it is stressed in the GINA report, which recommends how patient's preferences, goals, satisfaction, and beliefs about asthma and medications should be considered for choosing the best treatment option, in the framework of the personalised control-based asthma management. This is true in the choice of both medications and devices, especially for maintenance medications in chronic diseases like asthma, as they must be used daily even when symptoms are infrequent or absent [10].

Different types of inhaler devices have been shown to affect adherence to asthma maintenance medications [6] [11] [12] [13]. A good knowledge, perception, and familiarity with the device can result in increasing patient's adherence and satisfaction, consequently leading also to improved health outcomes and reduced expenditures for the health care system [14] [15] [16]. However, scarce data are available on asthmatic patients' perceptions of the devices and on the specific characteristics of the devices involved in their preference. Therefore, further investigation on this topic would be helpful to develop devices associated with the highest adherence, for the benefit not only of patients (e.g better control of asthma, satisfaction, and quality of life), but also of health care providers/system, due to reduced need of time and resources to manage exacerbations and hospitalisations.

Variation in adherence, in how patients respond to treatments and experience symptoms is partly attributable to placebo and nocebo effects [17], and previous studies suggest that other factors, such as appearance and external characteristics of medicines, play a role in the perception of diseases and medications, ultimately influencing the overall effectiveness of treatments [18] [19].
The importance of drugs' characteristics other than the active molecule and formulation, in patient education, is well-known even in asthma [20] [21].

This is an exploratory, double-blind, randomised, multicenter, psychopharmacological, 2x2 cross-over study, to assess the perception of symptoms and patient's preferences comparing two inhalers containing the same medication/formulation as Foster®100/6 µg (i.e. BDP/FF, pMDI). The target population is represented by adult subjects with moderate to severe asthma, controlled with Foster®

100/6 pMDI that must be already in use for six months before screening/randomisation. The study is designed to focus the attention on the psychopharmacological aspects, particularly on subjects' preference of device and on the impact of devices' features on subjects' perception of asthma symptoms. Therefore, the two inhalers (inhaler A and inhaler B) will be exactly the same in terms of the delivered medication (i.e. fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg, pMDI) but they will have different characteristics. The differences between the two inhalers will be disclosed at the end of the study, in line with a deception approach to avoid bias in the outcomes of interest.

1.3. Risk/benefit assessment

Foster® was licensed and marketed in 2006, and patients have been using it ever since for treatment of moderate to severe asthma. Since then, many studies had shown its favorable efficacy and safety profile [22] [23] [24] and it is now widely prescribed around the world.

The population in the proposed study (i.e. moderate to severe asthmatic subjects controlled on Foster® 100/6 µg pMDI maintenance treatment, started at least 6 months before screening) will be treated by the same chemical compounds (both active ingredients and excipients) and formulation for the entire duration of the study, hence are not exposed to any foreseen risks related to change of medication.
The exclusion criteria are defined in order to minimise potential risks for the participants (e.g. subjects with a history of "at risk" asthma, recent exacerbations, or any other concurrent uncontrolled diseases will be excluded).

Participants will have regular assessments including safety either at the clinical site or during remote video calls during the 6-week duration of the study, including daily recording of subjects' symptoms and perception, compliance and medication use via electronic diary. Remote access to these data will allow to closely monitor any disease worsening (including exacerbations) that will be managed accordingly.

The decision to discontinue the subject from further participation to the study will be at the investigator's discretion if deemed necessary due to any reason. Please see details in Subjects' withdrawal in section 4.4.

Participants will be informed about the objective, the potential risks and benefits of the study, as per Good Clinical Practice. In particular, they will be informed that during the study they will receive the same medication (with the same compound, strength, formulation, and frequency) they used to take before enrolment as maintenance therapy (i.e. Foster® 100/6 µg pMDI), but the inhaler will be different in terms of device's characteristics. Details about the differences between the two inhalers will be disclosed to the participants only at the end of the study, with a debriefing to be scheduled at the exit interview, according to the "authorised deception" approach [25]. This method is commonly used to be fully transparent with participants about the reasons of the deception adopted during the study. In line with this authorised deception approach, the current protocol will only provide a general description of the packaging and labeling information to maintain the investigator blind to the inhalers' changes and features.

Subjects will be asked for their availability to comply with the study procedures and assessments to evaluate their preferences and perceptions over the duration of the study.

Chiesi believes that the above reported background information supports the conduct of the proposed study and that the results of this study may help to elucidate the role the devices' characteristics in

patients' preferences and perceptions of both symptoms and overall burden of their asthma, potentially leading to higher adherence and effectiveness of treatment, in the future, as suggested by the GINA report.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) [26], current ICH E6 Good Clinical Practices [27] and all other applicable laws and regulations.
Considering the safety profile of the Investigational Medicinal Products (IMPs) and the measures in place to assure the subjects' safety, the overall risk/benefit assessment is considered acceptable for the proposed trial.

2. STUDY OBJECTIVES

In subjects with moderate to severe asthma, the following objectives will be assessed and compared:

- The perception of asthma symptoms;
- The psychopharmacological aspects;
- The subjects' preference and perception of the devices;
- The use of reliever medication;
- The quality of life,

after the use of two inhalers of CHF1535 100/6 µg pMDI.

3. STUDY DESIGN

This is a phase IIIb, exploratory, double-blind, randomised, multicenter, psychopharmacological, 2x2 cross-over study.

The study will be conducted in Italy, approximately 75 subjects will be randomised in 10 sites.

The whole study will last approximately 6 weeks for each subject and a total of 4 study visits (V1 to V4) will be performed during the study, as follows (See also Figure 1):

- 2 face-to-face clinic visits:
  - Screening/randomisation visit (Visit 1),
  - Visit 4 at Day 43.
- 2 remote video contact visits:
  - Visit 2 at Day 15,
  - Visit 3 at Day 29.

Subjects who will have signed an informed consent for this study will be screened at the investigational site during the Screening/Randomisation Visit (V1).
When all the inclusion and exclusion criteria have been checked, eligible subjects will be randomised on the same day.

The subject will follow the study treatment sequence as described below:

- Subjects will be treated with the commercial Foster® during the Baseline Period of 14 days;
- Subjects will then be instructed to take CHF1535 100/6 µg pMDI inhalers A and B during 2 consecutive periods of 14 days each (First and Second Treatment Periods) in a sequential way dictated by the randomisation:
  - Either CHF1535 100/6 µg pMDI with Inhaler A then CHF1535 100/6 µg pMDI with Inhaler B,
  - Or CHF1535 100/6 µg pMDI with Inhaler B then CHF1535 100/6 µg pMDI with Inhaler A.

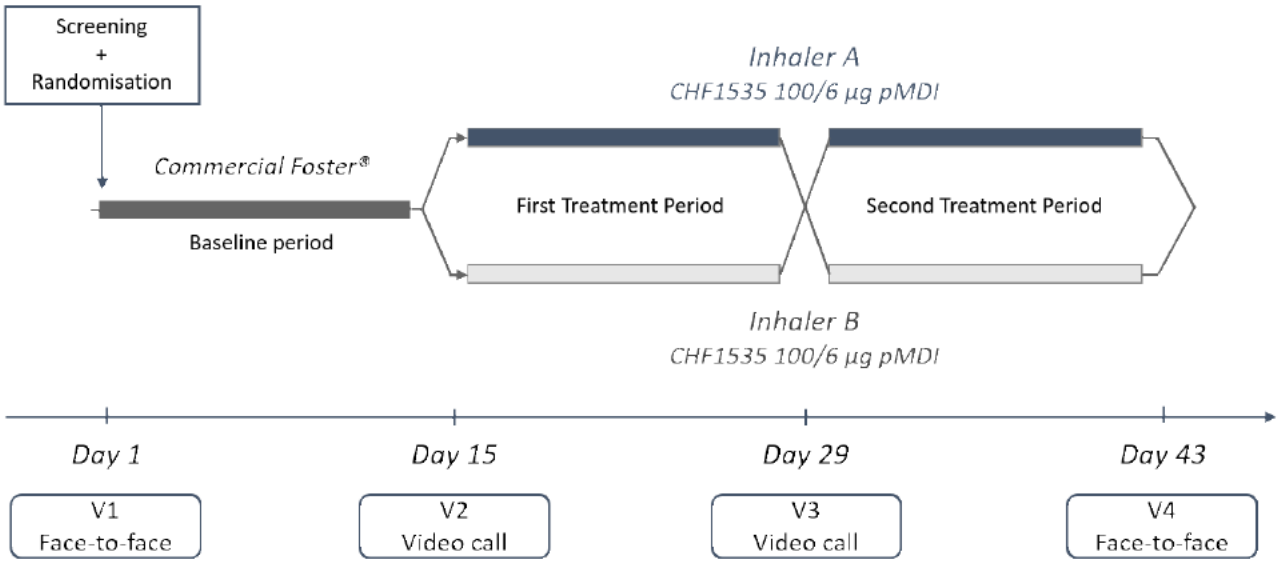
In order to maintain the study blind and to adequately gauge subjects' perception, an **Unblinded site personnel** will be assigned at each site by the Principal Investigator for the treatment dispensation and treatment return management, as well as the drug accountability activities (please refer to section 6.9). It is essential that this unblinded site personnel is distinct from the blinded investigator (who performs the other blinded activities such as the collection of ICF, demographics and other patients' data, the assessment of concomitant medication and AEs/SAEs etc.) and that communication between the unblinded personnel and the blinded team should be kept at minimum to avoid accidental unblinding. The Unblinded site personnel can be a pharmacist, a nurse, a study coordinator or another investigator, and should be qualified to perform the tasks delegated by the Principal Investigator.

A "window" of -1 to + 1 day is allowed for the dates of all study visits, except for Visit 1.

In case the subject is unable to physically come to the investigational site to attend the face to face visit at V4 (e.g. in case of emergency situation as described in section 9.2), it is possible to replace it by a remote video call. See detailed instructions in section 7.1.4.

The end of the trial is defined as the last visit (or last video call) of the last subject in the trial.

Figure 1. Study Design



4. SUBJECT SELECTION CRITERIA

4.1. Subject Recruitment

Outpatients attending the hospital clinics/study centres will be recruited.

The study will include adult subjects with moderate to severe asthma according to the steps of treatment prescribed as per GINA report [1], proven by established diagnosis of permanent asthma for at least 6 months prior to screening/randomisation visit and with documented history of variable respiratory symptoms and confirmed variable expiratory airflow limitation according to the description in the Box 1-2 of the 2020 GINA Report (See Appendix 2).

Participating sites will enroll subjects in a consecutive manner when subjects come for their regular visit, in order to minimise the risk of selection bias. Prior to data collection, all participating subjects must sign privacy and study Informed Consent Form (ICF).

Approximately 75 subjects will be randomised.

4.2. Inclusion Criteria

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

1. Subject's and/or subject legal representative's **written informed consent** obtained prior to any study related procedure.
2. **Age**: ≥18 and ≤75 years of age.
3. **Diagnosis of asthma**: Established diagnosis of permanent asthma for at least 6 months prior to screening/randomisation visit, with documented history of variable respiratory symptoms and confirmed variable expiratory airflow limitation according to the description in the Box 1-2 of the 2020 GINA Report (Appendix 2)
4. **Current asthma therapy:** Subject on maintenance therapy treated by Foster® (CHF1535 100/6 µg pMDI) for at least 6 months prior to screening/randomisation visit (A subject under Foster® MART indication is eligible).
5. **Asthma control**: Asthma Control Test (ACT) ≥ 20 at screening/randomisation visit.
6. **Ability to comply** with the protocol: Subjects must have a cooperative attitude and the ability to be trained to use correctly the diary and answer the Visual Analogue Scale (VAS), to be able to perform the required outcomes measurements and the ability to understand the risks involved.
7. Subject willing and able to use their electronic device to download the application to **fill in the study e-diary** and to enable **video communication.**
8. **Female subjects**:
    a. WOCBP fulfilling one of the following criteria:
        i. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until Visit 4 *or*
        ii. WOCBP with non-fertile male partners (contraception is not required in this case).

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

    or

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

4.3. Exclusion Criteria

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

1. **Pregnant or lactating woman** where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive urine pregnancy test.

Urine pregnancy test will be performed at screening/randomisation visit and at the end of the study on all women of childbearing potential.

2. **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.
3. **Recent exacerbation**: Asthma exacerbation requiring systemic corticosteroids or emergency room admission or hospitalisation within 4 weeks prior to screening/randomisation visit.
4. **Non-permanent asthma**: exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine.
5. **Asthma requiring more than 1 inhaler** for **maintenance** treatment and **more than 1 inhaler** for **reliever** treatment.
6. **Asthma requiring use of biologics**: asthma subject treated with chronic systemic corticosteroids or anti-IgE or other monoclonal or polyclonal antibodies.
7. **Respiratory disorders** other than asthma: Subject with known respiratory disorders other than asthma. This can include but is not limited to diagnosis of COPD as defined by the current guidelines (e.g. GOLD guidelines), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.
8. **Lower tract respiratory infection**: subject with lower respiratory tract infection that required use of antibiotics within 4 - 6 weeks prior to screening/randomisation.
9. **Smoking status**: current smoker or ex-smoker with a smoking current use/history of ≥ 10 pack-years (pack-years = the number of cigarette packs per day times the number of years).
10. **Cardiovascular diseases**: subject who has known clinically significant cardiovascular conditions such as but not limited to: unstable or acute ischemic heart disease within one year prior to study entry, NYHA class III/IV heart failure, history of atrial fibrillation, history of sustained and non-sustained cardiac arrhythmias diagnosed within 6 months prior to screening/randomisation visit not controlled with therapy according to the investigator's opinion.
11. **Other concurrent diseases**: subject 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, GERD), 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 interpretation of the study.
12. **Alcohol/drug abuse**: subject with a known or suspected history of alcohol and/or substance/drug abuse within 12 months prior to screening/randomisation visit.
13. **Participation to investigational trial**: subject who has received any investigational drug within the last 30 days (60 days for biologics) or a more appropriate time as determined by the investigator (e.g. approximately 5 half-lives of the investigational drug whatever is longer).
14. **Contra-indications**: contra-indications to Foster® constitute an exclusion criterion. For warnings, eligibility will be judged by the investigator.
15. **Hypersensitivity**: history of hypersensitivity to Foster® or any of its components or a history of other allergy that in the opinion of the investigator contraindicates the subject's participation.
16. **Subject mentally or legally incapacitated** or subjects accommodated in an establishment as a result of an official or judicial order.
17. **Blind, colour blind subject or any other dyschromatopsia**.
18. **Known psychiatric disorders** that may interfere with successful completion of this protocol according to the Investigator's judgment including schizophrenia, bipolar disorders and psychoses.

4.4. Subject Withdrawals

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

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

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided.
However, should a subject discontinue the study, all efforts will be made to complete and report the observations as thoroughly as possible.

All the assessments foreseen at Visit 4 (Day 43) should be done at early discontinuation to the extent possible, providing there is no safety issue for the subject (See Study schedule in section 7.1 and see section 7.1.5 for more details).

In case of withdrawal, the Investigator must fill in the form "Study Termination" page in the eCRF, reporting the main reason for withdrawal.

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the subject's study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as "Recovering/Not recovered" in the eCRF.
If a subject is withdrawn or drops-out of the study after receiving the test treatment, the subject study number and corresponding test treatments should not be reassigned to another subject.

5. CONCOMITANT MEDICATIONS

5.1. Permitted concomitant Medications

1. Inhaled short-acting β2-agonists (SABA) or Foster® administered as reliever medication on as-needed basis.
2. In case of other concomitant diseases, any appropriate non-inhaled treatment that, according to the Investigator, does not interfere with the study evaluation parameters is allowed

5.2. Non-permitted concomitant Medications

1. ICS/LABA fixed combinations other than Foster®
2. ICS/LABA/LAMA fixed combinations;
3. Inhaled ICS monotherapy;
4. Long-acting inhaled anticholinergics;
5. Long-acting inhaled β2-agonists;
6. Short-acting inhaled anticholinergics;
7. β-blocking drugs, including eye drops;
8. Any drug known to have a well-defined potential for hepatotoxicity (e.g. isoniazide, nimesulide, ketoconazole) within the previous 3 months before the screening/randomisation visit;
9. Enzyme-inducing or inhibiting drugs (e.g. glucocorticoids, ketoconazole) within the previous 3 months before the screening/randomisation visit;
10. Any drug that can cause significant Corrected by Heart Rate Q-T interval (QTc) prolongation.

Please refer to Appendix 5 for a list of relevant medications for items 8, 9 and 10 listed above.

6. TREATMENT(S)

The study medications including Baseline medication and medication during treatment periods will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity. Pharmacist/Investigator will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of temperature.

The Sponsor will not provide reliever medication. However, subjects are allowed to take their usual prescribed reliever medication on an as-needed basis and according to its Summary of Product Characteristics (SmPC), provided that the prescribed reliever medication is not listed as forbidden concomitant treatments as described in section 5.2.
The Sponsor will not provide any spacer. However, subjects who are used to inhale their asthma pMDI medications with a spacer shall continue using their usual spacer to take the pMDI study drug.

6.1. Appearance and Content

Baseline product

- **Foster® (CHF 1535 100/6 µg) pMDI (Chiesi Farmaceutici S.p.a.)**
  Active ingredient: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg.
  Excipients: HFA-134a, Ethanol anhydrous, Hydrochloric acid.
  Presentation: Canister containing 120 doses plus actuator with dose counter.

Test product

- **CHF 1535 100/6 µg pMDI**

  Active ingredient: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg.

  Excipients: HFA-134a, Ethanol anhydrous, Hydrochloric acid.

  Presentation: Canister containing 120 doses plus actuator.

Reference product

- **CHF 1535 100/6 µg pMDI**

  Active ingredient: Fixed combination of beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg.

  Excipients: HFA-134a, Ethanol anhydrous, Hydrochloric acid.

  Presentation: Canister containing 120 doses plus actuator.

6.2. Dosage and Administration

6.2.1. Selection of doses in the study

The selection of the dose for CHF 1535 pMDI (100/6 µg per inhalation) is based on the commercialised dose of Foster® (CHF 1535 100/6 µg) pMDI for moderate to severe asthma subjects. Study treatments will be used according to the Foster® SmPC.

6.2.2. Dosage

6.2.2.1. Baseline period

Baseline product: Commercial Foster® (CHF 1535 100/6 µg) pMDI 2 inhalations b.i.d.;

6.2.2.2. Randomised Treatment periods

Test product: CHF1535 100/6 µg pMDI 2 inhalations b.i.d.;

Reference product: CHF1535 100/6 µg pMDI 2 inhalations b.i.d..

Note: Subjects must use their own treatment for reliever use. None of the study treatments assigned to the subjects can be used as a reliever therapy. This is particularly the case for subjects under Foster® MART indication, who should use their own prescribed Foster® inhaler as reliever therapy.

6.2.3. Administration

At **Visit 1** (screening/randomisation), each eligible subject will receive one complete Subject box containing:

- Baseline treatment one commercialised Foster® 100/6 µg pMDI
- Test treatment: one CHF1535 100/6 µg pMDI, Inhaler A
- Reference treatment: one CHF1535 100/6 µg pMDI, Inhaler B

For the duration of the study, the provided maintenance treatments will come in replacement of subject's current maintenance therapy. For reliever treatment use (rescue medication), please refer below in section 6.2.3.4.

For all treatments provided to the subjects, subjects should be advised to read the corresponding Information Leaflet carefully and follow the instructions for use as given in the Leaflet.

Subjects used to inhale their asthma pMDI medications with a spacer shall continue using a spacer to take the pMDI study drug.

pMDI kits must be stored between 2˚C and 8˚C by the unblinded site personnel at site. **Once dispensed**, the subjects will be instructed to keep the boxes at home at ambient temperature not above 25°C.

At the time of drug intake at subject's home, the medication kits should be at room temperature, suitable for use. In case the pMDI kits have been stored in the refrigerator at subjects' homes by mistake, the kits have to be removed from the refrigerator at the time of the drug intake and warmed with the hands for a few minutes before administration to the subject. The canister must never be warmed by artificial means. **The subject should never inhale a cold medication.**

6.2.3.1. Baseline period (Period box #1)

For the Baseline period, the subjects should use the Baseline treatment, i.e. commercialised Foster®, labelled #1. The baseline treatment will be administered twice a day: **two** inhalations **in the morning** (preferably before 10.00 am) and **two** inhalations **in the evening** (preferably before 10.00 pm). To the extent possible, the time of dosing must remain constant for each subject for the whole duration of the study.

Note: If subject has **not taken** his morning dose of maintenance therapy (as prescribed before study start) before the PIS/ICF signature at study site, the first dose of study baseline medication will be administered at the clinic at Visit 1 preferably before 10.00 am, with the Unblinded site personnel.
If the subject **has already taken** his morning dose of maintenance therapy before the PIS/ICF signature at study site, the subject will be instructed to take the first dose of study baseline medication provided by the Unblinded site personnel at home in the evening of the Visit 1, preferably before 10.00 pm.

The baseline treatment provided is sufficient to cover the subjects' use during the Baseline period of 14 days.

6.2.3.2. Treatment periods (Period boxes #2 and #3)

At Visit 2, the unblinded site personnel will instruct the subject to switch study medication according to study schedule:

- Subject should put the baseline treatment numbered #1 back to its carton kit (Period box #1);
- Subject should open the treatment kit numbered #2, corresponding to the first treatment period (Period box #2);
- Subject should ensure that the treatment kit numbered #3 remains untouched (Period box #3).

At Visit 3, the unblinded site personnel will instruct the subject to switch study medication according to study schedule:

- Subject should put the treatment kit numbered #2 back to its carton kit (Period box #2);
- Subject should open the treatment kit numbered #3, corresponding to the second treatment period (Period box #3).

The randomised treatments will be administered twice a day: **two** inhalations **in the morning** (preferably before 10.00 am) and **two** inhalations **in the evening** (preferably before 10.00 pm). To the extent possible, the time of dosing must remain constant for each subject for the whole duration of the study.

Each randomised treatment provided is sufficient to cover the subjects' use during the corresponding Treatment Period of 14 days.

6.2.3.3. Administration via a spacer

In case subjects are used to inhaling their pMDI Asthma medications using a spacer device, they will continue using their own spacer with the study medications.

Spacer should be used according to its SmPC.

6.2.3.4. Use of reliever treatment (Rescue medication)

For the duration of the study, subjects will not be provided reliever treatment (rescue medication) but are allowed to take their own usual prescribed reliever on an as-needed basis, provided that it is not included in the list of Most relevant forbidden concomitant treatments as described in section 5.2.

None of the study treatments assigned to the subjects can be used as a reliever therapy.

Reliever therapy should be used according to its SmPC.

Note: Subjects under Foster® MART indication should use their own prescribed Foster® inhaler as reliever therapy and as per the Foster® SmPC. The maximum daily dose of Foster ® under MART indication is 8 inhalations.

6.2.4. Subject Training

During the screening/randomisation visit (Visit 1), the unblinded site personnel will provide the IMPs handling training to the subject using the instructions leaflet developed for the study. In particular, the trainer will show the content of Subject box and will provide clear instructions on when to open/use each medication in chronological order during the study:

- Baseline treatment– Period box #1: to be opened and administered at screening/randomisation visit (Visit 1) or at subjects' home after the Visit 1 occurred (see instructions in section 6.2.3.1);
- Randomised treatment – Period box #2: to be opened and used when instructed by unblinded personnel at the first remote video call (V2);
- Randomised treatment – Period box #3: to be opened and used when instructed by unblinded personnel at the second remote video call (V3).

If deemed necessary, subject can be instructed by the Unblinded site personnel on how to use the pressurised Meter Dose Inhaler (pMDI) according to the instructions provided along with the study drug.

If the subject is used to take asthma pMDI medications via a spacer, he/she can also be trained to use the study spacer.

6.3. Packaging

All investigational products will be prepared in accordance with Good Manufacturing Practices (GMP) as required by the current ICH E6 Good Clinical Practices (GCP).
Chiesi Farmaceutici S.p.A. will supply the material described in the following sections. Treatment kits will be supplied to the Investigator as one treatment kit for each Subject, referred as Subject box.

6.3.1. Baseline Period

- ***Primary packaging***: one labelled canister containing Foster® 100/6 µg solution for inhalation plus one labelled dose counter (120 doses) actuator.
- ***Secondary packaging***: one labelled commercial box containing 1 canister and 1 dose counter (120 doses) actuator.

Note: The box and the respective canister will be labelled with the number "1" identifying the sequence of administration to be followed and to help the subject in opening and using it in a chronological order.

6.3.2. Randomised Treatment for the first and the second Treatment Period

- ***Primary packaging:***

  - **Inhaler A**: one labelled canister containing CHF 1535 100/6 µg pMDI solution for inhalation plus one labelled actuator
  - **Inhaler B**: one labelled canister containing CHF 1535 100/6 µg pMDI solution for inhalation plus one labelled actuator

Note: The canisters will be labelled with the number "2" or "3" identifying the sequence of administration to be followed and to help the subject in opening and using it in a chronological order.

- ***Secondary packaging:***

- Treatment Period box for Inhaler A: one labelled box containing one labelled canister containing CHF 1535 100/6 µg pMDI solution for inhalation plus one labelled actuator to be used in one period;
- Treatment Period box for Inhaler B: one labelled box containing one labelled canister containing CHF 1535 100/6 µg pMDI solution for inhalation plus one labelled actuator to be used in one period.

Note: Each Period box (Inhaler A or Inhaler B) will be labelled with the number "2" or "3" identifying the sequence of administration to be followed and to help the subject in opening and using it in a chronological order.

6.3.3. Tertiary packaging

- One labelled (with English tear-off part) **Subject Box** containing 1 commercial box of Foster® 100/6 µg pMDI (Baseline Period), plus one box containing one CHF 1535 100/6µg pMDI (Treatment Period - Inhaler A), plus one box containing one CHF 1535 100/6 µg pMDI (Treatment Period - Inhaler B).

6.4. Labeling

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

6.5. Treatment allocation

A master randomisation list will be prepared using a ClinPro software (LBL version 8.5) computerised system. Each subject will be assigned to one of 2 treatment sequences. Each site will be provided with a site-specific randomisation list, specifying the correspondence between the subject's screening number and the subject's randomisation number.

Each subject will be identified by a unique subject number of 8 digits assigned at Screening:

- the 3 first digits correspond to the ISO country code (380 for Italy);
- the 2 second digits to the centre number;
- the 3 last digits to the screening number (chronological in each site).

On randomisation (Day1), each eligible subject will be assigned the lowest available randomisation number according to the pre-established site-specific randomisation list. Each subject will be randomised with a unique randomisation number of 3 digits:

- Subjects that do not meet inclusion and/or met exclusion criteria at or before randomisation will not be eligible to enter the study. They will be considered "screen failure subjects". Those subjects cannot be re-screened.
- Subjects that prematurely terminate the study, will be considered "drop-out subject". Those subjects cannot be re-screened.

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

6.6. Treatment Code

The master randomisation list will be generated by Statistics and Data Management Department of *Chiesi Farmaceutici S.p.A.* and distributed to the labelling facility, but will not be available to subjects, investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency. Individual subject code break envelopes will be provided by *Chiesi Farmaceutici S.p.A.* The investigator will keep the code break envelopes in a locked and secured storage facility.

A code break envelope may only be opened in an emergency situation where the Investigator considers it essential to know which treatment the subject was taking. The monitor shall be promptly notified when a treatment code envelope is opened. The Investigator shall provide a certified explanation of why the treatment code was opened in the electronic Case Report Form for the subject or directly on the opened treatment code envelope. All code break envelopes, either unopened or opened, will be returned to *Chiesi Farmaceutici S.p.A*. upon termination of the study.

Users from Chiesi Global Pharmacovigilance will be also provided with a set of code break envelopes to unblind subjects in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees.
The subject will be provided with a card on which the phone numbers of hospital site and investigator are reported, and these can be contacted in case of emergency.

6.7. Treatment compliance

Compliance will be evaluated on the basis of the information recorded daily by the subject in the e-diary.
The evaluation of compliance will be done using the following formula:

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

The total number of scheduled doses will be calculated on the basis of the extent (days) of exposure of each subject. A range of **80-120 %** will be taken into account for a satisfactory level of compliance.

6.8. Drug Storage

The **Unblinded site personnel** will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of temperature and humidity.

pMDI kits must be stored between 2˚C and 8˚C by the **Unblinded site personnel** at site. Once dispensed, the subjects will be instructed to keep the boxes at home at ambient temperature not above 25°C.
At the time of drug intake at subject's home, the medication kits should be at room temperature, suitable for use. In case, the pMDI kits have been stored in the refrigerator at subjects' homes by mistake, the kit has to be removed from the refrigerator at the time of the drug intake and warmed with the hands for a few minutes before administration to the subject. The canister must never be warmed by artificial means. **The subject should never inhale a cold medication.**
At this temperature condition, the actual use-by-date of the pMDI kits will be three months (**90 days**). Therefore, **the unblinded site personnel at the site must write the use-by-date on the kit labels** once the pMDI kits are removed from the refrigerator, before assigning to the subjects. The **use-by-date corresponds to the dispensing date plus 3 months.** Please note that the use-by-date must not exceed the total shelf life of the product.

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

6.9. Drug Accountability

In order to maintain the study blind and to adequately gauge subjects' perception, an unblinded site personnel (e.g. Sub-investigator, pharmacist) will be delegated by the Principal Investigator at each site for the management of all the study medications to be used for the study. Study medications should be stored in a locked, secure storage facility with access limited to those individuals authorised to dispense the study medications.
An inventory will be maintained by the delegated unblinded site personnel, to include a signed account of all the study medication(s) received, dispensed and returned by each subject during the trial.
At the conclusion or termination of the study, the delegated unblinded site personnel shall conduct and document a final drug supply (used and unused) inventory. An explanation will be given for any discrepancies.
All the study medications supplied, used or unused, will be returned to Chiesi or to the designated CRO under Chiesi's responsibility or will be destroyed directly at the investigational centres when authorised by Chiesi. In this case, a destruction certificate must be asked to the investigational centre and filed both at site and at Chiesi. Return and destruction will not occur until authorised by Chiesi.

6.10. Provision of additional care

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

7. STUDY PLAN

7.1. Study Schedule

The study plan includes 4 study visits (Visit 1 to Visit 4), as follows:

- **Visit 1 at Day 1 / Face to face clinic visit:** Screening/randomisation visit to explain the aim of the study to the subject, to obtain their written informed consent, to verify subject's eligibility and to randomise the eligible subject into one of the 2 treatment sequences. Eligible subjects will be provided with all the study treatments included in the Subject Box according to the randomisation number. For eligible subjects, this visit will be followed by a 2-week Baseline Period, where the subjects will receive the Baseline treatment, i.e. the commercialised Foster® 100/6 µg pMDI
- **Visit 2 at Day 15 / Remote video call:** 14 days (± 1 day) after the screening/randomisation visit, to switch study treatment to the corresponding randomised treatment for Treatment Period 1, i.e. CHF 1535 100/6 µg pMDI in Inhaler A or Inhaler B, and for any AEs and concomitant treatment collection
- **Visit 3 at Day 29 / Remote video call:** 14 days (± 1 day) after Visit 2, to switch study treatment to the corresponding randomised treatment for Treatment Period 2, i.e. CHF 1535 100/6 µg pMDI in Inhaler A or Inhaler B, and for any AEs and concomitant treatment collection

- **Visit 4 at Day 43 / Face to face clinic visit:** 14 days (± 1 day) after Visit 3, to return the study treatments, to collect any AEs and concomitant treatments and proceed to the study Exit Interview. In case the subject is unable to physically come to the investigational site to attend the face to face visit (e.g. in case of emergency situation as described in section 9.2), it is possible to replace it by a remote video call. See detailed instructions in section 7.1.4.

The subject will follow the study treatment sequence as described below:

- Subjects will be treated with the commercial Foster® during the Baseline Period of 14 days;
- Subjects will then be instructed to take CHF1535 100/6 µg pMDI inhalers A and B during 2 consecutive periods of 14 days each (First and Second Treatment Periods) in a sequential way dictated by the randomisation:
    - Either CHF1535 100/6 µg pMDI with Inhaler A then CHF1535 100/6 µg pMDI with Inhaler B,
    - Or CHF1535 100/6 µg pMDI with Inhaler B then CHF1535 100/6 µg pMDI with Inhaler A.

In order to maintain the study blind and to adequately gauge subjects' perception, an unblinded site personnel will be assigned at each site by the Principal Investigator for the treatment dispensation and treatment return management, the drug accountability activities (please refer to section 6.9) and to perform corresponding assessments during the subjects' visits, whether during face to face visit or during the remote video calls. It is essential that this unblinded site personnel is distinct from the blinded investigator (who performs the other blinded activities such as the collection of ICF, demographics and other subjects' data, the assessment of concomitant medication and AEs/SAEs etc.) and that communication between the unblinded personnel and the blinded team should be kept at minimum to avoid accidental unblinding.

A "window" of -1 to + 1 day is allowed for the dates of all study visits.

The study plan and scheduled tests are summarised in the following Schedule of events:

	Baseline	Treatment period		
Visits	**Visit 1 Screening/ Randomisation**	**Visit 2**	**Visit 3**	**Visit 4 or ED[1]**
Type of visit	**Face to face**	**Remote video call**	**Remote video call**	**Face to face[8]**
Time (days)	**Day 1**	**Day 15**	**Day 29**	**Day 43**
Visits' window (days)		**± 1 day**	**± 1 day**	**± 1 day**
Informed Consent Form	✓			
Inclusion and Exclusion Criteria	✓			
Asthma Diagnosis History (including Asthma exacerbation history)	✓			
Medical History/Previous Medications (including Asthma medication history)	✓			
ACT	✓			
Smoking status	✓			
Demographic Data	✓			
Physical Examination	✓			
Vital Signs	✓			
Body weight	✓			
Height	✓			
Body temperature	✓			
Urine pregnancy test[2]	✓			✓
Adverse Events assessment	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓
Randomisation	✓			
Training to treatment kit content and administration schedule[3]	✓			
Treatment kits dispensation[3]	✓			
Treatment administration[4]	✓			
Instruction to subject for treatment kit switch[3]		✓	✓	
Treatment kits return[3]				✓
Treatment kit accountability[3]	✓	✓	✓	✓
e-Diary app download on subject's device and training	✓			
Check of e-Diary completion by the investigator[5]		✓	✓	✓
AQLQ(S)[6]		✓	✓	✓
e-Diary completion by subjects[7]				
Daily questionnaire: Asthma symptom perception and medication intake	Daily completion			
Psychopharmacological and preference questions		✓	✓	✓
Exit Interview[9]				✓

[1] ED stands for Early Discontinuation visit to be performed in lieu of the V4 for randomised subjects withdrawn from study treatment before Day 43.
[2] For females of childbearing potential only. Urine pregnancy test performed locally.
[3] Assessments to be performed by a Unblinded site personnel, delegated by the Principal Investigator.
[4] This refers to the first drug administration at V1, except in case the subject has taken his/her morning dose of maintenance treatment at home before the visit. See detailed instructions in section 6.2.3.1.
[5] To be checked regularly, at least during scheduled visits and remote video calls. Investigator should retrain subjects on e-Diary timely completion if needed.
[6] Interviewer-administered questionnaire.
[7] Refer to Appendix 3 for the list of questions to be answered at each study time point.
[8] In case the subject is unable to physically come to the investigational site to attend the face to face visit, it is possible to replace it by a remote video call. See detailed instructions in section 7.1.4.
[9] The Exit Interview is conducted by the Unblinded Site Personnel. See details in section 7.2.1.1.

7.1.1. Visit 1 – Face to face Screening/Randomisation (Day 1)

A face to face screening/randomisation visit will be carried out at the investigational site, in the morning.

The procedures below will be performed during the visit at site and supervised by properly trained site staff:

- **Collection of the written informed consent** signed by the subject, after the study has been fully explained by the investigator. The investigator or his/her designee should provide subject time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial;
- Upon signature of the ICF(s), the investigator (or his/her designee) will allocate a unique **subject screening number** and record demographic data. This number will be sequentially assigned.
- **Medical/Asthma History**: The medical history including asthma history and asthma exacerbation history will be checked for eligibility and will be recorded in the eCRF. In particular, the Investigator must ensure that the subject has an established diagnosis of permanent asthma for at least 6 months prior to screening/randomisation visit, with documented history of variable respiratory symptoms and confirmed variable expiratory airflow limitation according to the description in the Box 1-2 of the 2020 GINA Report (Appendix 2)
- **Previous and concomitant medication**: all medications taken by the subjects within the last 3 months and all medications taken for asthma and asthma exacerbations within 6 months will be recorded in the eCRF. Intake of non-permitted medication constitutes non-eligibility criterion for enrolment in the study.
- **Surgical and medical procedures**: the occurrence of any procedure from the ICF signature will be checked and recorded in the eCRF.
- **Asthma Control Test (ACT)** will be completed at screening on paper format and entered by investigator or his/her delegate in the eCRF. Subjects with ACT score ≥ 20 are eligible (see section 7.2.1.3. and inclusion criterion #5).
- **Smoking status** will be checked to ensure it is not fulfilling the exclusion criterion #9. Data will be recorded in the eCRF.
- **Demography recording:** Recording of demographic data including gender at birth, race, date of birth (full date) and childbearing potential status (for female only).
- A full **physical examination** will be performed (see section 7.2.2).
- **Vital signs** will be recorded (systolic [SBP] and diastolic [DBP] blood pressure and Pulse rate (PR)), after supine position after 5-min rest (see section 7.2.3).
- **Height and body weight** will be measured (see section 7.2.3).
- **Body temperature will be measured.** The location of the temperature measurement (e.g. axillary, oral, auricular, forehead, rectal) is at the discretion of the investigator according to site's common practice (see section 7.2.3).
- A **urine pregnancy test** will be performed in women of childbearing potential (see section 7.2.4).
- **Adverse Events (AEs):** AEs occurred since the signature of informed consent will be checked and recorded. In case of any clinically significant abnormality revealed during the screening

procedures, it will be recorded in the subjects' medical history in the eCRF, unless its onset date is after the informed consent signature date and it is not due to a pre-existing condition. In this case it will be recorded as an AE in the eCRF.

- **All eligibility criteria will be reviewed.** In case subject is not eligible, subject will be withdrawn from the study and recorded as screen failure.

For eligible subjects:

- *To be performed with the blinded Investigator (or designee):*
  - As a Bring Your Own Device (BYOD) approach is used for the study, the investigator will follow the appropriate procedures to **activate the e-Diary account** for the subject. The investigator will then provide support to the subject to ensure that the proper application is installed and ready for use on subject's electronic device.
  - **Subject will then be trained** on the proper way of recording data in the e-Diary app (asthma symptom perception, medication intake and psychopharmacological questions) and on how to transmit the data daily on the digital platform (see section 7.2.1). In particular, subject should be instructed to always complete the e-Diary in the mornings, preferably at the same time and that all the daily questions will refer to the medication intake and symptoms perception of the previous day. In consequence, **first completion** of the daily e-Diary should be done the day after the visit,
- *To be performed with the Unblinded site personnel:*
  - The subject will be **randomised,** and the treatment sequence will be allocated according to the site-specific randomisation list. Once the randomisation number has been obtained, the Investigator will forward this number to the **Unblinded site personnel** who will identify the corresponding Subject Box number and will **dispense** the Subject box accordingly and for the entire duration of the study (Subject box will include the Period boxes for Baseline period and the 2 Treatment periods). The Unblinded site personnel will ensure that the corresponding study drug accountability logs are adequately filled-in to reflect the dispensation
  - The corresponding tear-off labels will be stuck in the dispensation tracking form and the kit numbers will be recorded in the eCRF. For pMDI, the use-by-date must be filled-in on the labels.
  - The unblinded site personnel will provide subjects with a thorough **IMPs handling training** to the subject using the instructions leaflet developed for the study. In particular, the trainer will show the content of subject box and will provide clear instructions on when to open/use each medication in chronological order during the study.
  - The **first administration of the study drug (baseline treatment)** will take place at the clinic visit as per instructions for use and according to section 6.2.3.1., unless subject has already taken his morning dose of maintenance treatment before the PIS/ICF signature at study site. In this latter case, subject will be instructed to take the first dose of study baseline medication provided by the unblinded site personnel at subject's home in the evening of the Visit 1, preferably before 10.00 pm.

Before discharge:

- Subjects will be reminded to **complete the daily questionnaire** in the electronic diary in the morning and transmit the data on a daily basis until visit 2. In case poor

compliance to e-Diary completion, to study medication and/or worsening of asthma symptoms are detected through the e-Diary completion, ad-hoc phone call(s) to the subject can be performed by the site, as deemed necessary.

Note: It is important to ensure a good compliance of the subject to the use of the electronic diary during the baseline period in order to obtain high quality and complete baseline data. To that aim, specific alerts will be set in the e-Diary platform to alert the Investigator in case of poor completion compliance. In that case and once the investigator receives the alerts, the investigator or designee should check by calling the subject and retrain if necessary.

- Subject will be provided with a **patient card** containing key site information and will be instructed to contact the investigator in case of any particular study-related issues or if any health or safety issues require the investigator's attention.
- Subject will be reminded that the **next study visit** is planned in 14 days and will be conducted as a remote video call from the investigator or designee.

7.1.2. Visit 2 – Remote video call (Day 15 ± 1 Day)

A remote video call will be performed with the subjects in the morning after 14 days (± 1 day) of the Screening/randomisation visit.
The video call will be split in two, where the investigator (or designee) will perform the first part and the delegated unblinded personnel will perform the second part. The blinded investigator should not attend the video call performed with the unblinded personnel.

The following procedures will take place:

- *Video call to be performed with blinded Investigator:*
  - The investigator (or designee) will check whether the subjects have been **filling-in and transmitting the e-Diary data.** In case no issues have been previously identified, the investigator should encourage the subject to continue to fill-in the daily e-Diary. In case low compliance has been identified, the investigator should try to identify the reason of non-compliance and re-train the subject if necessary.
  - The investigator will complete the **AQLQ(S) questionnaire** (interviewer-administered version) on paper on the basis of the answers provided by the subject during his/her phone interview. The corresponding subject's answers should then be entered in the eCRF by the Investigator (or designee).
  - The investigator (or designee) will inform the subjects that in addition to the daily questions, **questions specific for Visit 2** will also be asked in the e-Diary on the day of this visit. These questions should be answered once the video call with the unblinded personnel has occurred.
  - The status of **ongoing AEs** will be checked and updated in the e CRF when applicable. Any new AE/SAE occurred since the screening visit will be checked and recorded in the eCRF and **concomitant medications** will be verified and updated, if applicable.
  - Subject will be reminded that the **next study visit** is planned in 14 days and will be conducted again as a remote video call with the blinded investigator and the unblinded site personnel.
- *Video call to be performed with unblinded site personnel:*
  - The unblinded site personnel will instruct the subject to **switch study medication** according to study schedule:
    - Subject should put the baseline medication back to its carton kit;

- Subject should open the medication kit numbered #2, corresponding to the treatment for the first treatment period
- Subject should ensure that the medication kit numbered #3 remains untouched.

  - After ensuring that the subject has switched medication, the unblinded site personnel will fill-in the study drug accountability logs to ensure they adequately reflect the dispensation.

7.1.3. Visit 3 – Remote video call (Day 29 ± 1 Day)

A remote video call will be performed with the subjects in the morning and after 14 days (± 1 day) of the V2 video call visit.
The video call will be split in two, where the investigator (or designee) will perform the first part and the delegated unblinded personnel will perform the second part. The blinded investigator should not attend the video call performed with the unblinded personnel.

The following procedures will take place:

- *Video call to be performed with blinded Investigator:*
  - The investigator (or designee) will **check in the electronic diary (e-diary) portal** whether the subjects have been filling-in and transmitting the e-Diary data. In case no issues have been previously identified, the investigator should encourage the subject to continue to fill-in the daily e-Diary. In case low compliance has been identified, the investigator should try to identify the reason of non-compliance and re-train the subject if necessary.
  - The investigator will complete the **AQLQ(S) questionnaire** (interviewer-administered version) on paper on the basis of the answers provided by the subject during his/her phone interview. The corresponding subject's answers should then be entered in the eCRF by the Investigator (or designee).
  - The investigator (or designee) will inform the subjects that in addition to the daily questions, **questions specific for Visit 3** will also be asked in the e-Diary on the day of this visit. These questions should be answered once the video call with the unblinded personnel has occurred.

  - The status of **ongoing AEs** will be checked and updated in the eCRF when applicable. Any new AE/SAE occurred since the last visit will be checked and recorded in the eCRF and **concomitant medications** will be verified and updated, if applicable.
  - Subject will be reminded that the **next study visit** is planned in 14 days will be the last study visit that will be conducted face to face at the investigational site. In particular, subject will be instructed of the following:
    - Before coming to the investigational site, subject should take the morning dose of study treatment, which corresponds to the last dose of study treatment
    - Subject should come back to investigational site with the Subject box.

- *Video call to be performed with unblinded site personnel:*
  - The unblinded site personnel will instruct the subject to **switch study medication** according to study schedule:
    - Subject should put the medication kit numbered #2 back to its carton kit;
    - Subject should open the medication kit numbered #3, corresponding to the treatment for the second treatment period;

- After ensuring that the subject has switched medication, the unblinded site personnel will fill-in the **study drug accountability** logs to ensure they adequately reflect the dispensation.

7.1.4. Visit 4 – Face to Face (Day 43 ± 1 Day)

A face to face Visit 4 will be carried out at the investigational site.

Before coming to site, subject should have already taken his/her morning dose of study drug treatment, which corresponds to the **last dose of study treatment**. It is to be noted that since the daily medication intake questions only refers to the data of the previous day, the last dose of study treatment will not be captured in the e-Diary.

The following procedures will take place:

- *To be performed with the blinded Investigator (or designee):*
  - A urine pregnancy test will be performed in women of childbearing potential (see section 7.2.4).
  - The investigator will complete the **AQLQ(S) questionnaire** (interviewer-administered version) on paper on the basis of the answers provided by the subject during his/her interview. The answers should then be entered in the eCRF by the Investigator (or designee).
  - The status of **ongoing AEs** will be checked and updated in the eCRF when applicable. Any new AE/SAE occurred since the last visit will be checked and recorded in the eCRF and **concomitant medications** will be verified and updated, if applicable.
  - Subject will be asked to **complete their last daily e-Diary** at the investigational site, if not already done. Questions include daily questionnaire and V4-specific questions (please see Appendix 3). It is to be noted that questions #11-16 are part of the "Exit Interview" that should be conducted by the Unblinded site personnel (see below and section 7.2.1.1.).

- *To be performed with the Unblinded site personnel:*
  - Subject should **return all study medication** to the unblinded site personnel, who must ensure that all medications are present and proceed to the drug reconciliation by filling-in the appropriate drug accountability log. Any discrepancies should be documented.
  - The Unblinded site personnel will perform the **"Exit Interview"** with the subject, which aims at providing explanations about how the subject was deceived/misled and why it was necessary for the study (see section 7.2.1.1.). To that aim, the Unblinded site personnel will ensure that questions **#11-14** (see Appendix 3) have been answered by the subjects **before** providing the debriefing explanations. Once the explanations have been provided, it is expected that subjects will complete question **#15-16** (see Appendix 3).

Before discharge:

- The e-Diary will be uninstalled from the subject's electronic device once the investigator has checked that all data have been properly transferred to the application server

- The investigator will prescribe the most appropriate treatment (that will not be recorded in the eCRF) or restore the initial therapy or refer to the General Practitioner.

Note: In case the subject is unable to physically come to the investigational site to attend the face to face visit (e.g. in case of emergency situation as described in section 9.2), it is possible to replace it by a **remote video call.** In this case, all the assessments described above should be performed remotely. In addition, the unblinded site personnel will arrange the return of the study medication from subject's home to the investigational site using a courier.

7.1.5. Early Discontinuation Visit

If a subject is withdrawn before the end of the treatment period for any reason else than withdrawal of consent, the final procedures will be carried out to the extent possible.

All the assessments foreseen at Visit 4 (Day 43) should be done to the extent possible, providing there is **no safety issue for the subject.** In case subjects are discontinued before Visit 3 has been performed, then questions #11-16 of the list of e-Diary questions will not be applicable to those subjects and should not be answered. The Exit interview will only consist on the debriefing by Unblinded site personnel (i.e. how the subject was deceived/misled and why it was necessary for the study). The explanations regarding the reasons for withdrawal and all the assessments performed will be recorded. The corresponding forms should be completed in the eCRF.

In case of early discontinuation for withdrawal of consent, no further assessments will be done except the check of AEs/SAEs status up to the date of withdrawal of consent. The investigator must fill in the study termination form in the eCRF.

Before discharge:

- The e-Diary will be uninstalled from the subject's electronic device once the investigator has checked that all data have been properly transferred to the application server.
- The investigator will prescribe the most appropriate treatment or restore the initial therapy or refer to the General Practitioner.

7.2. Investigations

7.2.1. Patient Reported Outcomes (PROs) Instruments

7.2.1.1. Electronic Diary (e-Diary) and study-specific subject's questionnaire

e-Diary

e-Diary is implemented for this study and the Bring Your Own Device (BYOD) approach is used. Subjects will be instructed to use their own electronic device, with internet connection for the first activation and the subsequent completion of the e-Diary throughout the study. A comprehensive training will be performed at Screening/randomisation (V1) by the Investigator using the training module built-in the e-Diary app, so that the subject fully understands how and when to complete the e-Diary. Subjects will be asked to answer specific questions at specific timepoints as described below.

Study specific subject's questionnaire

A study-specific questionnaire was developed to collect patient reported outcomes. The questionnaire includes 16 questions that are to be completed by subjects through the e-Diary. Some questions are asked on a daily basis in the morning and other have to be completed only at specific timepoints at V2, V3 and V4, as specified in the Appendix 3. It takes approximately 5 minutes to complete the questionnaire which covers the below domains:

- 2 questions concern medication intake (both maintenance and reliever therapies) should be answered by the subject every morning from the day after the V1 to the end of the study at V4 (Question #1-2 in Appendix 3);
- 4 questions are asked about subjects' daily perception of asthma symptoms and should be answered by the subjects every morning from the day after the V1 to the end of the study at V4 (Questions #3-6 in Appendix 3);
- Psychopharmacological questions will also be asked at specific study visit time points (2 questions at V2, 4 questions at V3, 2 questions at V4; Questions #7-10).
- 2 questions are related to subject's visual preferences towards the inhaler and will be answered by the subject only at V4 (Questions #11-12 in Appendix 3).
- 4 questions about the subject perception of the changes applied to the inhalers will be answered by the subject only at V4 (Questions #13-16 in Appendix 3).

Questions are either assessed through numeral completion (medication intake), a Visual Analogue Scale (VAS) scaling from 0 to 100 or through multiple choices type question.

➢ ***The Exit Interview***

The questions related to the subject's visual preferences towards the inhaler (Questions #11-12 in Appendix 3) and related to subject's perception of the changes applied to the inhalers (Questions #13-16 in Appendix 3) are part of the "Exit Interview", to be conducted with the Unblinded site personnel at V4. This "Exit interview" aims at debriefing with the subject at the end of the study to provide explanations about how the subject was deceived/misled and why it was necessary for the study. To that aim, the Unblinded site personnel will ensure that questions #11-14 have been answered by the subjects before providing the debriefing explanations. Once the explanations have been provided, it is expected that subjects will complete question #15-16. In case subjects are discontinued before Visit 3 has been performed, then questions #11-16 will not be applicable to those subjects and will not be answered. The Exit Interview will only consist on the debriefing by Unblinded site personnel (i.e. how the subject was deceived/misled and why it was necessary for the study).

7.2.1.2. Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

The Asthma Quality of Life Questionnaire (AQLQ) is a disease-specific health-related quality of life instrument that taps both physical and emotional impact of disease in adult subjects [28] [29]. There are 32 questions and they are grouped in four domains (symptoms, activity limitation, emotional function and environmental stimuli). Subjects are asked to think about how they have been during the previous two weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all; 1 = severely impaired). It takes 5 – 15 minutes to be completed [30].

The version of the AQLQ questionnaire used in the current study is the Standardised AQLQ (AQLQ(S)) that differs from the original AQLQ in the 5 standardised activities replacing the patient-specific ones. These five generic activities incorporate the activities that were most frequently chosen by patients in studies in which the original AQLQ was used. The AQLQ(S) has been fully validated. Test-retest reliability and cross-sectional validity are almost identical to the original AQLQ as are responsiveness and longitudinal validity [31].

The AQLQ(S) will be filled in by the Investigator (or designee) on paper format according to answers provided by the subject during the remote video call at Visit 2, Visit 3 or during the face-to-face visit at Visit 4. The corresponding subject's answers should then be entered in the eCRF by the Investigator (or designee).

All translations of QOL Tech questionnaires (company owner of the AQLQs), including the AQLQ (and all its derived forms) have been developed exclusively by ICON languages services (former Mapi language services team) in collaboration with Prof. E. Juniper, the developer of the instruments, through a rigorous protocol which is known as to the "Linguistic Validation" process. This Linguistic Validation process was developed years ago by key experts in the field to precisely tackle the last of psychometric validation in translations. So the Linguistic Validation has been created with the objective of ensuring content validity of the original content would be reflected in the translation, and thus that the measurement properties would be maintained. This process was described in the ISPOR Guidelines published in 2005 [32], and implemented in the Linguistic validation manual developed by ICON/Mapi [33].
The protocol of Linguistic Validation for QOL Tech instruments include:

- 2 independent forward translations (in-country team);
- 1 backward translation (in-country team);
- Cognitive interviews by in-country clinician to 10 patients, native speakers of the target language, suffering from current symptoms of asthma with a wide range of disease severity;
- Review of the versions by the in-country clinician before and after cognitive interview;
- Proof reading and finalization;
- Certificate of translation;

The steps of forward translations, backward translation and cognitive interviews are all performed in the target country.

Today, the linguistic validation methodology is recognized by the scientific community as a robust process to develop translations of questionnaires to be used in clinical trials [34]. Regulatory authorities and ethic committees often require this specific certificate of translation ensuring the process was followed. After more than 30 years of use, this methodology has been considered enough evidence to ensure equivalence between the original content and the translation and to reflect measurement properties. Finally, as the use of the AQLQ is controlled by QOL Tech, the Italian version developed by ICON/Mapi language services is the only one in circulation that is used to ensure harmonization of data across studies and programs.

Although psychometric measurement for Italian version is currently not available, the risks associated with linguistic validation are extremely limited. In a number of psychometric studies of AQLQ in its original English language and other languages (English, Chinese, Turkish, Serbian, Spanish etc..), the AQLQ (or its derived forms) have been found as a reliable, valid, sensitive and responsive measure of quality of life in asthmatic patients and have strong correlations to other health related quality of life questionnaire such as Short Form-36 (SF-36) or St Georges Respiratory Questionnaire [31] [35] [36] [37] [38].
This demonstrates that the rigorous linguistic validation process ensures the content and measurements equivalence between the original language and the translated language.

7.2.1.3. Asthma Control Test (ACT)

ACT was developed in 2004 in the United States for evaluating asthma control in subjects of 12 years of age or older. The test consists of 5 items, with a 4-week recall period: 4 symptom and daily functioning items (concerning frequency of shortness of breath and general asthma symptoms, use of

reliever medications, effect of asthma on daily functioning) and 1 item referring to the overall subject's self-assessment of asthma control. For each item the subject chooses one from 5 possible answers, each of which is assigned a point value from 1 to 5 [39] [40] [41]. ACT will be completed by all subjects at Visit 1 in paper format for eligibility purposes and the corresponding subject's answers will be recorded in the eCRF by the site personnel.

7.2.2. Physical Examination

The physical examination will include the following assessments:

Cardiac	Hepatobiliary, Renal and Urinary	Reproductive System and Breast
Ear and Labyrinth	Mouth, Throat and Gastrointestinal	Respiratory, Thoracic and Mediastinal
Endocrine and Lymph	Muscoloskeletal and Connective Tissue	Skin and Subcutaneous tissue
Eye	Nervous System	Vascular

Other body system assessments can be collected in case of abnormalities are detected.

Any abnormalities will be reported as medical history or as adverse events according to the onset date, if considered as clinically significant in the opinion of the investigator.

7.2.3. Vital signs, height, body weight and body temperature

Pulse rate (PR), systolic and diastolic blood pressure (SBP, DBP – mmHg) will be measured in supine position after 5-min rest at screening/randomisation (V1).

Vital signs may be repeated at the discretion of the investigator for the purposes of safety. If the investigator performed more assessments than expected, these assessments will be recorded in the eCRF and a comment clarifying the reason for the unscheduled assessment should be made.

Vital signs abnormalities will be reported as medical history or as adverse events according to the onset date, if considered as clinically significant in the opinion of the investigator.

Height and body weight will be assessed at V1.

Body temperature will be assessed at V1. The location of the temperature measurement (e.g. axillary, oral, auricular, forehead, rectal) is at the discretion of the investigator according to site's common practice and should be documented in the eCRF.

7.2.4. Urine pregnancy test

A urine pregnancy test will be performed locally on site at screening/randomisation visit (Visit 1) and Visit 4 only for females of childbearing potential.

8. EFFICACY ASSESSMENTS

- Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days and over the entire 14 days treatment period (questions #3-#6 of the Study specific subject's questionnaire, Appendix 3);

- Summary measures for questions with continuous outcome covering subjects' psychopharmacological aspects (questions #7-#10 of the Study specific subject's questionnaire, Appendix 3);
- Percentages of subjects to questions covering subjects' preference and perception of the devices (questions #11-#16 of the Study specific subject's questionnaire, Appendix 3);
- Change from baseline in reliever medication use over the entire 14 days treatment period (questions #2 of the Study specific subject's questionnaire, Appendix 3);
- Change from baseline in AQLQ(S) score after 14 days of treatment.

9. SAFETY ASSESSMENTS

9.1. Safety variables

- Adverse events (AEs) and Serious adverse events (SAEs).

9.2. Emergency situation

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

In that particular case:

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

Special case of COVID-19 outbreak:

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

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

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

As of the date of this protocol version, there is no specific treatment for COVID-19 and several vaccine therapies have been developed and approved by health authorities with vaccination campaigning being initiated worldwide. For all confirmed cases of COVID-19/SARS-CoV-2 the

investigator must follow the standard of care in accordance with local treatment guidelines. All concomitant treatments must be recorded in the eCRF.

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

This may not be necessary if the results of tests can be obtained from the hospital where the event was diagnosed and/or managed.
The investigators will use their clinical assessment to report COVID-19 as AE based on the definition and assessment of event.

10. ADVERSE EVENT REPORTING

10.1. Definitions

An **Adverse Event** (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 adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

- **Results in death**

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

- **Is life-threatening**

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

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

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 adverse event**

This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the subject's health or may require intervention to prevent one of the above outcomes.
Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.
Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

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

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

10.2. Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (included in the Summary of Product Characteristics for CHF1535 pMDI), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.
In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3. Intensity of Adverse Event

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

- **Mild:** The event causes a minor discomfort or does not interfere with daily activity of the subject or does not lead to either modification of test treatment dosage or establishment of a correcting treatment.

- **Moderate:** The event perturbs the usual activity of the subject and is of a sufficient severity to make the subject uncomfortable. The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** The event prevents any usual routine activity of the subject and causes severe discomfort. It may be of such severity to cause the definitive interruption of test treatment.

10.4. Causality Assessment

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

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

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

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

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

10.5. Action taken with the study drug due to an AE

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

10.6. Other actions taken

- Specific therapy/Medication
- Concomitant Procedure

10.7. Outcome

Each Adverse Event must be rated by choosing among:

- Recovered/resolved

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

10.8. Recording Adverse Events

All Adverse Events occurring during the course of the study must be documented in the Adverse Event page of the electronic Case Report Form (eCRF). Moreover, if the Adverse Event is serious, the Serious Adverse Event Form must also be completed.
It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings.
The recording period for Adverse Events is the period starting from the Informed Consent signature until the subject's study participation ends.
Clinically significant abnormalities detected at Visit 1 not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the investigator must be reported as adverse events in the eCRF

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

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the subject's study participation ends should be evaluated up to 14 days after last study drug intake. After this period, all unresolved ADRs and SAEs will be reported as "recovering/not recovered" in the eCRF

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

10.9. Reporting Serious Adverse Events to Chiesi

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

Name and Title	Telephone no.	Fax no.	E-mail
PPD Safety manager PPD PPD Global Pharmacovigilance Operations Specialist Chiesi Farmaceutici S.p.A.	PPD	+39 045 82 50 574 +3905211885003	PPD PPD Ct_cds@chiesi.com

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, SAEs occurring to a subject should be reported if the investigator becomes aware of them.
- Up to the closure of the site, SAE reports should be reported to the PPD Safety Contact. New serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

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

All SUSARs, which occur with the investigational medicinal products within or outside the concerned clinical trial, if required, will be reported in compliance with the timelines and standards for reporting SUSARs set out in the EU Directive 2001/20/EC [Directive 2001/20/EC of the European parliament and of the council of 4/April/2001] and linked guidance [European Commission, Enterprise and Industry Directorate General: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use, latest version]. The EMA and the concerned national health authority (if applicable) will be informed through Eudravigilance or according to local requirements (as applicable), while the Ethics Committees and the investigators by CIOMS I form or by periodic line-listings produced by Chiesi Global Pharmacovigilance.
With regard to regulations in force for Pharmacovigilance, the Investigator must fulfill his/her obligation according to the law in force in his country.

10.11. General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the PPD Safety Contact within the Serious Adverse Event form.
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the PPD Safety Contact as soon as available, retaining a copy on site.
- All source documents provided by the Investigator or site staff to the PPD Safety contact must be carefully checked for respect of confidentiality. All personal subject's data must be redacted.
- In case of pregnancy, the subject will be immediately withdrawn from the study and she will be asked (with a separate consent) to be followed with due diligence until the outcome of the pregnancy is known and till the age of one year of the child to detect any congenital anomaly or birth defect. The pregnancy must be reported by the investigator within 24 hours by fax/e-mail to the PPD Safety Contact using the paper Pregnancy Report Form. The

PPD Safety Contact will inform Chiesi of the pregnancy within one working day of being notified.
The first two pages of the Pregnancy Report Form should be completed by the investigator with all the available information and sent to the PPD Safety Contact. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome, together with a follow-up of the first two pages, if necessary (e.g. an update in the medications received during pregnancy by the mother). If it meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator should follow the procedure for reporting SAEs.

- If it is the partner, rather than the subject, who is found to be pregnant, the same procedure regarding pregnancy reporting is to be followed and the Pregnancy Report Form should be completed, but the subject participating to the study should not be discontinued from the study.
- If the pregnancy is discovered before taking any dose either of study drug or of the run-in/rescue/background medication, the pregnancy does not need to be reported; it is only required that the subject is immediately withdrawn from the study.
- Any Adverse Drug Reaction (ADR) occurring with any marketed non-investigational medicinal product and/or concomitant medication during the study must be reported by the Investigator to his/her concerned Health Authority according to the applicable laws. The Investigator is also recommended to report all adverse drug reactions to the relevant Marketing Authorisation Holders of the involved medicinal products. Additionally, also conditions of use outside the marketing authorisation of the medicinal products (i.e. offlabel, overdose, misuse, abuse and medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy should be reported.

11. DATA MANAGEMENT

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

All subjects who sign the informed consent will be entered into the eCRF. For subjects who are screened but not randomised, a minimum set of information is required: date of informed consent signed, demography, assessment of inclusion/exclusion criteria when applicable, primary reason for not continuing, prior and concomitant medications and adverse events if any.

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.

Subject e-Diary app will be downloaded on the subject electronic device (BYOD approach) and filled in daily. Data will be sent to the clinical database and will be visible in the eCRF as soon as collected.

ACT questionnaire will be filled in on paper by the subjects and data will be entered in the eCRF by the investigator (or designee). AQLQ(S) questionnaire will be filled in by the Investigator (or designee) on paper format according to answers provided by the subject and then data will be entered in the eCRF by the Investigator (or designee). Medical history, asthma history, asthma exacerbation history adverse events and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC) up to ATC level 5.

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 and the planned statistical analysis will be performed.

If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be 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 calculation is not based on a formal statistical hypothesis, since this is an exploratory study. A total of 75 randomised subjects is deemed sufficient to assess the objectives of the study.

As per our knowledge at the time of the protocol redaction, this is the first psychopharmacological study in adult patients with moderate to severe asthma based on patients' perception of asthma symptoms. At the time of the sample size considerations, no scientific article from previous experiences was available to obtain at a minimum a rough indication of the key parameters (effect size and variability) needed for a proper sample size calculation.
In this study, and in general in every psychopharmacological study which aims at evaluating the "patients' perception", there is not a single formal primary variable to be used as outcome for the sample size calculation.
For these reasons it was decided to proceed with an exploratory study. The present study can be considered as a "pilot" to check for signals to be quantified and potentially used as reference in future studies.
The choice of the sample size, based on the scientific advice received from a Key Opinion Leader in the psychopharmacological and neurobiological field, was in line with previous psychopharmacological studies performed in other therapeutic areas [42] [43] [19] [44] [45] [46], and is deemed sufficient to ensure for the study outcomes a clinically acceptable degree of precision.
Below are listed some considerations on this regard.

Degree of precision for categorical outcomes.
The categorical outcomes are quantified as proportion of patients reporting, at the end of the Visit 4 (end of study) the preference on the inhalers used during the study and the changes/differences between them (items 11-16 of the e-diary). By using the formula for the approximation of the binomial distribution to the normal distribution, the degree of precision for the proportion is estimated by the half-width of the 95% confidence interval (CI). In case of a proportion equal to 50% (worst case) the half-width of the 95% CI would be 11.3%. For proportions greater or lower than 50% the half-with of the 95% CI would be smaller and the precision higher [47]

Degree of precision for "change from baseline in average VAS score".
In the present study the VAS scales measure asthma symptoms in a range 0-100. Based on symptom data from a previous Chiesi cross-over study in asthmatic patients (TRISKEL, NCT02127866 [48]), an estimate of the within-subject standard deviation (SD) of 5.4 units was obtained for change from baseline in average VAS score. By assuming 75 evaluable subjects, the above estimate of within-subject SD leads to a 95% confidence interval with an expected precision (i.e., half width) of ±1.8 units for the mean difference between treatments.

12.2. Populations for analysis

The following analysis sets will be considered:

- ✓ Safety set: all randomised subjects who receive at least one dose of study treatment (analysed according to an *as-treated* approach).
- ✓ Intention-to-Treat (ITT) set: all randomised subjects who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline (analysed *as-randomised*).
- ✓ Per Protocol (PP) set: all subjects from the ITT set without any major protocol deviations (e.g. wrong inclusions, poor compliance, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

Since the study has a cross-over design, the inclusion in each analysis set will be defined on a per-period basis.

12.3. Statistical analysis

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

12.3.1. Descriptive Statistics

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

12.3.2. Missing data

No imputation of missing data will be performed. Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP. Other critical missing data, if any, will be discussed during the blinded review of the data. Decisions will be fully documented in the Data Review Report.

12.3.3. Subject demographics and baseline characteristics

Demographics and baseline variables will be summarised by sequence and overall using descriptive statistics for the ITT population.
The following variables will be presented: age, gender, race, height, weight, medical history, concomitant diseases, physical examination, screening efficacy parameters, prior medications, vital signs.

Analysis will be presented for the Safety Population (if different from the ITT population) and the PP (if different from the ITT population) for the same variables.

12.3.4. Efficacy variables

- ***Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the entire 14 days treatment period*** will be analysed on the ITT using a linear mixed model for repeated measures including subject, period, treatment, timepoint (i.e. from Day 1 to Day 7 and from Day 8 to Day 14), period by timepoint interaction, and treatment by

timepoint interaction as fixed effects. Baseline value is defined as the average of the VAS scores collected during the baseline period. Baseline value will not be included as covariate because it is common for the two periods and the inter-subject differences are already accounted for by the subject effect. An unstructured covariance matrix within period will be assumed, and the Kenward-Roger adjustment will be used for the degrees of freedom. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% confidence intervals (CIs) will be estimated by the model (this analysis will assign equal weights to the two timepoints). Statistically significant difference between treatments is defined as $p<0.05$. Missing data will not be imputed. This analysis will be applied on questions collected daily using a VAS score (see Appendix 3 for the list of questions). Each question will be analysed separately.

- ***Change from baseline in average VAS score evaluating subject perceptions of asthma symptoms over the first 7 days of treatment*** will be analysed on the ITT set and derived from the previous statistical model (specifications will be provided in the SAP)..

- ***Summary measures (descriptive statistics) for questions with continuous outcome covering subjects' psychopharmacological aspects will*** be reported on the ITT and PP set by treatment group. This analysis will be applied on questions not collected daily. Each question will be analysed separately. The list of all the questions is reported in Appendix 3;

- ***Percentages of subjects to questions covering subjects' preference and perception of the devices*** will be reported on the ITT and PP set by treatment group. This analysis will be applied on questions not collected daily. Each question will be analysed separately. The list of all the questions is reported in Appendix 3***;***

- ***Change from baseline in reliever medication use over the entire 14 days treatment period*** will be summarised on the ITT set by treatment group by descriptive statistics. Baseline value is defined as the average value (puffs/day) collected during the baseline period.

- ***Change from baseline in AQLQ(S) score after 14 days of treatment*** will be analysed on the ITT set by an analysis of variance model (ANOVA) including treatment, period and subject as fixed effect. Baseline value is defined as the AQLQ(S) score collected at the end of the baseline period.

12.3.5. Safety variables

- ***Occurrence of TEAEs, adverse drug reactions (ADRs), severe ADRs, serious ADRs, serious TEAEs (SAEs), non-serious TEAEs, severe TEAEs, TEAEs leading to discontinuation from study treatment and TEAEs leading to death*** will be summarised on the safety set by treatment group as the number of subjects, percentage of subjects, and number of events. TEAEs will also be summarised by System Organ Class and Preferred Term using the MedDRA dictionary. All adverse events starting on or after the time of first study drug intake will be classified as TEAE. Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse event. All adverse events will be listed. Pre-treatment adverse event will be listed only.

12.3.6. Interim analysis

Interim analysis not planned.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

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

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorised by) according to the legal requirements in each participating country.
Selection of the subjects will not start before the approval of the Ethics Committee/Institutional Review Board has been obtained and the study notified to Health Authorities (or authorised by).

15. INFORMED CONSENT

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

Adequate time shall be given to the subject or his or her legal representative to enquiry the PI about any clarification needed and to consider his or her decision to participate to the trial.

If the subject and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the subject.

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

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

16. SOURCE DOCUMENTS/DATA

16.1. Recording of source data

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

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

16.2. Direct access to source document/data

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

17. STUDY MONITORING

Monitoring will be performed by PPD who has been designated by Chiesi. Monitoring will include on-site and off-site monitoring (with centralised or remote monitoring). A Risk-Based Monitoring strategy will be used for this study.

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

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 case report forms. For on-site visits, 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. Similarly, in case of remote monitoring, the Investigator and/or study staff will be expected to be available for a remote contact with the monitor to answer questions and to provide any missing information.
- It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

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

19. INSURANCE AND INDEMNITY

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

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

20. CONFIDENTIALITY

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

21. PREMATURE TERMINATION OF THE STUDY

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

22. CLINICAL STUDY REPORT

The clinical study report, including the statistical and clinical evaluations, shall be prepared and sent to the Coordinating Investigator for agreement and signature.
At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to the Competent Authority of the EU Member State or the US concerned and to Investigators.

23. RECORD RETENTION

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

Since the data resulted from this study is not to be used in any regulatory submissions, the essential documents should be retained for at least five years after completion of the trial.

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

24. PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities. Chiesi furthermore reserves the right to use such data for industrial purposes.

In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately.
Negative as well as positive results should be published or otherwise made publicly available according to the relevant regulatory requirements.

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

An exploratory, double-blind, randomised, multicenter, psychopharmacological study in adult patients with moderate to severe asthma to compare two pressurised Metered-Dose Inhalers (pMDIs) on patients' perception of asthma symptoms

Product: CHF 1535 100/6 µg pMDI (fixed combination of beclomethasone dipropionate 100µg plus formoterol fumarate 6µg / metered dose)

Pharmaceutical Form: Pressurised solution for inhalation

Approval of Clinical Study Protocol by the Investigator:

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

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

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

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

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Site Principal Investigator's Name: _____,MD

Centre No. :_____

_____ _____

Signature Date

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APPENDIX 2 – Diagnostic criteria for asthma in adults, adolescents, and children 6-11 years according to Box 1-2 of the GINA Full Report 2020

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Wherever possible, the diagnosis should be confirmed before ICS are started. See Box 1-3 of the GINA Full Report 2020 for how to confirm the diagnosis in patients already taking ICS.

DIAGNOSTIC FEATURE	CRITERIA FOR MAKING THE DIAGNOSIS OF ASTHMA
1. History of variable respiratory symptoms	
Wheeze, shortness of breath, chest tightness and cough. Descriptors may vary between cultures and by age, e.g. children may be described as having heavy breathing	• Generally more than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. Confirmed variable expiratory airflow limitation	
Documented excessive variability in lung function* (one or more of the tests below)	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis.
AND documented expiratory airflow limitation* Positive bronchodilator (BD) reversibility test* (more likely to be positive if BD medication is withheld before test: SABA ≥4 hours, LABA ≥15 hours)	At a time when FEV_1 is reduced, confirm that FEV_1/FVC is reduced (it is usually >0.75-0.80 in adults, >0.90 in children *Adults:* increase in FEV_1 of >12% and >200 mL from baseline, 10-15 minutes after 200-400 mcg salbutamol (albuterol) or equivalent (greater confidence if increase is >15% and > 400 mL) *Children:* increase in FEV_1 of >12% predicted
Excessive variability in twice-daily PEF over 2 weeks*	*Adults:* average daily diurnal PEF variability >10% *Children:* average daily diurnal PEF variability >13%
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults:* increase in FEV_1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test*	*Adults:* fall in FEV_1 of >10% and >200 mL from baseline *Children:* fall in FEV_1 of >12% predicted, or PEF >15%
Positive bronchial challenge test (usually only performed in adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine or histamine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits* (good specificity but poor sensitivity)	*Adults:* variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections *Children:* variation in FEV_1 of >12% in FEV_1 or >15% in PEF† between visits (may include respiratory infections)

BD: bronchodilator (SABA or rapid-acting LABA); FEV_1: Forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: Long-acting $beta_2$-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting $beta_2$-agonist. See Box 1-4 of the GINA Full Report 2020 for how to confirm the diagnosis in patients already taking maintenance treatment.

*These tests can be repeated during symptoms or in the early morning. **Daily diurnal PEF variability is calculated from twice daily PEF as ([day's highest minus day's lowest] / mean of day's highest and lowest), averaged over one week. †For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections, and airflow limitation may become persistent over time. If reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks (Box 1-4 of the GINA Full Report 2020), but other conditions that can mimic asthma (Box 1-5 of the GINA Full Report 2020) should be considered, and the diagnosis confirmed as soon as possible.

APPENDIX 3 – List of e-Diary questions to subjects during the study

	Assessments / Questions	V1 (Day 1)	V2 (Day 15)	V3 (Day 29)	V4 (Day 43)
1	"How many puffs of study maintenance treatment have you taken yesterday?" (number of puffs)	Daily collection from V1 to V4			
2	"How many puffs of rescue medication have you taken yesterday?" (number of puffs)	Daily collection from V1 to V4			
3	"How would you score your asthma symptoms yesterday?" (VAS 100, from "no symptoms at all" to "very symptomatic")	Daily collection from V1 to V4			
4	"How burdensome was your asthma yesterday?" (VAS 100, from "no burden at all" to "very burdensome")	Daily collection from V1 to V4			
5	"Did your asthma symptoms improve yesterday?" (VAS 100, from "no improvement" to "maximum improvement")	Daily collection from V1 to V4			
6	"Did your asthma symptoms worsen yesterday?" (VAS 100, from "no worsening" to "maximum worsening")	Daily collection from V1 to V4			
7	"Do you expect any improvement in asthma symptoms with this treatment? (VAS 100, from "none" to "maximum improvement")		X	X	
8	"Do you expect any worsening of your asthma symptoms with this treatment?" (VAS 100, from "none" to "maximum worsening")		X	X	
9	"How much do you think this treatment improved your overall asthma symptoms?" (VAS 100, from "no improvement" to "maximum improvement")			X	X
10	"How much do you think this treatment worsened your overall asthma symptoms?" (VAS 100, from "no worsening" to "maximum worsening")			X	X
11	"Which inhaler did you visually prefer?" [1] (Inhaler A / Inhaler B / No preference)				X
12	"Which inhaler did you prefer to use?" [1] (Inhaler A / Inhaler B / No preference)				X

Assessments / Questions		V1 (Day 1)	V2 (Day 15)	V3 (Day 29)	V4 (Day 43)
13	Do you think that changes were made to the inhalers? [1] (Yes / No / I do not know)				X
14	"Do you think the changes we made across the inhalers have impacted your asthma symptoms?" [1,2] (Yes / No / I do not know)				X
15	"Based on the information you've received, did it impact your perception of your asthma symptoms?" [1,3] (Yes / No / I do not know)				X
16	"Which of inhaler A or inhaler B had the biggest impact on the perception of your asthma symptoms?"[1,3] (Inhaler A / Inhaler B / I don't know)				X

[1] *Questions as part of the "Exit Interview"*
[2] *Dynamic question to be asked only if response to question #13 is 'yes'*
[3] *Question to be asked when changes are revealed to the subjects*

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

Birth control methods, which may be considered as highly effective

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

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

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

Definition of women of childbearing potential and of fertile men

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

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

APPENDIX 5 – List of relevant hepatotoxic drugs, enzyme-inducing or -inhibiting drugs and drugs that may prolong QTc

The following is a list of the most common/relevant drugs established to clarify items 8, 9 & 10 of section '5.2 – Non-permitted concomitant medications'.

The drugs are listed per class:
- strong CYP3A inhibitors: macrolides (clarithromicine, erythromycin, telithromycin, troleandomycin), systemic antimycotics (itroconazole, voriconazole, posaconazole, ketoconazole), antivirals (ritonavir, indinavir, nelfinavir, boceprevir, cobicistat, elvitegravir, saquinavir, danoprevir), systemic corticosteroids (dexamethasone, hydrocortisone), antineoplastic agents (ceritinib, Idelalisib, tucatinib), non-selective calcium channel blockers (mibefradil)
- strong CYP3A inducers: antiepileptics (carbamazepine, phenytoin), hormone antagonists (apalutamide, enzalutamide), anti-tubercolosis (rifampicine), herbal medicines (St. John's wort).
- Medications with well-defined potential for hepatotoxicity: isoniazide, nimesulide, ketoconazole.
- Medications with risk of significant QTc prolongation: quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors and tricyclic antidepressants.

Please note that this list may be non-comprehensive (e.g. new medical products approved during the study) and does not substitute the contraindications, special warnings, precautions of use, and interactions specified in the SmPC of the study drug.

NON-SUBSTANTIAL, GENERAL AMENDMENT No. 3

DATE: 21 March 2022

To Clinical Study Protocol
Version no.: 2.0, Date: 14 OCT 2021

STUDY CODE No.: CLI-01535AA0-02

EUDRACT No.: 2021-001449-11

An exploratory, double-blind, randomised, multicenter, psychopharmacological study in adult patients with moderate to severe asthma to compare two pressurised Metered-Dose Inhalers (pMDIs) on patients' perception of asthma symptoms

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43122 Parma – Italy

Information related to the Amendment

Regulatory Authority	☑	**Notification**
	☐	**Approval**
	☐	**Not applicable**
Ethics Committee/IRB	☑	**Notification**
	☐	**Approval**
	☐	**Not applicable**
Informed Consent	☐	**Modified**
	☑	**Unchanged**
Case Report Form	☐	**Modified**
	☑	**Unchanged**
Other Study Documents	☐	**Modified (specify)**
	☑	**Unchanged**

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

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

Previous version	New version	Rationale
6 TREATMENT(S) (§ 6.5. Treatment allocation) A master randomisation list will be prepared using a ClinPro software (LBL version 8.5) computerised system. Each subject will be assigned to one of 2 treatment sequences. Each site will be provided with a site-specific randomisation list, specifying the correspondence between the subject's screening number and the subject's randomisation number. Each subject will be identified by a unique subject number of 8 digits assigned at Screening: - the 3 first digits correspond to the ISO country code (380 for Italy); - the 2 second digits to the centre number; - the 3 last digits to the screening number (chronological in each site). On randomisation (Day1), each eligible subject will be assigned the lowest available randomisation number according to the pre-established	6 TREATMENT(S) (§ 6.5. Treatment allocation) A master randomisation list will be prepared using a ClinPro software (LBL version 8.5) computerised system. Each subject will be assigned to one of 2 treatment sequences. ~~Each site will be provided with a site-specific randomisation list, specifying the correspondence between the subject's screening number and the subject's randomisation number.~~ Each subject will be identified by a unique subject number of 8 digits assigned at Screening: - the 3 first digits correspond to the ISO country code (380 for Italy); - the 2 second digits to the centre number; - the 3 last digits to the screening number (chronological in each site). On randomisation (Day1), each eligible subject will be assigned the lowest available randomisation number according to the pre-established	The site-specific list specifying the correspondence between the subject's screening number and randomization number was removed because in case of screen-failures [non-eligible subjects] the sequence of randomization numbers per site could not be followed, thus potentially introducing a bias in the randomization process

site-specific randomisation list. Each subject will be randomised with a unique randomisation number of 3 digits:	~~site-specific~~ randomisation list. Each subject will be randomised with a unique randomisation number ~~of 3 digits:~~	

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Coordinating Investigator's Name: _____, MD

Centre No.: _____

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