A randomized, double-blind, double-dummy, activecontrolled, 3-period complete cross-over study to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone in patients with asthma.

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To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 *g o.d. and 150/50/80 *g o.d. compared to a FDC ofsalmeterol/fluticasone at a dose of 50/500 *g b.i.d. after 3 weeks of treatment in patients with asthma.

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

Summary

ID

NL-OMON47676

Source
ToetsingOnline

Brief title
QVM149B2208 (CS0280)

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthma, chronic lung inflammation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Asthma, Double blind, Randomized, Safety

Outcome measures

Primary outcome

The primary endpoint is the peak FEV1 (mL) defined as t he highest

bronchodilatory effect on FEV1 during a period of 5 min to 4 h after the last

dose of the preceding 3-week treatment period.

Safety:

* Physical examination

* Vital signs

* Laboratory evaluations; hematology, blood chemistry and urinalysis

* Electrocardiogram (ECG)

Secondary outcome

Please see page 23 and 24 of the study protocol

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 (GINA2016).

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 lactoseblended inhalation powder delivered via the Concept1 inhalation device (Breezhaler®), a single dose dry powder inhaler (SDDPI). The three mono-components of QVM149, indacaterol acetate, 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 demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 *g o.d. and 150/50/80 *g o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 *g b.i.d. after 3 weeks of treatment

in patients with asthma.

Study design

This is a confirmatory, randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study.

Intervention

The study will start with a screening visit. During the screening visit standard medical assesments including safety laboratory tests (blood draw, urine collection), an alcohol breath test, urine drug screen, a physical examination, ECG and a vital signs will be performed.

For each treatment period, the subject will be dispensed with one medication set of both study
medications listed below:

* QVM149 or matching placebo in blisters, will be administered via the Concept1 inhalation device
* Salmeterol xinafoate/fluticasone propionate or matching placebo pre-dispensed inhalation device, will be administered via the pre-dispensed inhalation device

In total, three medication kits of QVM149 blisters/Concept1 and three Salmeterol xinafoate/fluticasone propionate pre-dispensed inhalation devices will be provided for the whole duration of the study.
IP administration will occur at the site by the subject on Da y 1 morning and will be administered by the subject at the subject's home from Day 1 evening to Day 21 morning for each treatment period.

The evening dose on Day 21 should be taken at the site. A new medication set will be dispensed to the subject on Day 22 (same day as Day 1 of next Treatment period, applicable for Treatment period 2 & 3).

Subjects will be instructed to take both morning and evening doses of study medication at approximately the same time of day (both in the morning and evening). Subjects will be instructed to rinse their mouth after inhalation of study drug (2 times with approximately 30 mL water). Water used for mouth rinsing should be spat out and should NOT be swallowed. In the evening when sequential inhalations of study drugs from two devices are required, mouth rinsing should be done after the last inhalation.

The morning dose (to be taken between 05:00 and 08:00 am) will consist of a single inhalation of either salmeterol/fluticasone or placebo.

The evening dose (to be taken between 05:00 and 08:00 pm) will consist of sequential single inhalations:

* One inhalation of either QVM149 or placebo
* One inhalation of either salmeterol/fluticasone or placebo

Inhalations from the two devices should be taken as close together as possible. Instructions for use of the Concept1 and the device by which the FDC of salmeterol/fluticasone are administered are given in Appendix 2 and Appendix 3. Further details are provided in the SOM.

Administration of study medication at the same time of Day on Day 21 and 22 of each treatment period +/- 1 h will ensure that corresponding assessments are done at approximately the same time of the day in each treatment period.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Finaly a follow up examination will be performed. during this visit the subjects will be asked for possible side
effects. Blood will drawn for safety, the vital signs/ECG will be checked and physical examination will be
conducted.

Study burden and risks

NVT

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 adult patients * 18 years old and * 75 years.
* Patients with a documented physician diagnosis of asthma for a period of at least 12 months prior
to Visit 1 (Screening).
* Patients who have used ICS and LABA combinations for asthma for at least 3 months and at a stable
medium or high dose of ICS for at least 1 month prior to Visit 1 (Screening).
* Pre-bronchodilator FEV1 of < 80 % of the predicted normal value at screening Visit 1 (spirometry will not be repeated at
baseline prior to randomization).
* Patients who demonstrate an increase in FEV1 of * 12 % and 200 mL after administration of 400 *g salbutamol/360 *g
albuterol (or equivalent do se) at Visit 1 (Screening). All patients must perform a reversibility test at Visit 1 (Screening). If
reversibility is not demonstrated at Visit 1 (Screening), then, reversibility testing may be repeated once during the screening
period.
* If reversibility is not demonstrated at Visit 1 (retesting allowed once), patients must be screen failed. Spacer devices are not
permitted during reversibility testing.

Exclusion criteria

**Patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1
**Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1

**Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or severe renal
impairment or urinary retention
**Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Visit 1
**Patients with any chronic conditions affecting the upper respiratory tract
**Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease,
cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
**Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c >9% at screening).
**Patients who have a clinically significant ECG abnormality at Visit 1
**Patients with a history of hypersensitivity or intolerance to any of the study drugs (including excipients)
**Patients with narcolepsy and/or insomnia.
**Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 2 or patients on Maintenance
Immunotherapy for more than 3 months prior to Visit 2 but expected to change throughout the course of the study.
**Pregnant or nursing (lactating) women
**Women of child-bearing potential must use Highly effective contraception methods
**Patients who have discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason.
**History of paradoxical bronchospasm in response to inhaled medicines.
**Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
**Patient with a serum potassium level below the laboratory limit of normal at screening.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-05-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Indacaterol acetate /Glycopyrronium bromide/mometasone furoate
Product type:	Medicine
Brand name:	Seretide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2018
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	EUCTR2016-005164-34-NL
CCMO	NL61502.056.17