A 52-week, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of two doses of CHF6001 DPI add-on to maintenance triple therapy in subjects with Chronic Obstructive Pulmonary Disease (COPD) and Chronic Bronchitis.

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This study has been transitioned to CTIS with ID 2023-510175-60-00 check the CTIS register for the current data. The objective of the proposed study is to confirm the findings of the dose ranging trial by, primarily, assessing the effect of two…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON55971

Source
ToetsingOnline

Brief title
PILASTER study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
No synonym

Research involving
Human

Sponsors and support

Primary sponsor: Chiesi Farmaceutici
Source(s) of monetary or material Support: Chiesi Pharmaceuticals

Intervention

Keyword: Chronic Bronchitis, Chronic Obstructive PulmonaryDisease, Randomized

Outcome measures

Primary outcome

To evaluate the efficacy of two doses of CHF6001 add-on to maintenance triple therapy (ICS, LABA, LAMA) to reduce the rate of moderate and severe exacerbations after 52 weeks of treatment in comparison with maintenance triple therapy (i.e. placebo arm)

Secondary outcome

Key Secondary:

To evaluate the efficacy of the two doses of CHF6001 add-on to maintenance triple therapy on health-related quality of life after 52 weeks of treatment (change in SGRQ total score).

Secondary:

To evaluate

- the efficacy of the two doses of CHF6001 add-on to maintenance triple therapy on lung function, health-related quality of life, severe exacerbations in the pooled analysis of CLI-06001AA1-04 and CLI-06001AA1-05 studies and other

clinical outcome measures in comparison with maintenance triple therapy.

- the safety and tolerability of the two doses of CHF6001

Other:

- To evaluate the effect of the two doses of CHF6001 on blood biomarkers of inflammation

- To evaluate the efficacy of CHF6001 to reduce exacerbations in subjects categorized by their level of blood eosinophil count compared to maintenance triple therapy

- To investigate the inter-subject variability in the drug exposure and the effects of selected covariates on PK parameters by performing a population PK analysis in a subset of subjects treated with CHF6001

- To assess the impact of study treatments on health economic outcomes

Study description

Background summary

The pathogenesis and progression of chronic obstructive pulmonary disease (COPD) is, in part, due to chronic inflammation [2]. However, the nature and severity of inflammation in COPD varies, and pharmacological anti-inflammatory treatments are unlikely to be effective in all patients; a precision medicine approach is needed to selectively target patients to increase the chance of therapeutic success [3].
Phosphodiesterase-4 (PDE4) is an enzyme that mediates the breakdown of cyclic adenosine monophosphate (cAMP), with PDE4 inhibition having anti-inflammatory effects in a broad range of cell types [33]. The orally administered PDE4 inhibitor roflumilast prevents exacerbations in patients with COPD [4, 5]. However, systemic exposure after oral administration often causes side effects such as nausea, weight loss and gastrointestinal disturbance, which limit its use in clinical practice [5, 6]. CHF6001 is a novel inhaled PDE4 inhibitor [7], currently in clinical development that has been specifically designed and

formulated as an extra-fine formulation to be delivered via inhalation and to have a low systemic exposure. This allows CHF6001 to reach therapeutic concentration in the target organ, the lung, yet reduces exposure in the systemic circulation thus limiting systemic adverse effects.

CHF6001 has been developed up to the completion of Phase 2 showing significant anti-inflammatory effects and relevant exacerbation reduction signal [13, 14].
The activity on sputum inflammatory cells and biomarkers was strongly evidenced in the Biomarker study in which CHF6001 was administered on top of maintenance triple therapy in COPD patients with chronic bronchitis for 32 days [14]. It was demonstrated that CHF6001 significantly decreased a number of key biomarkers of airway inflammation in sputum and in blood. This observed anti-inflammatory effect of CHF6001 translated in a consistent and relevant reduction of moderate or severe exacerbations of COPD in patients with chronic bronchitis, on maintenance therapy with a LABA, in a 6-month dose finding trial [13]. All doses of CHF6001 in both Phase 2 studies were safe and well tolerated. The incidence of known *drug class* adverse effects (e.g. gastrointestinal side effects) was low and similar across the dose groups and comparable to that of placebo.

Study objective

This study has been transitioned to CTIS with ID 2023-510175-60-00 check the CTIS register for the current data.

The objective of the proposed study is to confirm the findings of the dose ranging trial by, primarily, assessing the effect of two doses of CHF6001 on the rate reduction of moderate and severe exacerbations, when added onto maintenance triple therapy (ICS+LABA+LAMA) in symptomatic COPD patients with chronic bronchitis, at risk of exacerbations, in comparison with triple therapy (i.e. placebo arm).
For detailed information on preclinical and clinical data please refer to the Investigator's Brochure

Study design

This is a phase III, randomized, double-blind, placebo-controlled, 3-arm parallel group study.
Approximately 2985 subjects will be randomized in approximately 270 sites.
The study entails three periods: a run-in period of 2-week duration, a treatment period of 52 weeks duration, and a post-treatment follow-up period of 1 week.

Intervention

Treatment A: CHF6001 400 µg/actuation - CHF6001 total daily dose 1600 µg

- 2 inhalations of CHF6001 400 µg in the morning and in the evening (giving a total daily dose of 1600 µg)

Treatment B: CHF6001 800 µg/actuation - CHF6001 total daily dose 3200 µg
- 2 inhalations of CHF6001 800 µg in the morning and in the evening (giving a total daily dose of 3200 µg)

Treatment C: Placebo
- 2 inhalations of CHF6001 matching Placebo in the morning and in the evening

Study burden and risks

The proposed study has been designed to confirm the efficacy and safety of two doses of CHF6001 (1600µg and 3200µg daily) in COPD patients with chronic bronchitis who are still symptomatic and at risk of exacerbations despite being on maintenance triple therapy for at least one year in comparison with triple therapy alone.
CHF6001 thus far, has been investigated in more than 1100 COPD patients assessing doses up to 3200µg/day for 6 months in moderate- to -very severe patients with COPD [13] and up to 4800µg in healthy subjects [10]. CHF6001 proved to be safe and well tolerated with no evidence of PDE4 inhibitors class related side effects (e.g. gastrointestinal, psychiatric side effects, weight loss) leading to treatment discontinuation [37]. Based on the number of patients exposed to CHF6001 so far, the incidence of PDE4 inhibitor drug class effects appeared low compared to that of roflumilast as reported in the literature [34 -37]. This may be explained by the inhaled route of delivery of the CHF6001 which limits the systemic exposure and thus the adverse effects.
The population in the proposed study i.e. moderate- to -very severe symptomatic (CAT score >=10) COPD patients with chronic bronchitis and a history of at least one moderate or severe exacerbation in the previous year, while on maintenance triple therapy for at least 12 months prior to study entry, has the potential to benefit from the effect of the IMPs on the reduction of exacerbations.
The exclusion criteria are defined in order to minimize potential risks for the participants. Participants will have regular clinical assessments at the clinical site during 1 year of observation. An electronic diary will be used to record patients* symptoms, compliance and rescue use daily. Remote access to these data will allow to closely monitor any disease worsening. Pre-specified criteria for exacerbation will be set, alerts will be triggered when they are met and patients will be advised to contact the site. In case of acute exacerbation, patients will be treated according to the Investigator standard clinical practice.
The decision to discontinue the patient from further participation to the study will be at the investigator*s discretion if he/she deems continuing the study will place the patient at undue risk. The efficacy and safety endpoints are those recommended by the guidelines for assessing anti-inflammatory drugs in COPD [18, 19, 22, 42].
The trial will be conducted in compliance with the Declaration of Helsinki

(1964 and amendments) current ICH E6 Good Clinical Practices and all other applicable laws and regulations. Considering the expected therapeutic value, the safety profile of the IMP, the measures in place to assure the patients* safety, the overall risk/benefit assessment can be considered acceptable for the proposed trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Males and females aged >= 40 years with written informed consent obtained prior to any study-related procedure.
2. Females are eligible to enter the study if they are of
a. non-childbearing potential i.e. physiologically incapable of becoming pregnant (e.g. postmenopausal women defined as being amenorrhoeic for >=12

consecutive months without an alternative medical cause*) or women permanently sterilized (e.g. bilateral oophorectomy, hysterectomy or bilateral salpingectomy).
or
b. childbearing potential, they must have a negative pregnancy test at screening and must agree to use one or more of the following acceptable contraceptive measures:
i. Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
ii. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
iii. Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
iv. Bilateral tubal occlusion.
v. Vasectomized partner.
vi. Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent
Reliable contraception should be maintained throughout the study.
Abstinence is acceptable where it is in line with the subject*s preferred and usual lifestyle. Pregnancy tests will be performed at screening (urine and serum tests) and at randomization (urine test only) in all women of childbearing potential.
3. Subjects with an established diagnosis of COPD (according to GOLD 2020), at least 12 months before the screening visit with chronic bronchitis (defined as productive cough for at least 3 months in each of the prior two consecutive years) and/or with chronic productive cough >=12 months prior to screening
4. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20] (If the subjects undergo smoking cessation therapy, it must be completed 3 months prior to the screening visit). E-cigarettes and pipe smokers are allowed. E-cigarettes cannot be used to calculate pack-year history.
5. A post-bronchodilator FEV1 < 60% of the subject predicted normal value and a post-bronchodilator FEV1/FVC ratio < 0.7 after 400µg (4 puffs x 100µg) of salbutamol pMDI or equivalent dose of albuterol pMDI in the US. If this criterion is not met at screening, the test can be repeated once before randomization.
6. A documented history (e.g. medical record verification) of at least one moderate or severe COPD exacerbation in previous year.
Documented visits to an emergency department due to COPD exacerbation associated with prescription of systemic steroids/antibiotics, are considered acceptable to fulfil this criterion. A stay in emergency room >24h will be considered a severe event.
7. Symptomatic subject at screening defined as having a CAT score >10
8. Subjects prescribed with maintenance triple therapy (free or fixed combination of ICS, LABA, LAMA) according to GOLD 2020 recommendations for at least 12 months prior to screening and receiving regular maintenance triple

therapy for at least 3 months prior to the screening.
9. Subjects are willing and able to be trained to use correctly the DPI inhalers (NEXThaler®).
10. Subjects are willing and able to be trained to use correctly the electronic devices with COPD questionnaires, to understand and to perform required outcome measurements of the protocol (e.g. spirometry manoeuvres etc.) and ability to understand the risks involved.

Exclusion criteria

1. Subjects with a diagnosis of current asthma. Those with prior history of asthma in childhood are eligible.
2. Subjects with a moderate or severe COPD exacerbation resulting in the use of systemic corticosteroids (oral/IV/IM corticosteroids) and/or antibiotics or need for hospitalisation or a lower respiratory tract infection 4 weeks prior to study entry and during run-in period.
3. Pregnant and Lactating women.
4. Subjects requiring long term (at least 15 hours daily) oxygen therapy for chronic hypoxemia.
5. Subjects with known α-1 antitrypsin deficiency as the underlying cause of COPD
6. Subjects with primary diagnosis of emphysema not related to COPD.
7. Subjects with clinically significant respiratory disorders other than COPD. This can include but is not limited to active tuberculosis, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.
8. Subjects with lung volume reduction surgery.
9. Subjects having lung cancer or a history of lung cancer fully recovery less than 1 year after completing cancer therapy.
10. Subjects with active cancer or a history of cancer (other than the lung) with full recovery less than 1 year after completing cancer therapy or any untreated localized carcinoma.
11. Subjects with a history of allergy or hypersensitivity to anticholinergics, β2-agonists, corticosteroids, PDE-4 inhibitors or any of the excipients contained in any of the formulations used in the trial or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that in the investigator*s opinion would contra-indicate study participation.
12. Subjects under Roflumilast treatment within 6 months before study entry
13. Subjects with a diagnosis of depression, generalised anxiety disorder, suicidal ideation or behaviour that might, according to the investigator judgement, place the subject at undue risk.
14. Subjects who have clinically significant cardiovascular condition such as, but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, acute ischemic heart disease within one year prior to

study entry, known history of atrial fibrillation or of sustained and non-sustained cardiac arrhythmias diagnosed within the last 6 months prior to study entry, not controlled with a rate and/or rhythm control strategy or with recurrent episodes in the last 6 months.
15. An abnormal and clinically significant 12-lead ECG finding in relation to the subject*s medical history that results in active medical problem which may impact the safety of the subject according to investigator*s judgement. An abnormal and clinically significant finding that would exclude the subject from study participation is defined as an ECG tracing that is interpreted as, but not limited to, any of the following:
• atrial fibrillation with rapid ventricular rate >120bpm
• sustained or non-sustained ventricular tachycardia
• second degree AV block Mobitz type II and third-degree AV block (unless pacemaker or defibrillator had been inserted)
• QTcF >=480 msec (at screening visit). Criterion not applicable for subjects with pacemaker and with permanent atrial fibrillation.
16. Subjects with a significant neurological disease including transient ischemic attack (TIA), stroke, seizure disorder or behavioural disturbances that in investigator*s opinion, would place the subject at risk by participating to the study.
17. Subjects who have a history or current evidence of clinically significant and uncontrolled disease: e.g. hyperthyroidism, diabetes mellitus or other endocrine disease; significant renal impairment; history of cerebrovascular, gastrointestinal (e.g. active peptic ulcer); neurological disease; uncontrolled haematological abnormalities; uncontrolled autoimmune disorders, or other disease. Significance of renal impairment should be assessed in case of CKD (Chronic Kidney Disease) presence in medical history. In this case, serum creatinine level should be checked. Patients will not be allowed to the study if eGFR value <60 mL/min/1.73 m2* (please see the note for reference to creatinine level).Uncontrolled is defined as any disease or condition that might, in the judgement of the investigator, place the subject at undue risk through participation to the study or might compromise the interpretation of the results if the disease/condition exacerbated during the study;
18. Subjects with clinically significant laboratory abnormalities indicating a significant or unstable concomitant disease that might, in the judgement of the investigator, place the subject at undue risk or potentially compromise the results or interpretation of the study. In case some parameters are clinically significant at V1, they can be retested once before randomization
19. Subjects with moderate or severe hepatic impairment (Child-Pugh B or C)
20. Subjects with a known or suspected history of alcohol abuse and/or substance/drug abuse within 12 months prior to screening visit
21. Subjects having received any other investigational drug within the preceding 30 days (60 days for biologics), or a longer and more appropriate time as determined by the investigator (e.g., approximately five half-lives of the previous investigational drug)
For the subset of subjects undergoing PK assessments
22. Subjects with unsuitable veins for repeated venipuncture.

23. Blood donation (excluding plasma donations) or blood loss equal or more than 450 mL less than 2 months prior to screening

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-03-2022
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CHF6001 (DPI NEXThaler)
Generic name:	DPI NEXThaler

Ethics review

Approved WMO

Date:	26-05-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	30-08-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	20-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-510175-60-00
EudraCT	EUCTR2020-003666-40-NL
ClinicalTrials.gov	NCT04636801
CCMO	NL77011.028.21