Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Indacaterol maleate/glycopyrronium bromide

Trial Indication(s)

Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number

CQVA149A2340

Protocol Title

A multi-center randomized double blind 52 -week study to assess the safety of QVA149 compared to QAB149 in patients with COPD who have moderate to severe airflow limitation.

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

26-Oct-2012 to 30-Jun-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

A multi-center, randomized, double-blind, 52-week study to assess the safety of QVA149 compared to QAB149 in patients with chronic obstructive pulmonary disease (COPD) who have moderate to severe airflow limitation. The study consisted of four periods: a screening period of up to 14 days, a run-in period up to 14 days, a 52 week double-blind treatment period and a follow-up period of 30 days.

Centers

Patients were screened across 88 sites in 6 countries: Bulgaria (5 centers), Finland (4 centers), Hungary (10 centers), Romania (10 centers), Spain (8 centers), United States (51 centers).

Publication

Currently no publications

Objectives:

Primary objective(s):

To evaluate the safety and tolerability of QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d. in terms of adverse event (AE) reporting rate in patients with COPD with moderate to severe airflow limitation during 52 weeks of treatment

Secondary objective(s):

- To evaluate the safety and tolerability of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d. with QAB149 75 µg o.d. over 52 weeks in terms of vital signs, electrocardiogram (ECG), and laboratory evaluations.
- To evaluate the effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d., with QAB149 75 µg o.d. in terms of time to treatment discontinuation.
- To evaluate the bronchodilator effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d, with QAB149 75 µg o.d. in terms of mean forced expiratory volume in 1 second (FEV_1) at 15 and 45 minutes pre-dose at Week 52.
- To evaluate the bronchodilator effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d, with QAB149 75 µg o.d. based on FEV_1 and forced vital capacity (FVC) measurements at all post- baseline time points.

- To evaluate the effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d., with QAB149 75 µg o.d. on time to first moderate or severe exacerbation.
- To evaluate the effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d., with QAB149 75 µg o.d. on symptoms reported over the 52-week treatment period.
- To evaluate the effect of QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d., with QAB149 75 µg o.d. on daily number of puffs of rescue medication over the 52-week treatment period.

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

Double-blind study treatment was supplied as identically appearing, powder filled inhalation capsules containing QVA149 27.5/12.5 µg, QVA149 27.5/25 µg or QAB149 75 µg packaged in blister packs, delivered via single dose dry powder inhaler (SDDPI).

Statistical Methods

The objective of this study was to evaluate the safety and tolerability of QVA149 (27.5/12.5 µg b.i.d. and 27.5/25 µg b.i.d.) in COPD patients with moderate to severe airflow limitation following 52 weeks of treatment. The assessment of safety included summarizing all safety measurements including AEs and COPD exacerbations. AE assessments included adjudicated AEs and various AE subgroup analysis. Particular attention was paid to the safety variables for this class of drug and to side effects occurring at higher rates in the QVA149 group than in the QAB149 group as well as increased heart rate, increased blood pressure, cerebrovascular and cardiovascular events (major cerebrovascular events, cardiac arrhythmias), hypokalaemia, diabetes and hyperglycaemia, QTc prolongation, paradoxical bronchospasm, narrow angle

glaucoma, blurred vision, urinary outflow obstruction, urinary retention and anticholinergic syndrome. No statistical hypothesis testing was done on AEs.

The change from baseline in pre-dose trough FEV_1 at Visits 202 to 209 was analyzed by a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) model on the full analysis set (FAS) and on the per protocol set (PPS). The model contained treatment, baseline FEV_1, visit, treatment by visit interaction, visit by baseline FEV_1 interaction, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, airflow limitation severity, and region as fixed effects with unstructured variance-covariance error matrix.

Similar analyses were performed for change from baseline in 1 hour post-dose FEV_1, change from baseline in pre-dose trough FVC, and change in 1 hour post-dose FVC on the FAS.

COPD exacerbations starting between first dose and one day after the date of last treatment were included in the analyses. Separate analyses of time to first COPD exacerbation and rate of COPD exacerbations were performed for:

- all COPD exacerbations (including mild)
- moderate or severe COPD exacerbations
- moderate COPD exacerbations only
- severe COPD exacerbations only

The time to first COPD exacerbation was displayed for each treatment group with a Kaplan-Meier curve and was analyzed using a Cox regression model for the FAS. The full Cox regression model included treatment, baseline total

symptom score, baseline COPD exacerbation history, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects.

The rate of COPD exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. The log (exposure time) was used as the offset variable in the model. The model included the same terms as the Cox regression model.

The change from baseline in mean daily, morning and evening total symptom scores was analyzed using a linear mixed model for the FAS. The model contained treatment, the baseline symptom score, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects with center nested within region as random effect. The percentage of nights with 'no nighttime awakenings', the percentage of days with no daytime symptoms, and the percentage of 'days able to perform usual daily activities' were analyzed similarly using corresponding baseline values replacing baseline symptom score.

Daily, daytime and nighttime rescue medication use and the percentage of 'days with no rescue medication use' were analyzed for the FAS similar to total symptom scores using corresponding baseline values replacing baseline symptom score.

Change from baseline in CAT total score at Visit 204, 206, 208 and 209 was analyzed for the FAS by a MMRM ANCOVA model. The model contained treatment, baseline CAT total score, visit, treatment by visit interaction, baseline CAT total score by visit interaction, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects with unstructured variance-covariance error matrix. For CAT score, a decrease from baseline of at least 2 units was considered a response. Descriptive by-visit summaries of CAT responder analysis were also conducted.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female adults aged ≥40 years
- Patients with stable COPD according to GOLD strategy (GOLD 2011).
- Patients with airflow limitation indicated by a post- bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70.
- Current or ex-smokers who have a smoking history of at least 10 pack years.
- Patients with an mMRC ≥ grade 2

Exclusion Criteria:

- History of long QT syndrome or prolonged QTc
- Patients who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1.
- Patients with Type I or uncontrolled Type II diabetes
- Patients with a history of asthma or have concomitant pulmonary disease
- Patients with paroxysmal (e.g. intermittent) atrial fibrillation. Only patients with persistent atrial fibrillation and controlled with a rate control strategy for at least six months could be eligible

- Patients who have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological
- abnormalities which could interfere with the assessment of safety
- Other protocol defined inclusion/exclusion criteria may apply

Participant Flow Table

Patient disposition (all patients)

Disposition Reason	QVA 27.5/12.5 bid n (%)	QVA 27.5/25 bid n (%)	QAB 75 od n (%)	Total n (%)
Screened	-	-	-	1233
Randomized	204	204	207	615
Completed planned treatment epoch	177 (86.8)	187 (91.7)	183 (88.4)	547 (88.9)
Discontinued planned treatment epoch	27 (13.2)	17 (8.3)	24 (11.6)	68 (11.1)
Primary reason for discontinuation of planned treatment epoch				
Subject/guardian decision	19 (9.3)	12 (5.9)	10 (4.8)	41 (6.7)
Lost to follow-up	5 (2.5)	1 (0.5)	6 (2.9)	12 (2.0)
Death	1 (0.5)	3 (1.5)	4 (1.9)	8 (1.3)
Protocol deviation	1 (0.5)	0	1 (0.5)	2 (0.3)
Technical problems	1 (0.5)	0	0	1 (0.2)

Disposition Reason	QVA 27.5/12.5 bid n (%)	QVA 27.5/25 bid n (%)	QAB 75 od n (%)	Total n (%)
Adverse event	0	1 (0.5)	2 (1.0)	3 (0.5)
Physician decision	0	0	1 (0.5)	1 (0.2)
Permanently discontinued study treatment prior to end of planned treatment epoch	32 (15.7)	26 (12.7)	33 (15.9)	91 (14.8)
Completed study treatment and planned treatment epoch	172 (84.3)	178 (87.3)	173 (83.6)	523 (85.2)
Randomized but not treated	0	0	1 (0.5)	1 (0.2)

Patients can discontinue from study treatment but continue participating in the study, therefore “completed planned treatment epoch” row includes all patients who have completed the treatment epoch whether on study treatment or not.
The primary reason for discontinuation as given by the investigator on the Treatment Epoch Disposition/ Premature Study Withdrawal eCRF.
Percentages are based on the number of randomized patients.

Baseline Characteristics

Demographics

Variable Statistic/Category	QVA 27.5/12.5 bid N=204	QVA 27.5/25 bid N=204	QAB 75 od N=207	Total N=615
Age (years)				
n	204	204	207	615
Mean (SD)	64.0 (7.90)	63.9 (8.50)	62.8 (8.52)	63.6 (8.32)
Median	63.0	64.0	63.0	63.0
Min - Max	42 - 82	41 - 89	41 - 85	41 - 89
Age group in years, n (%)				
40-64	113 (55.4)	104 (51.0)	117 (56.5)	334 (54.3)
65-74	67 (32.8)	77 (37.7)	71 (34.3)	215 (35.0)
>=75	24 (11.8)	23 (11.3)	19 (9.2)	66 (10.7)
Gender, n (%)				
Male	131 (64.2)	123 (60.3)	149 (72.0)	403 (65.5)
Female	73 (35.8)	81 (39.7)	58 (28.0)	212 (34.5)
Race, n (%)				
Caucasian	199 (97.5)	202 (99.0)	200 (96.6)	601 (97.7)

Variable Statistic/Category	QVA 27.5/12.5 bid N=204	QVA 27.5/25 bid N=204	QAB 75 od N=207	Total N=615
Black	3 (1.5)	2 (1.0)	4 (1.9)	9 (1.5)
Asian	0	0	0	0
Native American	1 (0.5)	0	1 (0.5)	2 (0.3)
Other	1 (0.5)	0	2 (1.0)	3 (0.5)
Ethnicity, n (%)				
Hispanic	6 (2.9)	5 (2.5)	13 (6.3)	24 (3.9)
Non-Hispanic	164 (80.4)	170 (83.3)	158 (76.3)	492 (80.0)
Not reported/unknown	34 (16.7)	29 (14.2)	36 (17.4)	99 (16.1)
At United States site, n (%)				
No	110 (53.9)	112 (54.9)	127 (61.4)	349 (56.7)
Yes	94 (46.1)	92 (45.1)	80 (38.6)	266 (43.3)
Height (cm)				
n	204	204	207	615
Mean (SD)	168 (9.0)	168 (9.4)	170 (9.2)	169 (9.2)
Median	169	170	170	170
Min - Max	146 - 195	146 - 191	147 - 193	146 - 195

Variable Statistic/Category	QVA 27.5/12.5 bid N=204	QVA 27.5/25 bid N=204	QAB 75 od N=207	Total N=615
Weight (kg)				
n	204	204	207	615
Mean (SD)	77.9 (17.24)	77.8 (18.12)	79.5 (17.73)	78.4 (17.69)
Median	76.9	77.7	79.5	77.4
Min - Max	37.9 - 124.1	44.1 - 133.3	35.2 - 142.4	35.2 - 142.4
Body mass index (kg/m^2)				
n	204	204	207	615
Mean (SD)	27.4 (5.12)	27.4 (5.22)	27.5 (5.20)	27.4 (5.17)
Median	27.2	27.1	27.1	27.1
Min - Max	15.4 - 39.7	16.5 - 39.6	12.5 - 39.7	12.5 - 39.7
Body mass index, n (%)				
<= 30.0 kg/m^2	143 (70.1)	141 (69.1)	145 (70.0)	429 (69.8)
> 30.0 kg/m^2	61 (29.9)	63 (30.9)	62 (30.0)	186 (30.2)

Ethnicity: Patients with mixed ethnicities are included in non-Hispanic.
Body Mass Index: BMI (kg/m**2) = weight (kg) / (height (m)**2).
Height and weight were taken at run-in visit 101.

Summary of Efficacy

Primary Outcome Result(s)

Number of patients with adverse events, serious adverse events, and death

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	QVA149 27.5/12.5 ug bid	QVA149 27.5/25 ug bid	QAB149 75 ug od
Number of Participants Analyzed:	204	204	206
Number of patients with adverse events, serious adverse events, and death	Number	Number	Number
Patients with at least one SAEs	26	25	24
Patients with at least one AE	139	142	139
Death	1	3	5

Secondary Outcome Result(s)

Time to premature discontinuation of treatment

	QVA149 27.5/12.5 ug bid		QVA149 27.5/25 ug bid		QAB149 75 ug od	
Number of Participants Analyzed:	204		204		206	
Time to premature discontinuation of treatment , Days	Median	95% Confidence Interval	Median	95% Confidence Interval	Median	95% Confidence Interval
	384.0	384.0 to NA	NA	NA	NA	NA

Change from baseline in pre-dose trough FEV1

	QVA149 27.5/12.5 ug bid	QVA149 27.5/25 ug bid	QAB149 75 ug od

Number of Participants Analyzed:	192		196		199	
change from baseline in pre - dose trough FEV1	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
	0.116	0.0169	0.116	0.0167	0.037	0.0169

Change from baseline in FEV1 measurements at all post-baseline time points

	QVA149 27.5/12.5 ug bid		**QVA149 27.5/25 ug bid**		**QAB149 75 ug od**	
Number of Participants Analyzed:	200		202		202	
Change from baseline in FEV1 measurements at all post - baseline time points in Liters	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
Day 1	0.166	0.0088	0.178	0.0088	0.122	0.0089

Day 29	0.257	0.0152	0.287	0.0151	0.173	0.0151
Day 57	0.267	0.0157	0.302	0.0155	0.173	0.0154
Day 85	0.269	0.0164	0.301	0.0162	0.170	0.0162
Day 141	0.268	0.0182	0.288	0.0179	0.170	0.0181
Day 197	0.229	0.0178	0.278	0.0175	0.157	0.0177
Day 253	0.231	0.0178	0.240	0.0175	0.140	0.0176
Day 309	0.199	0.0170	0.222	0.0169	0.125	0.0170
Day 365	0.212	0.0175	0.221	0.0173	0.104	0.0174

Change from baseline in FVC measurement at all post-baseline time points

	QVA149 27.5/12.5 ug bid		QVA149 27.5/25 ug bid		QAB149 75 ug od	
Number of Participants Analyzed:	200		202		202	
Change from baseline in FVC measurement at all post-baseline time points Liters	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error	Least Squares Mean	Standard Error
Day 1	0.316	0.0201	0.349	0.0200	0.248	0.0203
Day 29	0.375	0.0274	0.440	0.0271	0.280	0.0272
Day 57	0.390	0.0274	0.439	0.0271	0.279	0.0271
Day 85	0.388	0.0287	0.432	0.0283	0.268	0.0284
Day 141	0.382	0.0297	0.403	0.0292	0.235	0.0295

Day 197	0.313	0.0288	0.400	0.0284	0.220	0.0288
Day 253	0.310	0.0303	0.365	0.0298	0.205	0.0301
Day 309	0.272	0.0284	0.334	0.0281	0.185	0.0285
Day 365	0.312	0.0286	0.323	0.0282	0.139	0.0286

Rate of moderate or severe COPD exacerbations during study treatment (FAS)

Treatment	n	Comparator	Ratio of rates	95% CI	p-value
QVA 27.5/12.5 bid (N=204)	200	QAB 75 od	0.75	(0.51, 1.12)	0.163
		QVA 27.5/25 bid	0.87	(0.58, 1.30)	0.497
QVA 27.5/25 bid (N=204)	201	QAB 75 od	0.87	(0.59, 1.27)	0.464
QAB 75 od (N=206)	200				

A COPD exacerbation of moderate severity requires treatment with systemic corticosteroids and/or antibiotics and a severe COPD exacerbation requires hospitalization.
COPD exacerbations starting between first dose and one day after date of last treatment are included.
All analyses are based on data reported on the "COPD Exacerbation Episodes" eCRF.
n: number of patients included in the analysis.
Generalized linear model assuming a negative binomial distribution with fixed effects of treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the past 12 months prior to study), smoking status at baseline, ICS use at baseline, airflow limitation severity, and region.
As the offset variable log (exposure time) was used.
A ratio of rates <1 favors the treatment group in the numerator of the ratio.

Symptom endpoints over the 52 weeks of treatment based on data of the patient diary (FAS)

	---------- Treatment difference ----------

Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
CFB in mean daily total symptom score							
All	595	6.44					
QVA 27.5/12.5 bid	198	6.35	-1.57 (0.133)	QAB 75	-0.26 (0.177)	(-0.61, 0.09)	0.143
QVA 27.5/25 bid	199	6.50	-1.56 (0.133)	QAB 75	-0.25 (0.178)	(-0.60, 0.10)	0.166
QAB 75 od	198	6.48	-1.31 (0.135)				
CFB in mean daytime total symptom score							
All	587	5.88					
QVA 27.5/12.5 bid	194	5.71	-1.37 (0.130)	QAB 75	-0.21 (0.172)	(-0.55, 0.12)	0.215
QVA 27.5/25 bid	196	5.93	-1.35 (0.129)	QAB 75	-0.20 (0.172)	(-0.54, 0.14)	0.251
QAB 75 od	197	5.99	-1.15 (0.130)				
CFB in mean nighttime total symptom score							
All	590	5.28					
QVA 27.5/12.5 bid	196	5.26	-1.29 (0.133)	QAB 75	-0.27 (0.176)	(-0.61, 0.08)	0.130
QVA 27.5/25 bid	199	5.30	-1.28 (0.133)	QAB 75	-0.25 (0.176)	(-0.60, 0.09)	0.149
QAB 75 od	195	5.27	-1.02 (0.135)				
CFB in the percentage of nights with no nighttime awakenings							

					---------- Treatment difference ----------		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
All	590	48.2					
QVA 27.5/12.5 bid	196	50.3	18.0 (2.30)	QAB 75	5.1 (2.87)	(-0.6, 10.7)	0.078
QVA 27.5/25 bid	199	46.1	18.6 (2.29)	QAB 75	5.7 (2.88)	(0.0, 11.3)	0.049
QAB 75 od	195	48.2	12.9 (2.32)				
CFB in the percentage of days with no daytime symptoms							
All	587	4.3					
QVA 27.5/12.5 bid	194	4.7	10.2 (1.71)	QAB 75	5.5 (2.27)	(1.1, 10.0)	0.015
QVA 27.5/25 bid	196	4.8	6.5 (1.71)	QAB 75	1.8 (2.27)	(-2.7, 6.2)	0.440
QAB 75 od	197	3.6	4.7 (1.72)				
CFB in the percentage of days able to perform usual daily activities							
All	587	30.2					
QVA 27.5/12.5 bid	194	33.0	14.7 (2.25)	QAB 75	7.4 (2.86)	(1.8, 13.1)	0.010
QVA 27.5/25 bid	196	29.2	11.1 (2.24)	QAB 75	3.8 (2.86)	(-1.8, 9.4)	0.187
QAB 75 od	197	28.3	7.3 (2.26)				

All LS Means, SEs, CIs, and p-values are from a LMM: Change from baseline in mean score or percentage of nights/days = treatment + baseline value + smoking status at baseline + baseline ICS use + airflow limitation severity + region + random

					---------- Treatment difference ----------		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value

effect of center nested within country.
Baseline raw means are not from the model.
Only the scores for the 6 COPD symptoms (respiratory symptoms, cough, wheeze, production of sputum, sputum color, breathlessness) were used to derive the total symptom score.

Rescue medication intake over the 52 weeks of treatment based on data of the patient diary (FAS)

					---------- Treatment difference ----------		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
CFB in mean daily number of puffs of rescue medication							
All	595	4.03					
QVA 27.5/12.5 bid	198	4.13	-1.89 (0.164)	QAB 75	-0.16 (0.210)	(-0.58, 0.25)	0.440
QVA 27.5/25 bid	199	4.07	-1.62 (0.164)	QAB 75	0.11 (0.211)	(-0.30, 0.53)	0.592
QAB 75 od	198	3.88	-1.73 (0.166)				
CFB in mean daytime number of puffs of rescue medication							

					---------- Treatment difference ----------		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
All	587	2.33					
QVA 27.5/12.5 bid	194	2.41	-1.11 (0.093)	QAB 75	-0.08 (0.122)	(-0.32, 0.16)	0.508
QVA 27.5/25 bid	196	2.36	-0.95 (0.093)	QAB 75	0.08 (0.122)	(-0.16, 0.32)	0.517
QAB 75 od	197	2.21	-1.03 (0.093)				
CFB in mean nighttime number of puffs of rescue medication							
All	590	1.67					
QVA 27.5/12.5 bid	196	1.68	-0.77 (0.076)	QAB 75	-0.10 (0.098)	(-0.29, 0.09)	0.306
QVA 27.5/25 bid	199	1.69	-0.66 (0.075)	QAB 75	0.01 (0.098)	(-0.18, 0.20)	0.910
QAB 75 od	195	1.63	-0.67 (0.077)				
CFB in the percentage of days with no rescue medication use							
All	593	20.9					
QVA 27.5/12.5 bid	197	21.8	27.1 (2.76)	QAB 75	6.6 (3.51)	(-0.3, 13.5)	0.061
QVA 27.5/25 bid	199	20.4	18.1 (2.76)	QAB 75	-2.4 (3.51)	(-9.3, 4.5)	0.503
QAB 75 od	197	20.5	20.5 (2.79)				

					---------- Treatment difference ----------		
Treatment	n	Baseline Raw Mean	LS Mean (SE)	Comparator	LS Mean (SE)	(95% CI)	p-value
All LS Means, SEs, CIs, and p-values are from a LMM: Change from baseline in mean number of puffs or percentage of days = treatment + baseline value + smoking status at baseline + baseline ICS use + airflow limitation severity + region + random effect of center nested within region. Baseline raw means are not from the model.							

Summary of Safety

Safety Results

AEs (including COPD exacerbations) by primary SOC (Safety set)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
Patients with at least one AE	139 (68.1)	142 (69.6)	139 (67.5)
Primary system organ class			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	84 (41.2)	81 (39.7)	89 (43.2)
INFECTIONS AND INFESTATIONS	72 (35.3)	79 (38.7)	82 (39.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	29 (14.2)	24 (11.8)	14 (6.8)
GASTROINTESTINAL DISORDERS	21 (10.3)	22 (10.8)	21 (10.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (7.4)	10 (4.9)	11 (5.3)
NERVOUS SYSTEM DISORDERS	10 (4.9)	15 (7.4)	10 (4.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	10 (4.9)	7 (3.4)	6 (2.9)
METABOLISM AND NUTRITION DISORDERS	9 (4.4)	6 (2.9)	9 (4.4)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
VASCULAR DISORDERS	9 (4.4)	15 (7.4)	6 (2.9)
PSYCHIATRIC DISORDERS	8 (3.9)	3 (1.5)	5 (2.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (3.4)	17 (8.3)	12 (5.8)
CARDIAC DISORDERS	6 (2.9)	13 (6.4)	10 (4.9)
INVESTIGATIONS	6 (2.9)	2 (1.0)	7 (3.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6 (2.9)	5 (2.5)	4 (1.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (2.0)	2 (1.0)	3 (1.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	4 (2.0)	2 (1.0)	3 (1.5)
RENAL AND URINARY DISORDERS	3 (1.5)	7 (3.4)	3 (1.5)
EAR AND LABYRINTH DISORDERS	2 (1.0)	4 (2.0)	3 (1.5)
EYE DISORDERS	2 (1.0)	1 (0.5)	0
HEPATOBILIARY DISORDERS	2 (1.0)	2 (1.0)	3 (1.5)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.5)	0	0
IMMUNE SYSTEM DISORDERS	1 (0.5)	1 (0.5)	1 (0.5)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
ENDOCRINE DISORDERS	0	0	1 (0.5)
SOCIAL CIRCUMSTANCES	0	0	2 (1.0)
Primary SOCs are sorted in descending order of frequency in the QVA149 27.5/12.5 bid group. All AEs starting on or after the time of first administration of study drug but not later than 7 days (30 days in case of an SAE) after the last administration are included.			

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

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
Patients with at least one AE	139 (68.1)	142 (69.6)	139 (67.5)
Preferred term			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	74 (36.3)	67 (32.8)	76 (36.9)
NASOPHARYNGITIS	19 (9.3)	18 (8.8)	22 (10.7)
UPPER RESPIRATORY TRACT INFECTION BACTERIAL	12 (5.9)	14 (6.9)	13 (6.3)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
BACK PAIN	10 (4.9)	7 (3.4)	5 (2.4)
UPPER RESPIRATORY TRACT INFECTION	10 (4.9)	10 (4.9)	9 (4.4)
LOWER RESPIRATORY TRACT INFECTION	9 (4.4)	5 (2.5)	6 (2.9)
PNEUMONIA	7 (3.4)	4 (2.0)	2 (1.0)
VIRAL UPPER RESPIRATORY TRACT INFECTION	7 (3.4)	6 (2.9)	7 (3.4)
DIARRHOEA	5 (2.5)	2 (1.0)	3 (1.5)
HEADACHE	5 (2.5)	7 (3.4)	4 (1.9)
HYPERTENSION	5 (2.5)	10 (4.9)	4 (1.9)
SINUSITIS	5 (2.5)	8 (3.9)	6 (2.9)
GASTROOESOPHAGEAL REFLUX DISEASE	4 (2.0)	0	0
HYPERGLYCAEMIA	4 (2.0)	0	1 (0.5)
OROPHARYNGEAL PAIN	4 (2.0)	5 (2.5)	3 (1.5)
RHINITIS	4 (2.0)	3 (1.5)	2 (1.0)
BRONCHITIS	3 (1.5)	7 (3.4)	8 (3.9)
CONTUSION	3 (1.5)	2 (1.0)	1 (0.5)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
COUGH	3 (1.5)	13 (6.4)	7 (3.4)
INSOMNIA	3 (1.5)	2 (1.0)	1 (0.5)
PAIN IN EXTREMITY	3 (1.5)	1 (0.5)	2 (1.0)
PHARYNGITIS	3 (1.5)	0	3 (1.5)
PRURITUS	3 (1.5)	0	0
PYREXIA	3 (1.5)	4 (2.0)	0
RESPIRATORY TRACT INFECTION VIRAL	3 (1.5)	2 (1.0)	6 (2.9)
SKIN LESION	3 (1.5)	0	0
VOMITING	3 (1.5)	2 (1.0)	0
ARTHRALGIA	2 (1.0)	5 (2.5)	3 (1.5)
NAUSEA	2 (1.0)	4 (2.0)	1 (0.5)
ABDOMINAL PAIN	1 (0.5)	3 (1.5)	1 (0.5)
CONSTIPATION	1 (0.5)	3 (1.5)	1 (0.5)
DYSPNOEA	1 (0.5)	3 (1.5)	6 (2.9)
HYPOTENSION	1 (0.5)	3 (1.5)	0

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
INFLUENZA	1 (0.5)	2 (1.0)	4 (1.9)
MUSCLE SPASMS	1 (0.5)	4 (2.0)	1 (0.5)
OEDEMA PERIPHERAL	1 (0.5)	6 (2.9)	5 (2.4)
PRODUCTIVE COUGH	1 (0.5)	3 (1.5)	2 (1.0)
URINARY TRACT INFECTION	1 (0.5)	4 (2.0)	3 (1.5)
MUSCULOSKELETAL PAIN	0	3 (1.5)	1 (0.5)
NASAL CONGESTION	0	1 (0.5)	4 (1.9)
NON-CARDIAC CHEST PAIN	0	4 (2.0)	5 (2.4)
TOOTHACHE	0	5 (2.5)	4 (1.9)

Preferred terms are sorted in descending order of frequency in the QVA149 27.5/12.5 bid group.
All AEs starting on or after the time of first administration of study drug but not later than 7 days (30 days in case of an SAE) after the last administration are included.

Deaths, other SAEs, including COPD exacerbations, and AEs leading to permanent discontinuation of study drug (Safety set)

	QVA 27.5/12.5 bid N=204 n (%)	QVA 27.5/25 bid N=204 n (%)	QAB 75 od N=206 n (%)
	n (%)	**n (%)**	**n (%)**
Patients with at least one AE	139 (68.1)	142 (69.6)	139 (67.5)
Serious AEs or AE discontinuations			
Death	1 (0.5)	3 (1.5)	5 (2.4)
SAE(s)	26 (12.7)	25 (12.3)	24 (11.7)
Discontinuation due to AE(s)	5 (2.5)	8 (3.9)	12 (5.8)
Discontinuation due to SAE(s)	4 (2.0)	5 (2.5)	7 (3.4)
Discontinuation due to non-SAE(s)	1 (0.5)	4 (2.0)	7 (3.4)
AEs requiring dose adjustment	0	0	0
AEs requiring dose interruption	8 (3.9)	5 (2.5)	8 (3.9)
AEs requiring additional therapy	108 (52.9)	114 (55.9)	111 (53.9)

A patient could have discontinued study treatment due to both an SAE and non-SAE.
All AEs starting on or after the time of first administration of study drug but not later than 7 days (30 days in case of an SAE) after the last administration are included.
Deaths in this table are those that were reported between a patient's first treatment and within 30 days of the last dose of study drug.

Other Relevant Findings

None

Conclusion:

In conclusion, QVA149 27.5/12.5 µg b.i.d. demonstrated a good safety and tolerability profile, and provided effective bronchodilation with maintenance of lung function over 52 weeks in patients with moderate-to-severe COPD. These data support the safety and efficacy of QVA149 as a treatment option for patients with COPD.

Date of Clinical Trial Report

16 October 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

22 June 2015

Date of Latest Update

Reason for Update