A 24-week multi-center, double-blind, placebo controlled dose-range finding study to investigate the efficacy and safety of oral QBW251 in COPD patients on triple inhaled therapy (LABA/LAMA/ICS)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50119

Source
ToetsingOnline

Brief title
CQBW251B2201

Condition

- Respiratory disorders NEC

Synonym
Chronic Obstructive Pulmonary Disease, COPD

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: COPD, Oral therapy, QBW251, Triple inhaled therapy

Outcome measures

Primary outcome

The primary objective of this study is to characterize the dose-response relationship of QBW251 administered orally over 12 weeks on lung function, compared to placebo, when added to inhaled triple combination therapy (LABA/LAMA/ICS). Trough forced expiratory volume in one second (FEV1) will be assessed at Week 12 and evaluated as change from baseline after 12 weeks of treatment.

Secondary outcome

Objective 1: To evaluate symptoms (overall COPD symptoms, cough and sputum) across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo at Weeks 12 and 24.

Endpoints are

- Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS) weekly mean scores (total and subscale scores).

- Change from baseline in Patient Global Impression of Severity (PGIS) score.

- Change from baseline in the Cough and Sputum Assessment Questionnaire

(CASA-Q) domain scores - cough symptoms, cough impact, sputum symptoms, and sputum impact.

Objective 2: To evaluate health-related quality of life across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, at Weeks 12 and 24. The endpoint assessed is the change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores at Weeks 12 and 24.

Objective 3: To evaluate lung function across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, over 4, 8, 16, 20 and 24 weeks. Trough FEV1 change from baseline after 4, 8, 16, 20 and 24 weeks of treatment, respectively, will be evaluated.

Objective 4: To evaluate safety and tolerability across various dose levels of QBW251, administered orally over 24 weeks, compared to placebo, as assed by ECGs, laboratory tests (hematology and clinical chemistry, urinalysis), vital signs, and adverse events (AEs) per treatment group.

Objective 5: To assess the pharmacokinetics (PK) of QBW251 in COPD patients through measurement of trough concentration and minimum concentration (Cmin) on all visits and around maximum concentration (Cmax) on Days 1, 15 and 169. The area under the plasma concentration-time curve (AUC)

and Cmax on Days 1 and 15 will be assessed in a sub-group of patients.

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles/gases, in particular cigarette smoke. COPD is a critically important disease, with a prevalence of 10% to 15% in Europe. COPD is associated with episodic periods of symptom deterioration termed exacerbations. Despite currently available treatments almost 70% of patients remain significantly limited by breathlessness, therefore additional novel therapies are urgently needed.

Study objective

The purpose of this study is to support the dose selection for the future development program of QBW251 by evaluating efficacy and safety of different QBW251 doses in patients with Chronic Obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbations. QBW251 treatment will be added on top of a triple combination therapy of a long-active beta2-agonist (LABA), a long-acting muscarinic receptor-antagonist (LAMA) and an inhaled corticosteroid (ICS).

Study design

This study uses a 5 treatment arm, parallel-group, randomized, double-blind study design. The study is placebo-controlled with a standardized COPD background treatment. The treatment period lasts 24 weeks, the total duration of study participation for a patient is 31 weeks.

Intervention

- Treatment arm 1: QBW251, 300 mg, b.i.d.
- Treatment arm 2: QBW251, 150 mg, b.i.d.
- Treatment arm 3: QBW251, 75 mg, b.i.d.
- Treatment arm 4: QBW251, 25 mg, b.i.d.
- Treatment arm 5: Placebo matching QBW251, b.i.d.

All patients are receiving standardized background COPD medication consisting of fluticasone furoate, umeclinidium and vilanterol.

Study burden and risks

Potential burden and risk for participants includes potential side effects of study medication, time investment and additional tests and examinations.See protocol, Investigator's Brochure and above for additional information on risk and benefits.

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

* Male and female COPD patients aged *40 years, who have signed an Informed Consent Form prior to initiation of any study-related procedure.
* Current or ex-smokers who have a smoking history of at least 10 pack years.

* Patients who have been treated with a triple combination of LABA/LAMA/ICS for the last 3 months
prior to screening.
* A COPD Assessment Test (CAT) score of at least 10 at Run-In 1 visit.
* Patients with a post-bronchodilator FEV1/FVC <0.70 at Run-In 1 visit.
* Patients with airflow limitation indicated by EITHER a post-bronchodilator FEV1 * 30 % and FEV1 < 50 % of the predicted normal at Run-in 1, who must have had at least 1 documented moderate or severe healthcare resource utilization (HCRU) exacerbation in the 12 months prior to study entry (screening), OR a post-bronchodilator FEV1 * 50 % and <80 % of the predicted normal at Run-In 1, who must have had at least 2 documented moderate or at least 1 documented severe HCRU exacerbation(s) in the 12 months prior to study entry (screening)
* Patients featuring chronic bronchitis, defined by the presence of cough and bronchial hypersecretion, that occurs for at least three consecutive months in each of two consecutive years prior to study entry (screening), documented in patient history.

Exclusion criteria

* Patients who have a history of long-QT syndrome, a clinically significant ECG abnormality at
baseline, or whose QTc measured at baseline is prolonged.
* Patients who have clinically significant renal, cardiovascular, neurological, endocrine,
immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere
with the assessment of the efficacy and safety of the study treatment, with a clinically significant laboratory abnormality at baseline, or patients with Type I diabetes or uncontrolled Type II diabetes.
* Patients who have had a COPD exacerbation that required treatment with antibiotics and/or oral
corticosteroids and/or hospitalization, or a respiratory tract infection in the 4 weeks prior to screening, or between screening and randomization.
* Patients with any documented history of asthma, or with an onset of chronic respiratory symptoms,
including a COPD diagnosis, prior to age 40 years.
* Patients with a body mass index (BMI) of more than 40 kg/m2.
* Use of other investigational drugs (approved or unapproved) within 30 days or 5 half-lives prior to
screening, or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics),
whichever is longer; or longer if required by local regulations.
* Pregnant or nursing (lactating) women, and women of childbearing potential not willing to use

acceptable effective methods of contraception during study participation.

Study design

Design

Study phase:	2
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):	24-10-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	QBW251
Generic name:	QBW251

Ethics review

Approved WMO

Date:	08-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	22-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	12-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2018-003197-28-NL
CCMO	NL69760.056.19