A 52-week, randomized, double-blind, double-dummy, placebo- and active-controlled (Roflumilast, Daliresp® 500µg), 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.

Published: 18-05-2021
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This study has been transitioned to CTIS with ID 2023-510174-13-00 check the CTIS register for the current data. The objective of the proposed study is to confirm the findings of the dose finding 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-OMON56320

Source
ToetsingOnline

Brief title
PILLAR 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 Farmaceutici

Intervention

Keyword: Chronic Bronchitis, Chronic Obstructive Pulmonary Disease, Placebo-Controlled, Randomized

Outcome measures

Primary outcome

To evaluate the efficacy of two doses of CHF6001 add-on to maintenance triple therapy (free or fixed combination of 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

- the efficacy, safety and tolerability of the two doses of CHF6001 in

comparison with Roflumilast.

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 proved to prevent exacerbations in patients with COPD and chronic bronchitis with a history of exacerbations [4, 5]. However, the level of systemic exposure to the drug after oral administration, likely 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, in particular, showed additive anti-inflammatory effects in combination with fluticasone on virus-inducible cytokines in airway epithelial cells [29]. In vivo evidence of additive effect between CHF6001 and fluticasone was demonstrated in a model of induced neutrophilia by LPSchallenge in rats [7]. In subjects with COPD and chronic bronchitis, CHF6001 proved to significantly decrease a number of markers of airway inflammation when added onto maintenance triple therapy and reduced exacerbations when added onto LABA [13, 14]. Experience with Roflumilast added onto bronchodilators, showing a

higher response to the treatment in patients with chronic bronchitis compared to the broad COPD population, lends support to believe that PDE4 inhibitors as a class are more effective in this subgroup [30]. When added onto ICS/LABA±LAMA in COPD patients with chronic bronchitis and at risk of exacerbations, Roflumilast did significantly reduced moderate and severe exacerbations [31]. Thus, conceptually, the high level of inflammation seen in bronchitic COPD may be more responsive to an inhaled glucocorticoid and a PDE4 inhibitor if used together rather than individually [32].
Chiesi is developing CHF6001 NEXThaler® with the aim of providing a new treatment option for the management of COPD patients with chronic bronchitis who are still at risk of exacerbations despite 'maximized' therapy since we believe there is an unmet medical need.

Study objective

This study has been transitioned to CTIS with ID 2023-510174-13-00 check the CTIS register for the current data.

The objective of the proposed study is to confirm the findings of the dose finding 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) and secondarily, to compare its effect with Roflumilast add-on to triple therapy.

Study design

This is a phase III, randomized, double-blind, double-dummy, placebo and active-controlled, 4-arm parallel group study

Intervention

Treatment A: CHF6001 400µg/actuation - CHF6001 total daily dose 1600µg
- 2 inhalations of CHF6001 400µg in the morning and in the evening (giving a total daily dose of 1600µg)
- 1 tablet of Roflumilast matching placebo; once-daily

Treatment B: CHF6001 800µg/actuation - CHF6001 total daily dose 3200µg
- 2 inhalations of CHF6001 800µg in the morning and in the evening (giving a total daily dose of 3200 µg)
- 1 tablet of Roflumilast matching placebo; once-daily

Treatment C: Roflumilast (Daliresp®) tablets 250µg and 500µg
- Daliresp® 250µg one tablet once-daily during the first 4 weeks of treatment then one tablet of Daliresp® 500µg once- daily for the remaining treatment

period
- 2 inhalations of CHF6001 matching Placebo in the morning and in the evening

Treatment D: Placebo
- 2 inhalations of CHF6001 matching Placebo in the morning and in the evening
- 1 tablet of Roflumilast matching placebo, once daily

Study burden and risks

The proposed study has been designed to confirm the efficacy and safety of two doses of 6001 (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 and with Roflumilast added onto triple therapy. 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.
Roflumilast has been licensed since 2011 for the treatment of 'severe COPD associated with chronic bronchitis in patients with a history of exacerbations' as add-on to bronchodilators. Since then, many studies had shown its effect in reducing exacerbations when added onto ICS/LABA and triple therapy as well [31, 35, 36]. However, its use in clinical practice is somehow limited by its tolerability profile,
particularly, gastrointestinal side effects which may lead to patients discontinuing the treatment. The population in the proposed study i.e. severe- 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, 41].
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

Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:
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 she is 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 <50% of the patient predicted normal value and a post-bronchodilator FEV1/FVC ratio < 0.7 after 400µg
(4 puffs x 100µg) of salbutamol pMDI. 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 the 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 visit. ICS must be in an approved dose for COPD.
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

EXCLUSION CRITERIA
The presence of any of the following will exclude a patient from study enrolment:
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 i.e. 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 or lung cancer with full 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 patient 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 patient 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 >120 bpm
• 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 patient 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 patient 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 patient at undue risk or potentially compromise the results or interpretation of the study. In case some parameters are clinically significant at screening, 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).
22.Subjects with severe immunological diseases (eg: HIV infection, multiple sclerosis, lupus erythematosus, etc) confirmed in their medical history.
23.Subjects with current severe acute infectious diseases, or patients being treated with immunosuppressive medicinal products (ie, methotrexate, azathioprine, infliximab, etanercept, etc) 3 months prior to study entry and during run-in period.

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):	19-01-2022
Enrollment:	220
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-05-2021
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:	24-11-2021
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:	08-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-10-2022
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	CTIS2023-510174-13-00
EudraCT	EUCTR2020-003648-97-NL
ClinicalTrials.gov	NCT04636814
CCMO	NL77012.028.21