A randomized, double-blind, repeat dose cross-over study to assess the bronchodilator effects of once daily QVM149 following morning or evening dosing for 14 days compared to placebo in patients with asthma

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To investigate the potential influence of time of dosing (morning or evening)on the bronchodilator effect of once daily orally inhaled QVM149 compared toplacebo.

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

Summary

ID

NL-OMON44320

Source
ToetsingOnline

Brief title
CQVM149B2209 (CS0281)

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthma, chronic lung inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma AG

Intervention

Keyword: astma, Double-blind, Randomized, repeat-dose

Outcome measures

Primary outcome

To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo.

Secondary outcome

* To investigate the potential influence of time of dosing (morning or evening) on trough FEV1 of once daily orally inhaled QVM149 compared to placebo.

* To investigate the potential influence of time of dosing (morning or evening), on peak expiratory flow rate (PEF) of once daily orally inhaled QVM149 compared to placebo.

* To evaluate safety and tolerability of QVM149 when dosed in the morning or in the evening in patients with asthma after during two weeks of treatment in each treatment period.

Study description

Background summary

Asthma is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable bronchial airflow obstruction that is often reversible either spontaneously or with treatment. Airflow limitation occurs as a result of obstruction or narrowing of the airways, when exposed to precipitating factors (GINA 2016).
Despite existing therapies there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The Global Burden of Asthma Report estimates that 15 million disability*adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 (Beasley 2004).
Recently, tiotropium (long-acting muscarinic antagonist; LAMA) has been approved in the EU as an add-on maintenance bronchodilator treatment in adult patients (* 18 years) with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (ICS; * 800*g budesonide/day or equivalent) and long-acting beta2-agonists (LABA), and who experienced one or more severe exacerbations in the previous year. This is reflected in the GINA 2016 guideline by recommending tiotropium as an add-on option in patients requiring asthma therapy step 4 and 5 according to the GINA treatment algorithm.
There is mounting evidence that in patients who are poorly controlled on mid and high dose ICS/LABA a triple combination of LABA, LAMA and ICS can provide additional benefit in terms of lung function, symptom control and a reduction in exacerbations.
QVM149 is a fixed-dose combination of indacaterol acetate (LABA), glycopyrronium bromide (LAMA), and mometasone furoate (MF; ICS) in development for once-daily maintenance treatment of asthma GINA step * 4. QVM149 is formulated as lactose-blended inhalation powder delivered via the Concept1 inhalation device (Breezhaler®), a single dose dry powder inhaler (SDDPI). The three

mono-components of
QVM149, indacaterol, glycopyrronium bromide and MF have previously been developed as
individual drugs or dual combinations (indacaterol acetate/MF called QMF149; indacaterol
maleate/glycopyrronium bromide called QVA149) for treatment of either COPD or asthma
as detailed below, thereby supporting the efficacy and safety of individual components and
the selection of doses for their combination in QVM149.

Study objective

To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo.

Study design

This is a randomized, placebo-controlled, double-blind, six-sequence, three-period cross-over study in asthma patients.

Intervention

The study will consist of a
14-day screening period, followed by a 14-day run-in period, and a treatment epoch which consists of three treatment periods, with a minimum duration of 14 days each followed (for the 2 first treatment periods) by a wash-out period. The duration of each treatment period may be extended up to aduration of 18 days if needed for operational reasons. The third treatment period will be followed by a Study Completion evaluation at 1-7 days following the last dose. The treatment periods will be separated by wash-out periods of 14 to 21 days duration.
The total duration of the study is approximately 13 weeks (minimum) to 19 weeks (maximum) for each patient.

Study burden and risks

N.A.

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

Patients with a documented physician diagnosis of asthma and who additionally meet the following criteria:
* patients receiving daily treatment with an inhaled corticosteroid at a low or medium daily dose
* on a stable regimen for at least 4 weeks prior to screening.
* Pre-bronchodilator FEV1 * 60 % and < 100% of the predicted normal value for the patient during screening.
* Patients who demonstrate an increase in FEV1 of * 12 % and * 200 mL after administration of 400 *g salbutamol/360 *g albuterol (or equivalent dose) at Screening. All patients must perform a reversibility test at Screening.
* At screening, and baseline (day 1 pre-dose time) of the first treatment period, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again in the standing position as outlined in the SOM. Sitting and standing vital signs should be within the following ranges:
* oral body temperature between 35.0-37.5 °C
* systolic blood pressure, 90-159 mmHg

* diastolic blood pressure, 50-99 mmHg
* pulse rate, 40-90 bpm
* Hypertensive patients must have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial.
* Patients must weigh at least 50 kg at screening to participate in the study, and must have a body mass index (BMI) within the range of 18 to 40 kg/m2.

Exclusion criteria

* Contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the drugs of a similar class
* Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 1 year of Screening.
* Patients who have had previous intubation for a severe asthma attack/exacerbation.
* Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
* History of paradoxical bronchospasm in response to inhaled medicines.
* Patients who during the run-in period prior to randomization require the use of *12 puffs / 24 hours of rescue medication for 48 hours (over two consecutive days) or who have a decline in PEF from the reference PEF of * 30% for 6 consecutive scheduled PEF readings
* Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-06-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Indacaterol acetate / glycopyrronium bromide / mometasonfuroaat
Generic name:	N.A.

Ethics review

Approved WMO Date:	22-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
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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	EUCTR2017-000644-17-NL
ClinicalTrials.gov	NCT03108027
CCMO	NL61785.056.17