Sponsor

Novartis

Generic Drug Name

Indacaterol and glycopyrronium bromide

Therapeutic Area of Trial

Chronic Obstructive Pulmonary Disease

Approved Indication

Not applicable

Protocol Number

CQVA149A2305

Title

A Randomized, Blinded, Double Dummy, Multi-center, Placebo Controlled, 3 Period, Crossover Study to Assess the Effect of QVA149 (110/50 µg o.d.) on Exercise Endurance in Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD), Using Tiotropium as an Active Control

Phase of Development

Phase III

Study Start/End Dates

Study Start Date: March 2011
Study Completion Date: November 2011

Study Design/Methodology

This was a multi-center, randomized, blinded, double-dummy placebo-controlled, three-period cross-over study with a maximum 28-day screening period, baseline visit and three, 3- week treatment periods followed by a study completion evaluation. A washout of 21 days was used to separate the treatment periods.
It was planned to randomize approximately 80 patients with the intention that at least 68 would complete the study. A total of 85 patients were randomized into the study and 73 patients completed the study. In the Full Analysis Set (FAS) for this cross-over study there were 77 patients who were treated with QVA149, 83 patients who were treated with tiotropium and 77 patients who were treated with placebo.

Centers

14 centers participated in 2 countries: Germany (8), Spain (6)

Publication

Not applicable

Outcome measures

Primary outcome measures(s)

• The Effect of QVA149 Compared to Placebo Measured by Exercise Tolerance

Secondary outcome measures(s)

• Effect of QVA149 Compared to Placebo on Dynamic Inspiratory Capacity
• Effect of QVA149 Compared to Placebo on Trough 24 Hour Post Dose Inspiratory Capacity
• Effect of QVA149 Compared to Placebo on Trough 24 Hour Post Dose Forced Expiratory Volume in One Second
• Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Slow Vital Capacity
• Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Residual Volume
• Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Specific Airway Conductance
• Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Functional Residual Capacity
• Effect of QVA149 Compared to Placebo on Spirometry After Three Weeks of Treatment on Patients Not Exercising
• Effect of QVA149 Compared to Placebo on Exertional Dyspnea
• Effect of QVA149 Compared to Placebo on Leg Discomfort During Exercise
• Effect of QVA149 Compared With Tiotropium With Respect to Exercise Endurance Time
• Effect of a Single Dose of QVA149 Compared to Placebo With Respect to Exercise Endurance Time

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

QVA149 delivered once daily via single-dose dry powder inhaler
Placebo, delivered once daily via single-dose dry powder inhaler
Tiotropium delivered once daily via HandiHaler® device

Statistical Methods

The primary variable was exercise endurance time (in seconds) after three weeks of treatment. The primary variable was summarized by treatment group for the FAS. The effect of QVA149 110/50 µg compared to placebo was evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha) using a type I error of 5%: Ho: There is no difference in exercise duration time (in seconds) for patients with COPD treated with QVA149 compared to placebo. Ha: There is a difference in exercise duration time (in seconds) for patients with COPD treated with QVA149 compared to placebo. The primary variable was analyzed using a mixed model for the FAS.
The model contained patient (sequence) as a random effect, and treatment, pre-treatment exercise period baseline (measured at Visit 3 for period 1, Visit 6 for period 2 and Visit 9 for period 3), sequence and period as fixed effects. The LS means and the estimated treatment difference (QVA149 – Placebo) together with the associated 95% confidence interval and two-sided p-value were displayed.
Superiority of QVA149 110/50 µg over placebo was demonstrated if the p-value was less than the 5% significance level and the 95% confidence interval lay entirely to the right of 0 seconds. Treatment comparisons between tiotropium versus placebo and QVA149 versus tiotropium were not controlled for multiplicity.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diagnosis of moderate to severe stable Chronic Obstructive Pulmonary Disease (COPD) stage II or stage III according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines (2009)
- Qualifying spirometry, Forced Expiratory Volume in one second (FEV1) and post-bronchodilator FEV1/FVC (Forced Vital Capacity)
- Smoking history ≥ 10 pack years

Exclusion Criteria:

- Pregnant women or nursing mothers or women of child-bearing potential not using adequate contraception
- Cardiac abnormality
- History of asthma
- Contraindications to cardiopulmonary exercise testing
- Participation in active phase of pulmonary rehabilitation program
- History of cancer within the past 5 years

Participant Flow

	Total n (%)
Screened	126
Randomized	85 (100)
Completed	73 (85.9)
Discontinued	12 (14.1)
Reason for discontinuation	
Adverse Event(s)	6 (7.1)
Patient withdrew consent	3 (3.5)
Administrative problems	2 (2.4)
Subject's condition no longer requires study drug	1 (1.2)
Last treatment period before discontinuation	
Patient not exposed	1 (1.2)
Period I	5 (5.9)
Period II	5 (5.9)
Period III	1 (1.2)
Last treatment before discontinuation	
Patient not exposed	1 (1.2)
QVA149	0
Tiotropium	9 (10.6)
Placebo	2 (2.4)

Baseline Characteristics

Variable	Statistic	Total N=84
Age (years)	n	84
	Mean (SD)	62.1 (8.11)
	Min - Max	41 - 83
Age		
< 65 years	n (%)	54 (64.3)
65 - < 75 years	n (%)	24 (28.6)
≥ 75 years	n (%)	6 (7.1)
Gender		
Male	n (%)	53 (63.1)
Female	n (%)	31 (36.9)
Race		
Caucasian	n (%)	81 (96.4)
Native American	n (%)	1 (1.2)
Other	n (%)	2 (2.4)
Weight (kg)	n	84
	Mean (SD)	77.6 (14.49)
	Min - Max	48.0 - 114.0
Height (cm)	n	84
	Mean (SD)	170.3 (8.85)
	Min - Max	151 - 197
Body Mass Index (BMI) (kg/m^2)	n	84
	Mean (SD)	26.7 (3.97)
	Min - Max	18.8 - 36.8
Body Mass Index		
≤ 30.0 kg/m^2	n (%)	66 (78.6)
> 30.0 kg/m^2	n (%)	18 (21.4)

Outcome measures

Primary Outcome Result(s)

The Effect of QVA149 Compared to Placebo Measured by Exercise Tolerance

Measured by exercise endurance time during a sub-maximal constant load cycle ergometry test after three weeks of treatment

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
QVA149 (N=77)	77	435.1 (23.40)	507.8	19.30	QVA149 - Placebo	59.5	21.13	(17.7,101.3)	0.006
					QVA149 - Tiotropium	-6.7	20.61	(-47.5, 34.0)	0.744
Tiotropium (N=83)	80	438.5 (24.06)	514.6	18.99	Tiotropium - Placebo	66.3	20.95	(24.8,107.7)	0.002
Placebo (N=77)	74	438.8 (24.07)	448.3	19.49					

Secondary Outcome Result(s)

The Effect of QVA149 Compared to Placebo on Dynamic Inspiratory Capacity

Measured using dynamic inspiratory capacity at isotime during sub-maximal constant load cycle ergometry test after three weeks of treatment

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
QVA149 (N=77)	65	2.11 (0.078)	2.42	0.034	QVA149 - Placebo	0.32	0.044	(0.23, 0.40)	<.001
					QVA149 - Tiotropium	0.14	0.042	(0.05, 0.22)	0.002
Tiotropium (N=83)	67	2.11 (0.077)	2.29	0.033	Tiotropium - Placebo	0.18	0.043	(0.10, 0.27)	<.001
Placebo (N=77)	59	2.08 (0.071)	2.11	0.035					

Effect of QVA149 Compared to Placebo on Trough 24 Hour Post Dose Inspiratory Capacity

Measured using trough 24 hour post dose inspiratory capacity after three weeks of treatment

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
QVA149 (N=77)	67	2.12 (0.074)	2.25	0.035	QVA149 - Placebo	0.19	0.050	(0.09, 0.29)	<.001
					QVA149 - Tiotropium	0.15	0.048	(0.06, 0.25)	0.002
Tiotropium (N=83)	73	2.09 (0.070)	2.10	0.034	Tiotropium - Placebo	0.04	0.049	(-0.06, 0.13)	0.423
Placebo (N=77)	66	2.08 (0.078)	2.06	0.035					

Effect of QVA149 Compared to Placebo on Trough 24 Hour Post Dose Forced Expiratory Volume in One Second

Measured using trough 24 hour post dose Forced Expiratory Volume in one second (FEV1) after three weeks of treatment

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
QVA149 (N=77)	76	1.35 (0.055)	1.53	0.020	QVA149 - Placebo	0.20	0.026	(0.15, 0.26)	<.001
					QVA149 - Tiotropium	0.10	0.026	(0.05, 0.15)	<.001
Tiotropium (N=83)	78	1.38 (0.055)	1.43	0.020	Tiotropium - Placebo	0.10	0.026	(0.05, 0.15)	<.001
Placebo (N=77)	73	1.34 (0.053)	1.33	0.021					

Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Slow Vital Capacity

Measured using the pulmonary function test for Slow Vital Capacity (SVC) on day 1 and day 21, at 5 min and 15 min post dose as determined by body plethysmography

Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Residual Volume

Measured using the pulmonary function test for Residual Volume (RV) on day 1 and day 21, at 5 min and 15 min post dose as determined by body plethysmography

Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Specific Airway Conductance

Measured using the pulmonary function test for Specific Airway Conductance (SGaw) on day 1 and day 21, at 5 min and 15 min post dose as determined by body plethysmography

Effect of QVA149 Compared to Placebo on Pulmonary Function Test Using Functional Residual Capacity

Measured using the pulmonary function test for Functional Residual Capacity (FRC) on day 1 and day 21, at 5 min and 15 min post dose as determined by body plethysmography

Plethysmography (body box) at Day 1, 5 and 15 min post-dose dose (Full Analysis Set)

Assessment/ Time Point	QVA149 (LS mean)	Tio (LS mean)	Placebo (LS mean)	Treatment difference QVA149-Pbo LS mean (95% CI) P-value	Treatment difference QVA149-Tio LS mean (95% CI) P-value	Treatment difference Tio-Pbo LS mean (95% CI) P-value
FRC (L) 5 Min Post-dose	n=72 4.68	n=79 4.78	n=73 4.98	-0.30 (-0.44, -0.16) p<0.001	-0.10 (-0.24, 0.04) p=0.143	-0.20 (-0.34, -0.06) p=0.005
FRC (L) 15 min Post-dose	n=73 4.62	n=79 4.63	n=74 4.92	-0.30 (-0.45, -0.16) p<0.001	-0.01 (-0.15, 0.13) p=0.916	-0.30 (-0.44, -0.15) p<0.001

RV (L) 5 Min Post-dose	n=71 3.66	n=80 3.89	n=73 3.94	-0.28 (-0.41, -0.15) p<0.001	-0.23 (-0.36, -0.10) p<0.001	-0.05 (-0.18, 0.08) p=0.438
RV (L) 15 Min Post-dose	n=72 3.63	n=80 3.66	n=74 3.89	-0.26 (-0.38, -0.14) p<0.001	-0.03 (-0.14, 0.09) p=0.625	-0.23 (-0.35, -0.12) p<0.001
SVC (L) 5 Min Post-dose	n=76 3.37	n=82 3.22	n=75 3.14	0.23 (0.16, 0.30) p<0.001	0.16 (0.09, 0.23) p<0.001	0.08 (0.01, 0.14) p=0.033
SVC (L) 15 Min Post-dose	n=76 3.43	n=81 3.32	n=77 3.16	0.27 (0.20, 0.33) p<0.001	0.11 (0.05, 0.18) p<0.001	0.15 (0.09, 0.22) p<0.001
SGaw (1/kP*S) 5 Min Post-dose	n=71 0.71	n=81 0.58	n=72 0.50	0.21 (0.14, 0.29) p<0.001	0.13 (0.06, 0.21) p<0.001	0.08 (0, 0.15) p=0.039
SGaw (1/kP*S) 15 Min Post-dose	n=72 0.71	n=80 0.79	n=74 0.50	0.22 (0.04, 0.39) p=0.015	-0.07 (-0.25, 0.10) p=0.389	0.29 (0.12, 0.46) p<0.001

Plethysmography (body box) at Day 21, 5 and 15 min post-dose dose (Full Analysis Set)

Assessment/ Time Point	QVA149 (LS mean)	Tio (LS mean)	Placebo (LS mean)	Treatment difference QVA149-Pbo LS mean (95% CI) P-value	Treatment difference QVA149-Tio LS mean (95% CI) P-value	Treatment difference Tio-Pbo LS mean (95% CI) P-value
FRC (L) 5 Min Post-dose	n=73 4.58	n=78 4.66	n=71 5.00	-0.42 (-0.56, -0.28) p<0.001	-0.08 (-0.22, 0.05) p=0.227	-0.34 (-0.48, -0.20) p<0.001
FRC (L) 15 min Post-dose	n=71 4.53	n=78 4.55	n=72 4.94	-0.41 (-0.56, -0.26) p<0.001	-0.02 (-0.17, 0.13) p=0.781	-0.39 (-0.53, -0.24) p<0.001
RV (L) 5 Min Post-dose	n=73 3.58	n=79 3.69	n=71 4.03	-0.45 (-0.60, -0.30) p<0.001	-0.11 (-0.26, 0.03) p=0.126	-0.34 (-0.48, -0.19) p<0.001
RV (L) 15 Min Post-dose	n=71 3.54	n=79 3.59	n=72 3.96	-0.42 (-0.58, -0.26) p<0.001	-0.05 (-0.21, 0.11) p=0.515	-0.37 (-0.53, -0.21) p<0.001
SVC (L) 5 Min Post-dose	n=77 3.37	n=81 3.26	n=75 3.08	0.29 (0.19, 0.40) p<0.001	0.10 (0, 0.20) p=0.049	0.19 (0.09, 0.29) p<0.001
SVC (L) 15 Min Post-dose	n=74 3.38	n=81 3.29	n=75 3.09	0.29 (0.19, 0.40) p<0.001	0.09 (-0.01, 0.19) p=0.092	0.21 (0.11, 0.31) p<0.001
SGaw (1/kP*S) 5 Min Post-dose	n=72 0.76	n=80 0.64	n=71 0.50	0.26 (0.17, 0.35) p<0.001	0.12 (0.03, 0.21) p=0.007	0.14 (0.04, 0.23) p=0.004

SGaw (1/kP*S) 15 Min Post-dose	n=70 0.79	n=80 0.67	n=72 0.47	0.32 (0.26, 0.38) p<0.001	0.12 (0.06, 0.18) p<0.001	0.20 (0.14, 0.26) p<0.001

Effect of QVA149 Compared to Placebo on Spirometry After Three Weeks of Treatment on Patients Not Exercising

Measured using dynamic inspiratory capacity post-dose pre-exercise after three weeks of treatment

		Treatment				Treatment difference			
Treatment	**n**	**Baseline Mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
QVA149 (N=77)	76	2.01 (0.065)	2.34	0.032	QVA149 - Placebo	0.34	0.042	(0.25, 0.42)	<.001
					QVA149 - Tiotropium	0.15	0.040	(0.07, 0.23)	<.001
Tiotropium (N=83)	80	2.07 (0.074)	2.19	0.031	Tiotropium - Placebo	0.18	0.041	(0.10, 0.27)	<.001
Placebo (N=77)	70	2.08 (0.070)	2.01	0.033					

Effect of QVA149 Compared to Placebo on Exertional Dyspnea

Measured using exertional dyspnea Borg CR10 Scale® during exercise after three weeks treatment

		Treatment				Treatment difference			
Treatment	**n**	**Baseline Mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
QVA149 (N=77)	66	3.86 (0.308)	3.77	0.256	QVA149 - Placebo	-0.10	0.271	(-0.64, 0.44)	0.711
					QVA149 - Tiotropium	0.19	0.259	(-0.33, 0.70)	0.471
Tiotropium (N=83)	70	3.81 (0.282)	3.59	0.248	Tiotropium - Placebo	-0.29	0.267	(-0.82, 0.24)	0.282
Placebo (N=77)	61	3.69 (0.337)	3.87	0.259					

Effect of QVA149 Compared to Placebo on Leg Discomfort During Exercise

Measured using Borg CR10 Scale® during sub-maximal constant load cycle ergometry test after three weeks treatment

		Treatment				Treatment difference			
Treatment	**n**	**Baseline Mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
QVA149 (N=77)	66	4.46 (0.314)	4.53	0.243	QVA149 - Placebo	0.10	0.274	(-0.44, 0.65)	0.703
					QVA149 - Tiotropium	-0.04	0.262	(-0.56, 0.48)	0.881
Tiotropium (N=83)	70	3.95 (0.269)	4.57	0.234	Tiotropium - Placebo	0.14	0.269	(-0.39, 0.68)	0.594
Placebo (N=77)	61	4.23 (0.340)	4.43	0.245					

Effect of QVA149 Compared With Tiotropium With Respect to Exercise Endurance Time

Measured by a sub-maximal constant load cycle ergometry test (SMETT) after three weeks of treatment

		Treatment			Treatment difference			
Treatment	**n**	**Baseline Mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
QVA149 (N=77)	77	435.1 (23.40)	507.8	19.30	QVA149 - Placebo	59.5	21.13	(17.7,101.3)	0.006
					QVA149 - Tiotropium	-6.7	20.61	(-47.5, 34.0)	0.744
Tiotropium (N=83)	80	438.5 (24.06)	514.6	18.99	Tiotropium - Placebo	66.3	20.95	(24.8,107.7)	0.002
Placebo (N=77)	74	438.8 (24.07)	448.3	19.49					

Effect of a Single Dose of QVA149 Compared to Placebo With Respect to Exercise Endurance Time

Measured with respect to exercise endurance time during sub-maximal constant load cycle ergometry test

			Baseline Mean	Treatment			Treatment difference			
Visit	Treatment	n	(SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Day 1	QVA149 (N=77)	77	435.1 (23.40)	492.8	17.28	QVA149 - Pbo	23.9	20.14	(-15.9, 63.8)	0.237
						QVA149 - Tio	11.7	19.82	(-27.5, 50.9)	0.556
	Tio (N=83)	82	441.3 (24.01)	481.0	16.77	Tio - Pbo	12.2	19.87	(-27.1, 51.5)	0.540
	Pbo (N=77)	77	435.6 (23.34)	468.8	17.18					

Adverse Events by System Organ Class

Primary MedDRA system organ class	QVA149 N=77 n (%)	Tiotropium N=83 n (%)	Placebo N=77 n (%)
Any primary system organ class			
-Total	29 (37.7)	23 (27.7)	28 (36.4)
Respiratory, thoracic and mediastinal disorders	14 (18.2)	7 (8.4)	6 (7.8)
Infections and infestations	7 (9.1)	4 (4.8)	6 (7.8)
Gastrointestinal disorders	5 (6.5)	3 (3.6)	4 (5.2)
Injury, poisoning and procedural complications	4 (5.2)	3 (3.6)	2 (2.6)
Ear and labyrinth disorders	2 (2.6)	0	0
General disorders and administration site conditions	2 (2.6)	1 (1.2)	1 (1.3)
Musculoskeletal and connective tissue disorders	2 (2.6)	4 (4.8)	5 (6.5)
Vascular disorders	2 (2.6)	0	0
Investigations	1 (1.3)	0	0
Metabolism and nutrition disorders	1 (1.3)	0	1 (1.3)
Nervous system disorders	1 (1.3)	1 (1.2)	2 (2.6)
Psychiatric disorders	1 (1.3)	1 (1.2)	1 (1.3)
Cardiac disorders	0	1 (1.2)	0
Immune system disorders	0	1 (1.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (1.2)	0
Reproductive system and breast disorders	0	0	1 (1.3)
Skin and subcutaneous tissue disorders	0	1 (1.2)	1 (1.3)

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

This table does not exist in the CSR.

Serious Adverse Events and Deaths

Primary system organ class Preferred term	QVA149 N=77 n (%)	Tiotropium N=83 n (%)	Placebo N=77 n (%)
Patients with any serious AE(s)	1 (1.3)	1 (1.2)	1 (1.3)
Cardiac disorders			
-Total	0	1 (1.2)	0
Acute myocardial infarction	0	1 (1.2)	0
Gastrointestinal disorders			
-Total	1 (1.3)	0	0
Colitis	1 (1.3)	0	0
Infections and infestations			
-Total	0	0	1 (1.3)
Pneumonia	0	0	1 (1.3)

Other Relevant Findings –

Not applicable

Date of Clinical Trial Report

20 June 2012

Date Inclusion on Novartis Clinical Trial Results Database

30 Nov 2012

Date of Latest Update

Not applicable