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Sponsor Novartis
Generic Drug Name QVA149
Therapeutic Area of Trial Chronic Obstructive Pulmonary Disease (COPD)
Approved Indication Investigational
Protocol Number QVA149A2307
Title A multicenter, randomized, double-blind, placebo -controlled study, to assess the long term safety of 52 weeks treatment with QVA149 (110µg indacaterol / 50µg glycopyrrolate) in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)
Phase of Development Phase III
Study Start/End Dates 22-Apr-2010 to 14-Dec-2011
Study Design/Methodology This was a multicenter, double-blind, placebo-controlled, stratified according to smoking status (randomization ratio 2:1, QVA149 once a day (o.d).: placebo o.d.), with a 14 day run-in period and a 52 week treatment period.
Centres 49 centres in 10 countries: Canada (4), France (5), United Kingdom (8), Hungary (5), India (7), Korea (4), Latvia (4), Lithuania (6), Romania (5), South Africa (1)

Publication

None

Outcome measures

Primary outcome measures(s)

Number of participants with adverse events, serious adverse events or death

Secondary outcome measures(s)

- Pre-dose FEV_1 (ie average of the FEV_1 15 minutes pre-dose and FEV_1 45 minutes pre-dose) at week 52
- Number of patients with newly occurring or worsening clinically notable haematology values at any timepoint over the whole treatment period
- Number of patients with newly occurring or worsening clinically notable biochemistry values at any timepoint over the whole treatment period
- Number of patients with newly occurring or worsening clinically notable vital signs values at any timepoint over the whole treatment period
- Number of patients with notable change from baseline in Fredericia QTc values at any timepoint over the whole treatment period

Test Product (s), Dose(s), and Mode(s) of Administration

QVA149 capsules for oral inhalation, once daily, delivered by a single dose dry powder inhaler (SDDPI).

Placebo to match QVA149, capsules for inhalation, once daily, delivered by SDDPI

Statistical Methods

The primary objective of the study was to evaluate the overall safety of QVA149, multiplicity-unadjusted hypotheses of no difference between the two treatment groups were tested for key safety variables for this class of drug namely, serum potassium and glucose, increased heart rate, blood pressure and QTc.

No statistical hypothesis testing were done on adverse events.

The secondary objectives for this study included an evaluation of the effect of QVA149 110µg/50µg o.d. on pulmonary function assessments. The key parameter, average of 45 and 15 minutes pre-dose FEV_1 at week 52 (Visit 9) was analyzed using a mixed model for the full analysis set (FAS) population. The model contained treatment as a fixed effect with average of the 45 min and 15 min pre dose FEV_1 measurements at Visit 3 as the baseline measurement, FEV_1 prior to inhalation and FEV_1 60 min post inhalation of two short acting bronchodilators (components of reversibility at Visit 2) as covariates. The model will also include smoking status at baseline, history of inhaled corticosteroid (ICS) use and country as fixed effects with center nested within country as a random effect.

For the treatment contrast with placebo 95% confidence interval will be provided together with

the associated p-value for a difference.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male or female adults aged ≥40 years, who had signed an Informed Consent Form prior to initiation of any study-related procedure
2. Patients with moderate to severe stable COPD (Stage II or Stage III) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)guidelines (2008)
3. Current or ex-smokers who had a smoking history of at least 10 pack years. (Ten pack-years was defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
4. Patients with post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and postbronchodilator FEV1/forced vital capacity (FVC) < 0.7 at Visit 2. (Post refers to 1 hour after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol or equivalent dose of albuterol)
5. Patients, according to daily electronic diary data between Visit 2 and Visit 3, with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3.

Key exclusion criteria were:

Patients who had a COPD exacerbation that required treatment with antibiotics or oral steroids or hospitalization in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 3. Patients with a COPD exacerbation during the period between Visits 1 and 3 were not eligible but were permitted to be rescreened after a minimum of 6 weeks after resolution,
Patients with a respiratory tract infection within 4 weeks prior to Visit 1, patients with an upper or lower tract infection during screening and up to Visit 3 but were permitted to be re-screened 4 weeks after resolution,
Patients with concomitant pulmonary disease, patients with lung lobectomy, or lung volume reduction, or lung transplantation,
Patients with a clinically relevant laboratory abnormality or a clinically significant condition,
Patients with any history of asthma, patients with eczema, known high IgE levels or known positive skin prick test,
Patients with allergic rhinitis that used H1 antagonists or intranasal corticosteroids intermittently,
Patients with known history and diagnosis of alpha-1 antitrypsin deficiency,
Patients participating in the active phase of a supervised pulmonary rehabilitation program,
Patients with Type I or uncontrolled Type II diabetes,
Patients contraindicated for treatment with or having a history of reactions/hypersensitivity to anticholinergic agents, long and short acting β-2-agonists and sympathomimetic amines,
Patients with a history of long QT syndrome or a prolonged QTc at Visit 2,
Patients with a clinically significant ECG abnormality at screening or baseline.

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Participant Flow

	QVA149 N=226 n (%)	Placebo N=113 n (%)	Total N=339 n (%)
Screened			498
Randomized	226	113	339
Completed	194 (85.8)	89 (78.8)	283 (83.5)
Discontinued	32 (14.2)	24 (21.2)	56 (16.5)
Primary reason for discontinuation			
Subject withdrew consent	11 (4.9)	6 (5.3)	17 (5.0)
Adverse Event(s)	10 (4.4)	6 (5.3)	16 (4.7)
Protocol deviation	2 (0.9)	5 (4.4)	7 (2.1)
Unsatisfactory therapeutic effect	3 (1.3)	3 (2.7)	6 (1.8)
Lost to follow-up	2 (0.9)	3 (2.7)	5 (1.5)
Death	3 (1.3)	1 (0.9)	4 (1.2)
Abnormal test procedure result(s)	1 (0.4)	0	1 (0.3)

Baseline Characteristics

Variable	Statistic	QVA149 N=225	Placebo N=113	Total N=338
Age (years)	n	225	113	338
	Mean	62.5	62.9	62.6
	SD	8.81	8.14	8.58
	Median	63.0	63.0	63.0
	Min - Max	40 - 88	40 – 82	40 - 88
Age				
< 65 years	n (%)	127 (56.4)	64 (56.6)	191 (56.5)
65 - < 75 years	n (%)	78 (34.7)	40 (35.4)	118 (34.9)
≥ 75 years	n (%)	20 (8.9)	9 (8.0)	29 (8.6)
Gender				
Male	n (%)	174 (77.3)	86 (76.1)	260 (76.9)
Female	n (%)	51 (22.7)	27 (23.9)	78 (23.1)
Race				
Caucasian	n (%)	178 (79.1)	94 (83.2)	272 (80.5)
Black	n (%)	0	0	0
Asian*	n (%)	47 (20.9)	19 (16.8)	66 (19.5)
Native American	n (%)	0	0	0
Pacific Islander	n (%)	0	0	0
Other	n (%)	0	0	0
Weight (kg)	n	225	113	338
	Mean	75.2	77.5	76.0

	SD	19.87	19.17	19.64
	Median	72.0	79.0	74.0
	Min - Max	34 - 160	43 - 147	34 - 160
Height (cm)	n	225	113	338
	Mean	169.1	169.0	169.0
	SD	9.36	8.66	9.12
	Median	169.0	168.0	169.0
	Min - Max	145 - 198	152 - 193	145 - 198
Body Mass Index (kg/m^2)	n	225	113	338
	Mean	26.2	27.0	26.5
	SD	6.15	5.81	6.04
	Median	24.9	26.8	25.7
	Min - Max	13.2 - 56.0	15.6 - 52.7	13.2 - 56.0
Body Mass Index				
≤ 30.0 kg/m^2	n (%)	174 (77.3)	80 (70.8)	254 (75.1)
> 30.0 kg/m^2	n (%)	51 (22.7)	33 (29.2)	84 (24.9)

Outcome measures

Primary Outcome Result(s)

Number of participants with adverse events, serious adverse events or death

	QVA149 N=225 n (%)	Placebo N=113 n (%)
Adverse events	130 (57.8)	64 (56.6)
Serious adverse events	37 (16.4)	12 (10.6)
Death (number of patients who died between first treatment day and 30 days after last treatment)	4 (1.8)	1 (0.9)
Death (number of patients who died between first treatment day + 30days and last day of follow up)	1 (0.4)	0

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Secondary Outcome Result(s)

Analysis of pre-dose FEV_1 (L) after 52 weeks of treatment (FAS)

		Treatment			Treatment difference				
Treatment	n	Baseline mean	LSM	SE	Comparison	LSM	SE	95% CI	p-value
QVA149 (N=225)	191	1.428	1.607	0.0230	QVA149 - Placebo	0.189	0.0320	(0.1259,0.2519)	<0.001
Placebo (N=113)	88	1.494	1.418	0.0297					

ANCOVA model: Predose FEV1 = treatment+baseline FEV1+baseline ICS+FEV1 reversibility components+smoking status+country+center(country).
Center is included as a random effect nested within country.
Predose FEV1 is defined as the average of the -15 min and the -45 min FEV1 values.
FEV1 data taken within 6h of rescue medication or within 7 days of systemic corticosteroid is excluded from this analysis.
Baseline is defined as the average of the 15 min and the 45 min predose at day 1.

Number (%) of patients with newly occurring or worsening clinically notable hematology values at any time-point over the whole treatment period by parameter (Safety set)

Parameter	Criterion	QVA149 N=225 n/N' (%)	Pbo N=113 n/N' (%)
Haemoglobin	Male < 115 g/L	9/164(5.5)	1/ 77(1.3)
	Female < 95 g/L	0/ 50(0.0)	0/ 25(0.0)
	Total	9/214(4.2)	1/102(1.0)
Haematocrit	Male < 0.37 v/v	11/164(6.7)	3/ 77(3.9)
	Female < 0.32 v/v	0/ 49(0.0)	0/ 25(0.0)
	Total	11/213(5.2)	3/102(2.9)
WBC (total)	< 2.8 10E9/L	0/214(0.0)	0/102(0.0)
	> 16.0 10E9/L	0/214(0.0)	0/102(0.0)
Platelet count (direct)	< 75 10E9/L	1/214(0.5)	0/102(0.0)
	> 700 10E9/L	0/214(0.0)	0/102(0.0)

Percentages for male/female patients are based on the total number of male/female patients
n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable abnormal value at any post-baseline time-point or had a worsening of a value during treatment which was already notable at baseline.
Percentage is calculated using the number of available patients as the denominator.
Patients with missing baseline values are excluded.

Number (%) of patients with newly occurring or worsening clinically notable biochemistry parameters at any time-point over the whole treatment period by parameter (Safety set)

Parameter	Criterion	QVA149 N=225 n/N' (%)	Placebo N=113 n/N' (%)
Sodium	< 125 mmol/L	0/214 (0.0)	0/101 (0.0)
	> 160 mmol/L	0/214 (0.0)	0/101 (0.0)
Potassium	< 3.0 mmol/L	0/214 (0.0)	0/101 (0.0)
	> 6.0 mmol/L	2/214 (0.9)	1/101 (1.0)
Blood urea nitrogen (BUN)	> 9.99 mmol/L	14/214 (6.5)	4/101 (4.0)
Creatinine	> 176.8 µmol/L	1/214 (0.5)	1/101 (1.0)
Total protein (serum)	< 40 g/L	0/214 (0.0)	0/101 (0.0)
	> 95 g/L	0/214 (0.0)	0/101 (0.0)
Albumin	< 25 g/L	0/214 (0.0)	0/101 (0.0)
Bilirubin (total)	> 34.2 µmol/L	0/213 (0.0)	0/101 (0.0)
SGPT (ALT)	> 3 x ULN	2/214 (0.9)	1/101 (1.0)
SGOT (AST)	> 3 x ULN	1/214 (0.5)	2/101 (2.0)
Gamma glutamyltransferase	> 3 x ULN	8/214 (3.7)	7/101 (6.9)
Alkaline phosphatase, serum	> 3 x ULN	0/214 (0.0)	0/101 (0.0)
Glucose	< 2.78 mmol/L	0/214 (0.0)	0/101 (0.0)
	> 9.99 mmol/L	16/214 (7.5)	3/101 (3.0)

Percentages for male/female patients are based on the total number of male/female patients
n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable abnormal value at any post-baseline time-point or had a worsening of a value during treatment which was already notable at baseline.
Percentage is calculated using the number of available patients as the denominator.
Patients with missing baseline values are excluded.

Number (%) of patients with newly occurring or worsening clinically notable vital signs values at any time during the whole treatment period (Safety set)

Parameter	Criterion	QVA149 N=225 n / N' (%)	Placebo N=113 n / N' (%)
Pulse rate	Low: < 40 bpm, or ≤ 50 bpm and decrease from baseline ≥ 15 bpm	0/225 (0.0)	1/113 (0.9)
	High: > 130 bpm, or ≥ 120 bpm and increase from baseline ≥ 15 bpm	0/225 (0.0)	0/113 (0.0)
	Low and High	0/225 (0.0)	0/113 (0.0)
Systolic blood pressure	Low: < 75 mm Hg, or ≤ 90 mm Hg and decrease from baseline ≥ 20 mm Hg	0/225 (0.0)	0/113 (0.0)
	High: > 200 mm Hg, or ≥ 180 mm Hg and increase from baseline ≥ 20 mm Hg	3/225 (1.3)	0/113 (0.0)
	Low and High	0/225 (0.0)	0/113 (0.0)
Diastolic blood pressure	Low: < 40 mm Hg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mm Hg	0/225 (0.0)	3/113 (2.7)

High: > 115 mm Hg, or ≥ 105 mm Hg and increase from baseline ≥ 15 mm Hg	2/225 (0.9)	2/113 (1.8)
Low and High	0/225 (0.0)	0/113 (0.0)

n = Number of patients meeting the criterion, i.e. who had a newly occurring clinically notable value at any post-baseline time-point or had a worsening of a value during treatment which was already notable at baseline.
Percentage is calculated using the number of available patients as the denominator.
The criterion categories for each test are mutually exclusive.

Number (%) of patients with newly occurring or worsening notable Fridericia's QTc and notable change from baseline at any time during the whole treatment period (Safety set)

Criterion	QVA149 N=225 n (%)	Placebo N=113 n (%)
QTc >450 ms	11/225 (4.9)	10/113 (8.8)
QTc >480 ms	1/225 (0.4)	1/113 (0.9)
QTc >500 ms	1/225 (0.4)	0
Change from baseline		
30 - 60 ms	7/225 (3.1)	5/113 (4.4)
> 60 ms	0	1/113 (0.9)
Total notable change from baseline	7/225 (3.1)	6/113 (5.3)

Fridericia's formula is calculated at the QT interval / cube root (RR).
Percentage is based on the number of patients available. Total number of patients with notable changes are the number of patients with 30-60 and >60.

Safety Results

Adverse events (including COPD exacerbations) overall and by primary system organ class - n (%) of patients (Safety set)

	QVA149 N=225 n (%)	Placebo N=113 n (%)
Primary system organ class		
Total	130 (57.8)	64 (56.6)
Respiratory, thoracic and mediastinal disorders	79 (35.1)	33 (29.2)
Infections and infestations	75 (33.3)	29 (25.7)
Musculoskeletal and connective tissue disorders	22 (9.8)	5 (4.4)
Gastrointestinal disorders	21 (9.3)	11 (9.7)
Nervous system disorders	20 (8.9)	8 (7.1)
General disorders and administration site conditions	14 (6.2)	8 (7.1)
Injury, poisoning and procedural complications	14 (6.2)	2 (1.8)
Cardiac disorders	11 (4.9)	2 (1.8)
Eye disorders	9 (4.0)	4 (3.5)
Skin and subcutaneous tissue disorders	9 (4.0)	6 (5.3)
Vascular disorders	9 (4.0)	7 (6.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (3.1)	3 (2.7)
Metabolism and nutrition disorders	6 (2.7)	1 (0.9)
Psychiatric disorders	6 (2.7)	4 (3.5)
Renal and urinary disorders	6 (2.7)	1 (0.9)
Investigations	5 (2.2)	4 (3.5)
Reproductive system and breast disorders	3 (1.3)	3 (2.7)
Ear and labyrinth disorders	2 (0.9)	1 (0.9)
Endocrine disorders	2 (0.9)	1 (0.9)
Blood and lymphatic system disorders	1 (0.4)	1 (0.9)
Congenital, familial and genetic disorders	1 (0.4)	0
Hepatobiliary disorders	1 (0.4)	2 (1.8)
Immune system disorders	1 (0.4)	0
Surgical and medical procedures	0	2 (1.8)

Primary system organ classes in descending order of percentage according to the QVA149 group.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
A patient with multiple adverse events within multiple primary system organ classes is counted multiple times.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

MedDRA Preferred term	QVA149 N=225 n(%)	Placebo N=113 n(%)
Chronic obstructive pulmonary disease	63(28.0)	29(25.7)
Cough	18(8.0)	7(6.2)
Viral upper respiratory tract infection	18(8.0)	15(13.3)
Lower respiratory tract infection	15(6.7)	4(3.5)
Upper respiratory tract infection	12(5.3)	9(8.0)
Upper respiratory tract infection bacterial	11(4.9)	5(4.4)
Pyrexia	10(4.4)	1(0.9)
Headache	8(3.6)	3(2.7)
Pneumonia	8(3.6)	0
Dizziness	7(3.1)	1(0.9)

Serious Adverse Events and Deaths

Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug – n (%) of patients (Safety set)

	QVA149 N=225 n (%)	Placebo N=113 n (%)
Patients with any AE(s)	130 (57.8)	64 (56.6)
Serious AEs or AE discontinuations		
Death*	4 (1.8)	1 (0.9)
Death**	1 (0.4)	0
SAE(s)	37 (16.4)	12 (10.6)
Discontinued due to AE(s)	13 (5.8)	7 (6.2)
Discontinued due to SAE(s)	12 (5.3)	3 (2.7)
Discontinued due to non-SAE(s)	1 (0.4)	4 (3.5)

Death*= number of patients who died between the first treatment day and 30 days after the last treatment.
Death=number of patients who died after the last dose+30days but before end of the follow-up day.**

Other Relevant Findings

Adjudicated cause of deaths adjusted for exposure by category (Safety set)

	QVA149 N=225 n (%)	Placebo N=113 n (%)
Exposure in patient years	207.4	96.7
Deaths: n (n per 100 patient-year)	4 (1.9)	1 (1.0)
Deaths occurred during active treatment		
Causes of death		
All cause mortality	4 (1.9)	1 (1.0)
Cardiovascular cause	1 (0.5)	0 (0.0)
Sudden death	1 (0.5)	0 (0.0)
Respiratory cause	3 (1.4)	0 (0.0)
COPD exacerbation with pneumonia	1 (0.5)	0 (0.0)
COPD exacerbation without pneumonia	2 (1.0)	0 (0.0)
Other non-cardiovascular causes	0 (0.0)	1 (1.0)
Accidental	0 (0.0)	1 (1.0)

Preferred terms are sorted in descending order of frequency in the QVA149 treatment group.
Duration of exposure = date of last dose – date of first dose + 1.
Deaths that occurred during the active treatment period only are summarized.

Date of Clinical Trial Report

01 Jun 2012

Date Inclusion on Novartis Clinical Trial Results Database

13 Dec 2012

Date of Latest Update