A 26-week, randomized, double blind, parallel-group multicenter study to assess the efficacy and safety of QVA149 (110/50 mcg o.d.) vs tiotropium (18 mcg o.d.) + salmeterol/fluticasone propionate FDC (50/500 mcg b.i.d.) in patients with moderate to severe COPD

Published: 18-08-2015
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The purpose of this study is to determine whether the efficacy and safetyof QVA149 (110/50 *g o.d.) and triple treatment with tiotropium (18 *go.d.) + salmeterol/fluticasone propionate FDC (50/500 *g b.i.d.) arecomparable in patients with moderate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON43821

Source
ToetsingOnline

Brief title
NOV741

Condition

- Respiratory tract infections

Synonym
airflow limitation, COPD

Research involving
Human

Sponsors and support

Primary sponsor: TFS Trial Form Support BV
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: COPD, dual broncho dilation, QVA149, triple therapy

Outcome measures

Primary outcome

Patients who have signed Informed Consent Form prior to

initiation of any study-related procedure.

* Male and female adults aged * 40 years.

* Patients with moderate to severe airflow obstruction with stable

COPD according to the 2014 GOLD Guidelines.

* Patients with a post-bronchodilator FEV1 *40 and < 80% of the

predicted normal value, and post-bronchodilator FEV1/FVC <

0.70 at run-in Visit 101.

(Post refers to 15 min after inhalation of 400 *g of salbutamol).

* Current or ex-smokers who have a smoking history of at least 10

pack years (e.g. 10 pack years = 1 pack /day x 10 years, or *

pack/day x 20 years). An ex-smoker is defined as a patient who

has not smoked for * 6 months at screening.

* Patients who are on triple treatment at least for the last 6 months

(LAMA +LABA/ICS).

Secondary outcome

* Key exclusion criteria. Full criteria are within the protocol:

* Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:

* long and short acting anticholinergic agents

* long and short acting beta-2 agonists

* sympathomimetic amines

* lactose or any of the other excipients of trial medication

* History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:

* Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker

* History of familial long QT syndrome or known family history of Torsades de Pointes

* Resting QTc (Fridericia method) *450 msec for males and females at Visit 101.

* Concomitant use of agents known to significantly prolong the QT interval unless they can be permanently discontinued for the duration of study.

* Patients who have clinically significant renal, cardiovascular

(such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.

* Patients who have had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the 12 months prior to Visit 1.

* Patients who developed a COPD exacerbation of any severity either 6 weeks before the screening (Visit 1) or between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.

* Patients with any history of asthma.

* Patients with a blood eosinophil count > 600/mm3 during screening (Visit 101).

* Patients unable to use an electronic patient diary.

* Patients unable to use a dry powder inhaler device or a pressurized MDI (rescue medication) or unable to comply with the study regimen. Spacer devices are not permitted.

* History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the

past 5 years, regardless of whether there is evidence of local

recurrence or metastases.

Study description

Background summary

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and
associated with an enhanced chronic inflammatory response in the airways and the lung to
noxious particles or gases. Current treatment guidelines for COPD recommend the use of
bronchodilators for all severities, either on an as-required basis, or regular basis (GOLD 2014).
Inhaled long-acting bronchodilator therapy such as *2 agonists (LABAs, such as formoterol,
salmeterol and indacaterol) and muscarinic antagonists (LAMAs, such as tiotropium and
glycopyrronium bromide) are established and widely used treatment options for COPD
(GOLD 2014).
Published studies (Mak et al 1990; Carstairs et al 1985; Ikeda et al 2012) have shown that the
mechanisms of action of long-acting bronchodilator therapy such as LABAs and LAMAs are
complementary due to the differential density of *2-adrenoceptors and M3-receptors in
central versus smaller airways. Thus, LABAs should be more effective in relaxing small
airways and LAMAs in large airways. There is also clinical evidence that suggests that
combining bronchodilators from these two pharmacological classes results in significantly
greater improvements in lung function (FEV1) compared with the individual components
alone (Cazzola and Molimard 2010, Wang et al 2011). Studies to date have also shown other
meaningful outcomes such as improvement in inspiratory capacity, reduction in dyspnea,
improved symptom scores, and less rescue medication use, as compared with individual drugs

used alone (Van der Molen and Cazzola 2012).
QVA149 is a fixed combination of a long acting *2-agonist (Indacaterol maleate * QAB149)
and a long acting muscarinic antagonist (Glycopyrronium bromide * NVA237). This combination product will be delivered by the Novartis Single Dose Dry Powder Inhaler
(SDDPI).
QVA149 was investigated in a comprehensive phase III program development comprising
more than 11,000 COPD patients across more than 40 countries. Data from this QVA149
Phase III Development Program have demonstrated improvement in lung function, quality of
life, decrease in COPD symptoms and decrease in short-acting *2 agonist (SABA) use with a
safety profile similar to placebo (Vogelmeier et al 2013, Bateman et al 2013).
When compared to current standard of care treatments like fluticasone/salmeterol or OL
tiotropium, QVA149 phase III studies demonstrated significant improvements in terms of
lung function, dyspnea, symptoms, quality of life and short-acting *2 agonist)- free days
(Vogelmeier et al 2013, Bateman et al 2013). Additional information can be found in the
QVA149 Investigator*s Brochure.
These comparative studies have been performed in COPD populations with comparable stage
and clinical characteristics between the treatments arms.
Building on the strength and value of combination therapies, the clinical practice of using
triple therapy for COPD treatment has become popular in recent years. This approach
generally consists of combining a LABA and an ICS fixed-dose combination such as salmeterol/fluticasone propionate (SFC) with an anticholinergic/muscarinic antagonist (i.e.,
long-acting tiotropium bromide or short-acting ipratropium bromide). The rationale for using
these compounds together lies in the fact that they have different molecular mechanisms of
action and, consequently, their combined use could maximize their clinical benefits for
patients suffering from this debilitating disease (Salama et al 2011).
According to GOLD 2014 COPD guidelines long term treatment with inhaled corticosteroids
is recommended for patients with severe and very severe COPD and frequent exacerbations
that are not adequately controlled by long-acting bronchodilators (Evidence A).

These guidelines also emphasize that long-term treatment containing inhaled corticosteroids should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure. QVA149 once daily provided clinically relevant improvements in lung function compared with SFC twice daily with significant symptomatic benefits in patients with moderate-to-severe COPD and no history of exacerbation in the last year. (Vogelmeier et al 2013). This study confirmed the superiority of dual bronchodilator treatment to a Fixed Dose Combination (FDC) of ICS/LABA in this population.
Current GOLD guidelines (GOLD 2014) recommend the use of triple therapy as an alternative first-line choice for the maintenance treatment of only group D patients. While current guidelines suggest using LABAs and/or muscarinic antagonists and ICSs in only a small number of patients, the use of this triple therapy (in which a combination inhaler is prescribed in combination with another single drug inhaler) is more widely used in clinical practice than recommended (Jones 2009, Salama et al 2011). In research conducted at US primary care sites, it has been found that 20% of Stage 1 and 39% of Stage 2 COPD patients are currently using ICS (Small et al 2012) In fact, there is evidence of widespread use of triple therapy for COPD even in primary care where patients have predominantly mild disease and occasional bronchitis (Gaebel et al 2011).
There is insufficient evidence to determine if triple therapy is superior to dual bronchodilator therapy in patients without a history of frequent exacerbations (Gaebel et al 2011). It is also unclear whether these patients could be managed just as effectively with dual bronchodilator therapy as triple, with less cost and improved patient convenience.
The effect of QVA149 vs. triple treatment with LABA/ICS FDC+LAMA has not been studied.

Study objective

The purpose of this study is to determine whether the efficacy and safety

of QVA149 (110/50 *g o.d.) and triple treatment with tiotropium (18 *g o.d.) + salmeterol/fluticasone propionate FDC (50/500 *g b.i.d.) are comparable in patients with moderate to severe COPD without a history of frequent exacerbations.

Study design

The study is a multicenter, randomized, parallel-group, double-blind, triple-dummy study to assess the efficacy of the two active treatment arms of QVA149 (110/50 *g o.d.) and tiotropium (18 *g o.d) + salmeterol/fluticasone propionate FDC (50/500 b.i.d) in patients with moderate-to-severe COPD.

Intervention

QVA149 110/50 *g capsules o.d. for inhalation, supplied in blisters delivered via Novartis single dose dry powder inhaler Novartis single dose dry powder inhalerNovartis single dose dry powder inhaler.
Salmeterol/fluticasone propionate FDC 50/500 *g dry inhalation powder delivered via Accuhaler*.
Tiotropium 18 *g capsules o.d. for inhalation, supplied as commercially available blisters, delivered via HandiHaler®.

Study burden and risks

The risk to patients in this trial will be minimized by compliance with all of the eligibility
criteria and by close clinical monitoring. Altering the current COPD medication regimen
during the run-in period and switching from one triple treatment to another one (if the current
triple combination is different than study triple combination) or randomizing the patients
during the study treatment either to the same triple treatment as in run-in or QVA149 is not
likely to pose any risk of *under-treatment*. Although ICS is withdrawn in the QVA149 arm
ICS is not recommended in these patients according to the current GOLD COPD strategy
document (GOLD 2014). Therefore all patients are receiving sufficient COPD treatment in
both arms, along with appropriate rescue medication.
Providing the patients with rescue medication (short acting beta agonist; SABA) and active
treatment during the screening, run-in period and throughout the study mitigates any

deterioration risk. Repetitive lung function measurement maneuvers during the study can lead
to cough, shortness of breath, dizziness, or exhaustion. Since the patient only carries out
forced maneuvers during clinic visits (not at home), these are performed under medical
supervision to ensure availability of immediate aid if required. The assessments are infrequent
and part of the regular medical assessments of this patient population.
The risk of side effects from the study medication are known for compounds QVA149,
QAB149 and NVA237. The most frequently reported side effects seen for QVA149 to date
are; nasopharyngitis, upper respiratory tract infection, cough, and headache. See QVA149
Investigator*s Brochure and for QAB149 and NVA237 see QAB149 and NVA237 sections of
the QVA149 Investigator*s Brochure.
The risk of side effects for the active comparator salmeterol/fluticasone 50/500 *g b.i.d) are
those known for salmeterol and fluticasone, such as tremor, headache, palpitations,
pneumonia, bronchitis, hypokalemia, nasopharyngitis, throat irritation, sinusitis, muscle
cramps, traumatic fractures, hoarseness and candidiasis in the mouth and throat. (Seretide
Accuhaler® 50/500 *g SmPC).
The most common adverse reactions for the other active comparator, Tiotropium (>5%
incidence in the 1-year placebo-controlled trials) are upper respiratory tract infection, dry
mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and
rhinitis (Spiriva Handihaler* 18 *g SmPC).
The United States Food and Drug Administration (FDA) issued a warning concerning long
acting beta-2 agonists (LABA). The warning states that LABAs may increase the chance of
severe asthma episodes and asthma related death in patients with asthma. The warning was
based on a study that evaluated the safety of salmeterol, which showed an increase in asthma
related deaths in patients with asthma receiving salmeterol and their usual asthma medication.
This increased risk has not been demonstrated in patients with COPD.

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 eligible for inclusion in this study have to fulfill all of the following criteria:
1. Patients who have signed Informed Consent Form prior to initiation of any study-related procedure.
2. Male and female adults aged * 40 years.
3. Patients with moderate to severe airflow obstruction with stable COPD (Stage 2 or Stage 3) according to the 2014 GOLD Guidelines.
4. Patients with a post-bronchodilator FEV1 *40 and < 80% of the predicted normal value, and post-bronchodilator FEV1/FVC < 0.70 at run-in Visit 101.
(Post refers to 15 min after inhalation of 400 *g of salbutamol) (Readings assessed by site and checked centrally).
5. Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years <= 1 pack /day x 10 years, or * pack/day x 20 years). An ex-smoker is defined as a

patient who has not smoked for * 6 months at screening.
6. Patients who are on triple treatment at least for the last 6 months (LAMA +LABA/ICS).

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.
1. Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
2. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
* long and short anticholinergic agents
* long and short acting beta-2 agonists
* sympathomimetic amines
* lactose or any of the other excipients of trial medication
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
* Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
* History of familial long QT syndrome or known family history of Torsades de Pointes
4. Resting QTc (Fridericia method) *450 msec for males and females at Visit 101.
5. Concomitant use of agents known to significantly prolong the QT interval unless it can be permanently discontinued for the duration of study.
6. Patients who have a clinically significant laboratory abnormality at Visit 101 and would be at potential risk if enrolled into the study.
7. Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.
8. Patients with paroxysmal (e.g. intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 101 and Visit 102) visits, with a resting ventricular rate < 100/min. At visit 101, atrial fibrillation must be confirmed by central reading.
9. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention (BPH patients who are stable on treatment can be considered).
10. Patients who have not achieved acceptable spirometry results at Visit 101 in accordance

with ATS (American Thoracic Society)/ERS (European Respiratory Society) criteria for acceptability (one retest may be performed for patients that don*t meet the acceptability criteria).
11. Patients who have had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the last year prior to Visit 1.
12. Patients who developed a COPD exacerbation of any severity either 6 weeks before the screening (Visit 1) or between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
13. Patients who have had a respiratory tract infection within 4 weeks prior to screening Visit 1.
14. Patients who develop a respiratory tract infection between screening and treatment will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
15. Patients requiring long term oxygen therapy prescribed for >12 hours per day.
16. Patients with any history of asthma.
17. Patients with a blood eosinophil count > 600/mm3 during screening (Visit 101).
18. Patients with allergic rhinitis who use a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen is permitted).
19. Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis).
20. Patients with a diagnosis of *-1 anti-trypsin deficiency.
21. Patients with active pulmonary tuberculosis.
22. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
23. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study (Maintenance program is permitted).
24. Patients receiving any medications in the classes listed in Table 5-1.
25. Patients receiving any COPD related medications in the classes specified in Table 5-2 must undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.
26. Patients receiving medications in the classes listed in Table 5-3 should be excluded unless
the medication has been stable for the specified period and the stated conditions have been met.
27. Patients unable to use an electronic patient diary.
28. Patients unable to use a dry powder inhaler device or a pressurized MDI (rescue medication) or unable to comply with the study regimen. Spacer devices are not permitted.
29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
30. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female
after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during

dosing of study treatment. Effective contraception methods include:
* Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
* Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
* Male sterilization (at least 6 m prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
* Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
* Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
* Placement of an intrauterine device (IUD) or intrauterine system (IUS)
In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
Women are considered post-menopausal and not of child bearing potential if they have had 12
months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Study design

Design

Study phase:	4
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):	25-04-2016
Enrollment:	95
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	salmeterol / fluticasone
Generic name:	Seretide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	tiotropium
Generic name:	Spiriva
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ultibro Breezhaler
Generic name:	indacaterol maleate / glycopyrronium bromide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-08-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-03-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015□000114□22-NL
CCMO	NL54207.100.15

Study results

Date completed:	18-07-2017
Actual enrolment:	28

Summary results
Trial is onging in other countries