PHASE Ib, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE SAFETY OF SELNOFLAST IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Primary: To assess the safety profile of selnoflast compared with that of placeboSecondary: - To evaluate the efficacy of selnoflast compared with that of placebo- To assess the pharmacokinetic properties of selnoflast and metabolite(s) as...

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

Summary

ID

NL-OMON51550

Source
ToetsingOnline

Brief title
Roche BP43098 Study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD; lung disease

Research involving

Human

Sponsors and support

Primary sponsor: F.Hoffmann-La Roche Ltd.
Source(s) of monetary or material Support: F.Hoffmann-La Roche Ltd.

Intervention

Keyword: COPD, Phase 1, SELNOFLAST

Outcome measures

Primary outcome

- Incidence, severity, and causal relationship ofadverse events (AEs),

incidence of serious AEs (SAEs) and AEs leading to treatment discontinuation

- Incidence of abnormal laboratory findings

- Incidence of abnormal vital signs and electrocardiogram (ECG) parameters

Secondary outcome

Change in:

o Pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV1)

o Post-bronchodilator (post-BD) FEV1

o Pre-BD FEV1 percentage of predicted

o Post-BD FEV1 percentage of predicted

o Pre-BD total lung capacity (TLC)

o Pre-BD residual volume (RV)

o Pre-BD functional residual capacity (FRC)

o RV/TLC ratio

o Pre-BD forced expiratory flow over the middle

o one half of the FVC (FEF25-75)

o Post-BD FEF25-75

Pharmacokinetic parameters of RO7486967 in blood by PK population analysis.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is usually progressive and associated with chronic airway inflammation. The airflow limitation is caused by a mixture of small airways, disease, and parenchymal destruction (emphysema) and may be associated with gas exchange abnormalities and hyperinflation. Clinically, the characteristic symptoms of COPD are dyspnea, cough, and sputum production. In 2013, COPD was the fourth leading cause of death globally, and it is predicted that COPD will become the third leading cause of death by 2020. Worldwide estimation of the overall prevalence of Stage 2 COPD is 10.1%. Current treatment of COPD includes non-pharmacologic (i.e., smoking cessation) and pharmacologic (i.e., bronchodilators, inhaled and systemic corticosteroids, methylxanthines, and phosphodiesterase inhibitors) interventions.
Inflammasomes are large multimeric protein complexes that actively regulate cellular immunity and homeostasis through sensing and responding to microbial or other danger signals. The hypothesis is that blocking the NLRP3 inflammasome by selnoflast may dampen the inflammation in the lung of patients with COPD, thereby reducing symptoms and improving lung function.
Selnoflast is a selective and reversible small molecule NLRP3 inflammasome inhibitor that has been shown to inhibit IL-1β release ex vivo. The results of Phase I study showed that multiple doses of selnoflast administered orally as 450 mg once daily (QD) or 180 mg twice daily (BID) over 7 days were safe and well tolerated in healthy volunteers. The pharmacokinetic (PK) results showed rapid absorption of selnoflast, a moderate half-life, and no indication of change in the exposure on repeated dosing for 7 days.
Study BP43098 is the first study involving dosing of selnoflast in participants with COPD to assess the PK at the blood level. A therapeutic effect on lung function parameters or patient-reported outcomes (PROs) in COPD might be limited as there are only 4 weeks of treatment duration. Safety data in healthy volunteers from the Phase I study are available and summarized in the Investigators Brochure. Potential risks that had been identified on the basis of clinical experience in healthy volunteers and non-clinical pharmacology and toxicology data in the relevant animal species will be closely monitored in this study.
The eligibility criteria, design, and procedures adopted are considered to be

appropriate for the safe conduct of the planned study. Participants will be closely monitored for safety consistent with standard practices and under close medical observation during the study.
The selected dose of 200 mg BID is expected to elicit a higher exposure than that observed after administration of 180 mg BID but a lower exposure than that observed after administration of 450 mg QD. Both 180 mg BID and 450 mg QD were administered in Phase 1 study for 7 days and were well tolerated.

Study objective

Primary: To assess the safety profile of selnoflast compared with that of placebo
Secondary:
- To evaluate the efficacy of selnoflast compared with that of placebo
- To assess the pharmacokinetic properties of selnoflast and metabolite(s) as appropriate

Study design

This is a Phase Ib, randomized, double-blind, placebo-controlled, parallel-group clinical trial of selnoflast in participants with COPD of inflammatory phenotype and a history of exacerbations who are treated with at least one long-acting bronchodilator inhaler medication (long-acting β-agonist [LABA] and/or long-acting muscarinic antagonist [LAMA]).

Intervention

The study has a duration of approximately 12 weeks. After screening is completed, eligible participants will be randomized in a 1:1 ratio to receive selnoflast or placebo and commence a 2-week, blinded, placebo run-in. Randomization will be stratified by smoking status (current/former) to obtain an approximately 1:1 ratio between the two treatment arms within each stratum. After the last dose of blinded placebo, participants will have their baseline assessments and then receive treatment with oral RO7486967 200 mg BID or placebo for 4 weeks. After the last dose of study drug in the placebo-controlled period, all participants will enter a safety follow-up period for 2 weeks. The investigational medicinal products for this study are selnoflast and placebo.

Study burden and risks

A therapeutic effect on lung function parameters or patient-reported outcomes (PROs) in COPD might be limited as there are only 4 weeks of treatment duration. Safety data in healthy volunteers from the Phase I study are available and summarized in the Investigators Brochure. Potential risks that had been identified on the basis of clinical experience in healthy volunteers

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The eligibility criteria, design, and procedures adopted are considered to be appropriate for the safe conduct of the planned study. Participants will be closely monitored for safety consistent with standard practices and under close medical observation during the study.
Patients will undergo procedures as described in the table 1 (Schedule of activities) of the study protocol. These procedures include: Physical exam, vital signs, demographic, medical history, ECG, HCRT scan, blood and urine tests, virus testing, tests for drugs of abuse, alcohol, and smoke, nasal MLF samples, questionnaires, Spirometry (pre- and post-BD) and lung volumes, pulse oximetry, breathing test for DLCO, breathing test for FeNO, completion of questionnaires and ediary.

Contacts

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Between 35 and 75 years of age (inclusive)
- Patients with a >= 12-month diagnosis of COPD
- Radiologic evidence of air trapping at screening based on chest HRCT conducted per imaging acquisition protocol and reviewed by the imaging central reader
- Extent of emphysema on HRCT at screening is < 25%
- GOLD 2020 Grade 2/3, characterized by a post-bronchodilator forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio <= 0.70 and a post-bronchodilator FEV1 of >= 30% and =< 79% of predicted at screening and with an exacerbation history >= 2 or >= 1 leading to hospitalization within the last 12 months
- COPD assessment test (CAT) score >=10 and with a clinical diagnosis of chronic bronchitis, characterized by cough and sputum production on most days for a minimum of 3 months during the last year
- Participant must have a body mass index (BMI) between 18 and 35 kg/m^2
- Abnormal laboratory values: high sensitivity CRP (hs-CRP) >= 3 mg/L at screening AND absolute neutrophil count >= 6.0 x 10 high 9 /L in whole blood at screening
- Vital signs (body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate) will be assessed in the sitting position after the subject has rested for at least 3 minute
- Unchanged standard regimen of care for >= 4 weeks prior to screening
- Ex-smokers with at least a 10-pack year smoking history or current smokers with at least a 10 pack-year smoking history who smoke =< 1 pack-year on average in the last 3 months as reported at screening
- Able to perform reliable, reproducible pulmonary function test maneuvers per American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines
- Female participants: female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: Women of non-childbearing potential or Women of childbearing potential who Agree to remain abstinent or use at least acceptable contraceptive methods during the treatment period and for at least 14 days after the final dose of selnoflast/placebo
- Male participants: No contraception required for male participants

Exclusion criteria

- Any condition or disease detected during the medical interview/physical examination that would render the patient unsuitable for the study, place the patient at undue risk, or interfere with the ability of the patient to complete the study
- Known active or uncontrolled bacterial, viral, fungal, mycobacterial, or

other infection, excluding fungal infection of nail beds, including participants exhibiting symptoms consistent with SARS-CoV-2 within 2 weeks prior to screening
- Positive polymerase chain reaction (PCR) test for SARS-CoV-2 within 6 weeks prior to Day 1
- Diagnosis of severe bronchiectasis in chart or history
- Patients with another concomitant pulmonary disease, including but not exclusive of, interstitial pulmonary fibrosis, sarcoidosis, or other granulomatous or infectious process
- Patients treated for active asthma within 2 years prior to the screening visit
- Any COPD exacerbation or upper or lower respiratory tract infection requiring antibiotics, oral steroids, or hospitalization within 2 weeks prior to screening, during the screening period, or during the run-in period
- Patients requiring long-term oxygen therapy for daytime hypoxemia
- Patients with a diagnosis of alpha-1 antitrypsin deficiency
- History of lung transplant or malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 5 years
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study
- History of clinically significant ECG abnormalities, or ECG abnormalities at screening or baseline
- Known family history or known presence of long QT syndrome
- Patients with a history of acute coronary syndrome in 3 months prior to the screening visit
- Patients with a history of coronary artery bypass surgery or other major vascular surgery within 6 months prior to the screening visit
- Evidence of urinary obstruction or difficulty in voiding
- History of any clinically significant hepatic disease or cirrhosis
- Significant illness not resolved within 2 weeks prior to screening
- Use of systemic steroids, ICS, theophylline, and phosphodiesterase 4 (PDE4) inhibitors within 4 weeks of screening
- Vaccines within 4 weeks prior to the first dose
- Current treatment with medications that are well known to prolong the QT interval
- Donation or loss of 450 mL or more of blood within 8 weeks prior to initial dosing, or longer if required by local regulation
- Plasma donation > 150 mL within 7 days prior to first dosing
- Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
- History of hypersensitivity to the study drugs or to drugs of similar chemical classes or excipients
- QTcF > 450 ms in male participants and > 470 ms in female participants demonstrated by at least two ECGs > 30 minutes apart
- Liver function test abnormalities at screening. Re-testing during the screening period is possible once. This laboratory assessment may be repeated

once during the screening period, if necessary
- Anemia (hemoglobin levels > 10.0 g/dL at screening). This laboratory assessment may be repeated once during the screening period, if necessary
- Clinical evidence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g., albuminuria) at screening. This laboratory assessment may be repeated once during the screening period, if necessary
- History of immunodeficiency diseases, including a positive HIV (ELISA, CMIA and Western blot) test result
- Presence of hepatitis B surface antigen (HBsAg) or positive for total hepatitis B core antibody (HBcAb), or positive hepatitis C by PCR test result at screening or within 3 months prior to starting study treatment
- History of tuberculosis or a positive Quantiferon Gold test
- Patients with a known history of noncompliance to medication, or who are unable or unwilling to complete an electronic patient diary (medication adherence platform), or who are unable to demonstrate good medication compliance during the run-in period
- Inability to comply with all study requirements and demonstrate good medication compliance during the treatment run-in period
- Patients with any medical or psychological condition that renders the patient unable to understand the nature, scope, and possible consequences of the study
- Patients with a history of being unable to swallow size 0 capsules
- History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening
- Clinically significant history of psychiatric disorders that preclude understanding or compliance with the protocol
- Recent (within the last 3 years) and/or recurrent history of autonomic dysfunction

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Selnoflast
Generic name:	RO7486967

Ethics review

Approved WMO Date:	08-12-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2021-000558-25-NL
CCMO	NL79518.042.21