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To evaluate the efficacy and safety of a medium dose of Trimbow® (100/6/12.5 µg) compared to high dose Foster® (200/6 µg) in patients with asthma

Submission date
23/02/2022

Recruitment status
No longer recruiting

Registration date
26/05/2022

Overall study status
Completed

Last Edited
07/06/2022

Condition category
Respiratory

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The purpose of this study is to assess the efficacy (effectiveness) and safety of Trimbow® medium dose, compared with Foster® high dose, in participants with asthma. Participation will help the sponsor to further understand which treatment works better in achieving specific goals in the management of participants disease, including control of symptoms, quality of life, and prevention of disease worsening and side effects of the study drugs.

Who can participate?
Participants are invited to take part because their asthma is not well controlled with their current asthma treatment

What does the study involve?
It is expected that approx. 1,400 participants will be included in the study in about 200 sites in approx. 16 countries. It will last 30 weeks with 7 visits in total. At the first visit (Visit 0), the Study Doctor will explain the study procedures and give participants a contact card. The 2nd visit (v1 - screening) is where study Dr will check they are suitable for the study. Participants will be given CHF 1535 medication (100/6 micrograms) to be used for the first 2 weeks of the study (run-in period) at the dose of 2 puffs twice a day (2 inhalations in the morning and 2 inhalations in the evening). The 3rd visit (v2 - randomisation) is where participants will be assigned to either Treatment A: CHF 5993 100/6/12.5 micrograms (i.e. 100 micrograms of beclometasone dipropionate plus 6 micrograms of formoterol fumarate plus 12.5 micrograms of glycopyrronium bromide) or Treatment B: CHF 1535 200/6 micrograms (i.e. 200 micrograms of beclometasone dipropionate plus 6 micrograms of formoterol fumarate) to be taken for 26 weeks (v2-v6). Dosing will be 2 puffs twice a day (2 inhalations in the morning and 2 in the evening). Neither participant or study Dr will know which treatment is assigned until study end. Study procedures include: physical exam, ECG, tests relating to your lungs (Oscillometry/lung function) /airway (FeNO test), blood & urine samples, covid testing, questionnaires, e-diary questions

What are the possible benefits and risks of participating?
Benefits:
There might be benefits for participating in this study. If patients are found suitable to participate, it means that their asthma is not currently ideally controlled and depending on the treatment assigned to them, their symptoms are likely to improve. More importantly, their disease and overall condition will be carefully and closely evaluated by the Study Doctor. This will help the Study Doctor to assign a more suitable drug therapy when the study is over (either by changing the dose of the drugs they were taking previously or by adding additional drug(s)). We cannot promise that the study will help patients but the information we get could help treat people with asthma with better medicines in the future,
Risks:
The probabilities of side effects are defined as follows: very common (>10%), common (1-10%), uncommon (0.1-1%), rare (0.01-0.1%) and very rare (<0.01%), unknown (probability cannot be evaluated with available data).
The side effects known to be related to the use of the combination of beclometasone plus formoterol (Foster®) or any of the single substances are listed below:
• Common: Pharyngitis (sore throat), oral candidiasis (fungal infection of oral cavity), headache and voice alteration.
The side effects mentioned above apply also for CHF 5993 (Trimbow®), that contains beclometasone plus formoterol plus glycopyrronium. Additional side effects have been reported for CHF 5993 and are listed below:
• Common: urinary tract infection, runny or stuffy nose and sneezing (nasopharyngitis). Will you mention only the common side effects?
Inhalation of high doses of corticosteroids (like beclometasone) for prolonged periods may cause systemic effects. These include: depression of adrenal function, delayed growth in children and adolescents, reduced bone mineral density (thinning of the bones), eye diseases such as cataract (opacity of lens) and glaucoma (increased pressure in the eye, causing poor night vision, blind spots, and loss of vision to either side), sleeping problems, depression or feeling worried, restless, nervous, over-excited or irritated (these events are more likely to occur in children but the frequency is unknown). Systemic side effects are however extremely improbable with the recommended doses.
As with other inhalation therapy, paradoxical bronchospasm (a difficulty in breathing caused by a sudden constriction of the muscles in the walls of the bronchioles) may occur.
There is a potential risk of unforeseeable allergic reactions as for any drugs. Hypersensitivity reactions like skin allergies, skin itching, skin rash, reddening of the skin, swelling of the skin or mucous membranes especially of the eyes, face, lips and throat may occure.
Side effects from using rescue medication (salbutamol), the most common are headache, tremor and increased heart rate and occasionally, muscle cramps, mouth and throat irritation and palpitations. Fall in the blood level of potassium and increased blood flow to the extremities (peripheral dilatation) may also occur
minor discomfort from the blood sampling procedures, and occasionally some bruising or inflammation of the veins used can occur. These effects normally disappear within a few days.
The ECG pads that are placed on the chest to monitor heart occasionally may irritate the skin and cause itching and redness.
Participants are informed they should report any side effects and report them to the study doctor. The study team will be monitoring participants for any side effects/issues during the study
For Females: There may be unknown so participants must not be pregnant or intend to become pregnant during the study period and will need to use reliable methods of contraception. These are detailed in the PIS/ICF and the study doctor can discuss in greater detail. Pregnancy testing will be carried out throughout the study. If they do become pregnant they will be withdrawn from the study immediately

Where is the study run from?
Not provided at time of registration

When is the study starting and how long is it expected to run for?
February 2022 to December 2023

Who is funding the study?
Chiesi Farmaceutici SpA (Italy)

Who is the main contact?
Dr Brian Leaker, brian.leaker@qasmc.com

Contact information

Type(s)
Scientific

Contact name
Dr Giorgia Loddo

Contact details
Osprey House
Maidenhead Office Park
Westacott Way
Maidenhead
United Kingdom
SL6 3QH
+39 342 5238714
submissions@labcorp.com

Type(s)
Principal investigator

Contact name
Dr Brian Leaker

Contact details
13-14 Fitzroy Square
London
United Kingdom
W1T 5HP
+44 800 023 4824
brian.leaker@qasmc.com

Additional identifiers

ClinicalTrials.gov (NCT)
NCT05018598

Clinical Trials Information System (CTIS)
2021-002391-39

Integrated Research Application System (IRAS)
1004813

Central Portfolio Management System (CPMS)
50590

Protocol serial number
CLI-05993AB1-06

Study information

Scientific Title
A 26 week, randomized, double blind, multinational, multicentre, active controlled, 2-arm parallel group trial comparing CHF 5993 100/6/12.5 µg pMDI (fixed combination of extrafine formulation of beclometasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6 µg pMDI (fixed combination of extrafine formulation of beclometasone dipropionate plus formoterol fumarate) in subjects with asthma uncontrolled on medium doses of inhaled corticosteroids in combination with long-acting ß2-agonists

Acronym
MiSTIC

Study objectives
To demonstrate the superiority of medium-dose BDP/FF/GB pMDI (100/6/12.5 µg, 2 puffs bid) compared to high-dose BDP/FF pMDI (200/6 pMDI µg, 2 puffs bid) in terms of the proportion of subjects exhibiting on average no Persistent Airflow Limitation (NPAL) over 26 weeks of treatment in the study sub-population with Persistent Airflow Limitation (PAL) at screening.
•A subject is defined as having PAL at screening if their post-bronchodilator (salbutamol) FEV1 /FVC ratio is <0.7.
•A subject is defined as having NPAL during the treatment period if the mean of their 2h post-dose FEV1/FVC ratios collected during the 26-week treatment period (i.e. from Week 0 to Week 26) is ≥0.7.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 2071048248; haydock.rec@hra.nhs.uk), ref: 22/NW/0077

Study design
Interventional double blind randomized parallel group controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Asthma

Interventions
It is expected that approx. 1,400 participants will be included in the study in about 200 sites in approx. 16 countries. It will last 30 weeks with 7 visits in total.

At the first visit (Visit 0), the Study Doctor will explain the study procedures and give participants a contact card. The 2nd visit (v1 - screening) is where study Dr will check they are suitable for the study. Participants will be given CHF 1535 medication (100/6 micrograms) to be used for the first 2 weeks of the study (run-in period) at the dose of 2 puffs twice a day (2 inhalations in the morning and 2 inhalations in the evening). The 3rd visit (v2 - randomisation) is where participants will be assigned to either
Treatment A: CHF 5993 100/6/12.5 micrograms (i.e. 100 micrograms of beclometasone dipropionate plus 6 micrograms of formoterol fumarate plus 12.5 micrograms of glycopyrronium bromide) or
Treatment B: CHF 1535 200/6 micrograms (i.e. 200 micrograms of beclometasone dipropionate plus 6 micrograms of formoterol fumarate) to be taken for 26 weeks (v2-v6). Dosing will be 2 puffs twice a day (2 inhalations in the morning and 2 in the evening).

Neither participant or study Dr will know which treatment is assigned until study end. Study procedures include: physical exam, ECG, tests relating to your lungs (Oscillometry/lung function) /airway (FeNO test), blood & urine samples, covid testing, questionnaires, e-diary questions.

The dosing will be 2 puffs twice a day (2inhalations in the morning and 2 inhalations in the evening). Follow up is 1 week after last treatment visit for a final review of patient help

The treatment arm allocation will be based on 3 stratification factors:
1. The Region (Eastern Europe or Western Europe)
2. The Persistent Airflow Limitation Status at screening after salbutamol intake (NPAL or PAL) (Note: The group “NPAL” will include 35% of the 1400 randomized patients; the group “PAL“ will include 65% of the 1400 randomized patients
3. The Age group (<50 or ≥ 50)

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Trimbow®, Foster®

Primary outcome(s)
Proportion of subjects exhibiting on average NPAL - status over 26 weeks of treatment in the study sub-population meeting PAL criterion screening.

1. PAL status is measured by a Post-bronchodilator spirometry manoeuver at screening (within 30 minutes after inhaling 400 µg of salbutamol pMDI).
2. NPAL status is measured by a 2h post-dose spirometry manoeuvers from V2 to V6

Key secondary outcome(s))
Change from baseline in pre-dose morning FEV1 at Week 26 in the study sub-population meeting PAL criterion at screening. The change from baseline in pre-dose morning FEV1 is measured by a pre-dose spirometry manoeuver done at V2 and V6

Completion date
20/12/2023

Eligibility

Key inclusion criteria
1. Informed consent: Subject's written informed consent obtained prior to any study related procedures;
2. Gender and age: Male or female subjects aged ≥18 and ≤75 years;
3. Diagnosis of asthma: A documented diagnosis of permanent asthma for at least 1 year according to GINA recommendations (Box 1-2, GINA report 2021), and with diagnosis before the subject's age of 40 years;
4. Stable asthma therapy: a stable treatment with medium dose of Inhaled corticosteroids (ICS) (extrafine BDP daily dose >200 and ≤400 µg or estimated clinically comparable dose) plus a long-acting ß2-agonist (LABA) (formoterol 24 µg or salmeterol 100 µg or vilanterol 25 µg or other approved dose of LABA as clinically comparable to the others) for at least 4 weeks prior to screening;
5. Lung function: A pre bronchodilator FEV1 <80% of the predicted normal value, after appropriate washout from bronchodilators, at the screening and randomisation visits;
6. Reversibility of bronchoconstriction: A demonstrated increase in FEV1 >12% and >200 mL over baseline within 30 minutes after inhaling 400 µg of salbutamol pMDI (based on ATS/ERS guidelines);
7. A Post-bronchodilator FEV1/FVC ratio ≥0.5 within 30 minutes after inhaling 400 µg of salbutamol pMDI at screening (based on ATS/ERS guidelines);
8. Poor Asthma control: Evidence of poorly controlled or uncontrolled asthma as based on an Asthma Control Questionnaire© (ACQ-7) score ≥1.5 at screening and at randomisation;
9. History of exacerbations: A documented history of one or more asthma exacerbations requiring treatment with systemic corticosteroids or emergency department visit or inpatient hospitalisation in the last 3 years prior to screening;
10. A cooperative attitude and ability:
10.1 to correctly use the pMDI inhalers;
10.2 to perform all trial related procedures including technically acceptable pulmonary function tests;
10.3 to correctly use the e-Diary/e-Peak flow meter and home-spirometry device.
11. Female subjects:
11.1. Woman of Childbearing Potential (WOCBP) fulfilling one of the following criteria:
11.1.1. WOCBP with fertile male partners: they and/or their partner must be willing to use a highly effective birth control method from the signature of the informed consent and until the follow-up call or
11.1.2. WOCBP with non-fertile male partners (contraception is not required in this case).
11.2. Female patient of non-childbearing potential defined as physiologically incapable of becoming pregnant (i.e. post-menopausal or permanently sterile). 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).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Pregnant or lactating woman where pregnancy is defined as the state of a female after conception and until termination of the gestation, confirmed by a positive pregnancy test (serum pregnancy test to be performed at screening visit and urine pregnancy test to be performed prior to randomisation);
2. Run-in compliance to study drug and e-Diary completion <50% at randomisation;
3. History of "at risk" asthma: History of near fatal asthma or of a past hospitalisation for asthma in intensive care unit which, in the judgement of the Investigator, may place the subject at undue risk;
4. Recent exacerbation: hospitalisation, emergency room admission or use of systemic corticosteroids for an asthma exacerbation in the 4 weeks prior to screening visit or during the run-in period;
Note: Subjects experiencing an exacerbation during the run-in period may be re-screened once, at least 4 weeks after recovery.
5. Non-permanent asthma: exercise-induced, seasonal asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine;
6. Subjects using systemic corticosteroid medication in the 4 weeks or slow release corticosteroids in the 12 weeks, prior to screening;
7. Asthma requiring use of biologics: Subjects receiving asthma treatment with an injectable biologic drug such as monoclonal antibodies;
8. Respiratory disorders other than asthma: Subjects with known respiratory disorders other than asthma. This can include but is not limited to: diagnosis of COPD as defined by the current guidelines (e.g. GOLD Report), known α1-antitrypsine deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
9. Lung cancer or history of lung cancer: Subjects with an active diagnosis of lung cancer or a history of lung cancer;
10. Lung resection: Subjects with a history of lung volume resection;
11. Respiratory tract infection: Subjects with respiratory tract infection within 4 weeks prior to screening or during the run-in period;Note: Subjects experiencing a respiratory tract infection during the run-in period may be re-screened once, at least 4 weeks after recovery.
12. Smoking status: Current smoker or ex-smoker with a smoking history of ≥10 pack-years (pack-years = the number of cigarette packs per day times the number of years). Ex-smokers must have

stopped smoking for ≥1 year (≥6 months for e-cigarettes).
13. Cancer or history of cancer (other than lung): Subjects with active cancer or a history of cancer with less than 5 years disease free survival time (whether or not there is evidence of local recurrence or metastases). Localised carcinoma (e.g. basal cell carcinoma, in situ carcinoma of the cervix adequately treated, …) is acceptable;
14. Cardiovascular diseases: Subjects who have clinically significant (CS) cardiovascular condition according to Investigator's judgement, such as but not limited to: congestive heart failure (NYHA class IV), unstable or acute ischaemic heart disease in the last year prior to screening, history of sustained and non-sustained cardiac arrhythmias diagnosed in the last 6 months prior to screening (sustained meant lasting more than 30 seconds or ending only with external action, or led to haemodynamic collapse; non-sustained meant >3 beats <30 seconds, and or ending spontaneously, and or asymptomatic), high degree impulse conduction blocks (>2nd degree atrioventricular block type 2),persistent, long standing or paroxysmal atrial fibrillation (AF);Note: Subjects with permanent AF (for at least 6 months prior screening) with a resting ventricular rate <100/min, controlled with a rate control strategy (i.e. selective β blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) can be considered for enrolment;
15. ECG criteria: Any abnormal and clinically significant 12-lead ECG that in the investigator's opinion would affect efficacy or safety evaluation or place the subjects at risk.
16. ECG QTcF: Male subjects with a Fridericia's corrected QT interval (QTcF) >450 msec and female subjects with a QTcF >470 msec at screening are not eligible (not applicable for subjects with permanent atrial fibrillation and for subjects with pacemaker);
17. Subjects with a medical history or current diagnosis of narrow angle glaucoma, symptomatic prostatic hypertrophy, urinary retention bladder neck obstruction that, in the opinion of the Investigator, would prevent use of anticholinergic agents;Note: Benign prostatic hyperplasia subjects who are stable under treatment can be considered for inclusion.
18. CNS disorders: Subjects with a history of symptoms or significant neurological disease such as but not limited to transient ischemic attack (TIA), stroke, seizure disorder or behavioural disturbances according to the investigator's opinion;

Date of first enrolment
15/02/2022

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Wales

Belgium

Bulgaria

Finland

France

Germany

Greece

Hungary

Italy

Latvia

Netherlands

Poland

Slovakia

Spain

Sweden

Study participating centre
Ormeau Clinical Trials Ltd
120a Ormeau Road
Belfast
United Kingdom
BT7 2EB

Study participating centre
Queen Anne Street Medical Centre (Heart Lung Centre)
13-14 Fitzroy Square
London
United Kingdom
W1T 5HP

Study participating centre
Prince Philip Hospital
Prince Philip Clinical Research Centre
Bryngwyn Mawr
Llanelli
United Kingdom
SA14 8QF

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Water Green Medical Centre
Sunderland Street
Macclesfield
United Kingdom
SK11 6JL

Sponsor information

Organisation
Chiesi Farmaceutici S.p.A.

Funder(s)

Funder type
Industry

Funder Name
Chiesi Farmaceutici

Alternative Name(s)
Chiesi Pharmaceuticals, CHIESI Farmaceutici S.p.A., CHIESI, CHIESI GROUP

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Italy

Results and Publications

Individual participant data (IPD) sharing plan

The Sponsor may share the patient's Coded Data with other companies within its group, with its service providers, its contractors, current and future commercial partners and with other research institutions who will use the patient's Coded Data only for the purposes described above.
Furthermore, the patient's Coded Data might be retained, used and processed outside the purpose of this study exclusively for legitimate scientific reasons

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2.1	01/02/2022	03/03/2022	No	Yes
Protocol file	version 2.0	04/10/2021	03/03/2022	No	No