Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Indacaterol maleate-glycopyrronium bromide

Trial Indication(s)

Chronic obstructive pulmonary disease

Protocol Number

CQVA149A2339

Protocol Title

A placebo and active controlled study to assess the long-term safety of once daily QVA149 for 52 weeks in Chronic Obstructive Pulmonary Disease (COPD) patients with moderate to severe airflow limitation

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: October 2012 (Actual)
Primary Completion Date: February 2015 (Actual)
Study Completion Date: February 2015 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

A 52 week multi-center, randomized, double-blind, parallel-group, placebo and active- controlled study to assess the safety of QVA149 vs. placebo and tiotropium in COPD patients with moderate to severe airflow limitation. The study consisted of 4 periods: a screening period, run-in period, 52 week double blind treatment period and a follow-up period of 30 days.

Patients were randomized to QVA149 (110/50 µg o.d.), tiotropium (18 µg o.d.) or placebo (50% Concept1, 50% Handi Haler) in a ratio of 1:1:1 for the 52 week treatment period. Randomization was stratified by current smoking status, inhaled corticosteroid use, and airflow limitation

Centers

124 centers in 17 countries: Slovenia(1), Serbia(2), Poland(5), Panama(4), Israel(4), India(16), Hungary(11), Croatia(4), United Kingdom(11), Estonia(3), Colombia(4), Argentina(27), Korea, Republic of(9), Russia(11), Mexico(4), Latvia(3), Turkey(5)

Objectives:

Primary objective:

- To demonstrate the non-inferiority of QVA149 110/50 µg o.d. compared to placebo in terms of overall (serious adverse event) SAE rate from initiation of study treatment through 30 days post last treatment.

Secondary objectives:

- To evaluate QVA149 110/50 µg o.d. compared to placebo in terms of a composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular (CCV) events.
- To evaluate the relative effect of treatment with QVA149 110/50 µg o.d. compared to placebo and tiotropium on safety and tolerability (particularly in regard to electrocardiogram (ECG), laboratory tests, vital signs, adverse events (AEs) during 52 weeks of treatment.
- To compare the bronchodilator effect of QVA149 110/50 µg o.d. with tiotropium and placebo based on the mean pre-dose forced expiratory volume in 1 second (FEV1) at Week 52.
- To assess changes in health status as measured by the St. George's Respiratory

Questionnaire for COPD (SGRQ-C) after 52 weeks of treatment with QVA149 110/50 µg o.d. compared with tiotropium and placebo.

- To compare the effect of QVA149 110/50 µg o.d. with tiotropium and placebo on patient reported symptoms during the treatment period.
- To compare the bronchodilator effect of QVA149 110/50 µg o.d. with tiotropium and placebo based on forced vital capacity (FVC) and FEV1 measurements at all post-baseline time points.
- To compare the effect of QVA149 110/50 µg o.d. with placebo on time to premature discontinuation

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

QVA149 (110 µg/50 µg) capsules for oral inhalation, once-daily, delivered via Novartis Concept1 SDDPI.

Statistical Methods

The objective of this study was to evaluate the safety QVA149 (110 µg/50 µg) in COPD patients with moderate to severe airflow limitation following 52 weeks of treatment. The assessment of safety included all safety measurements including AEs and COPD exacerbations; however, particular attention was paid to overall SAE, all-cause mortality, serious CCV events, AEs of special interests (CCV events reported as overall and for each of the following subcategories (ischemic heart disease, myocardial infarction (MI), cardiac failure, cardiac arrhythmias (including brady and tachyarrhythmias), cerebrovascular events, tachyarrhythmia, QT prolongation, pneumonia, pneumonia and lower respiratory tract infections, lower respiratory tract infection, respiratory composite endpoint, paradoxical bronchospasm, bladder obstruction/urinary retention, constipation, diabetes mellitus/hyperglycemia, dry mouth, glaucoma/increased intraocular pressure), adjudicated serious CCV events (MACE and events not considered MACE), and adjudicated atrial fibrillation/flutter events.

The primary objective of this study was to demonstrate non-inferiority of QVA149 (110 µg/50 µg) to placebo with respect to overall SAE rate after 52 weeks of treatment in patients with moderate to severe COPD.
The non-inferiority was evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha):

- H0: QVA149 was inferior to placebo with respect to overall SAE rate after 52 weeks of treatment in patients with moderate to severe COPD (or odds ratio of QVA149 vs. placebo is greater than or equal to 1.8).
- Ha: QVA149 was no-inferior to placebo with respect to overall SAE rate after 52 weeks of treatment in patients with moderate to severe COPD (or odds ratio of QVA149 vs placebo is less than 1.8).

The non-inferiority of QVA149 vs placebo can be claimed if the upper bound of the 2-sided 95% confidence interval (CI) is less than 1.8. The primary analysis was performed on the full analysis set (FAS) with a logistic regression model. The model included treatment, baseline measurement of pre dose FEV1, smoking status at baseline (current/ex-smoker), history of ICS use, region and airflow limitation as fixed effects, and center (region) as a random effect.
Analysis on the composite end-point of all-cause mortality and serious CCV events was performed on the full analysis set (FAS). The patients with an event in the analysis were those who had at least one of the 2 events namely, all-cause mortality and serious CCV, during treatment or within 30 days after the date of last dose of study drug. This variable was analyzed with a Mantel-Haenszel test statistics for odds ratio. Stratification variables included baseline CCV risk factor (0 / > =1), smoking status at baseline (current/ex-), history of inhaled corticosteroids (ICS) use and airflow limitation. The estimated

adjusted odds ratio between QVA and placebo was displayed along with the associated 95% confidence interval. This analysis was also repeated for the comparisons of QVA149 vs tiotropium and tiotropium vs placebo. The post-hoc analysis was done similarly for composite end-point of cardiovascular deaths and MACE.

The average pre-dose (-45 and -15 min assessments) FEV1 at visits 4, 5, 6, 7, 8 and 9 were analyzed using a mixed model repeated measures (MMRM) model. The model contained treatment, baseline FEV1 (defined as the average value of -45 and -15 min (pre-dose) FEV1 measurements taken at Visit 3), visit, treatment by visit interaction, visit by baseline FEV1 interaction, FEV1 prior to inhalation and FEV1 60 min post inhalation of 2 short acting bronchodilators (components of reversibility at Visit 2), region, smoking status at baseline, history of ICS use, and airflow limitation as fixed effects with center nested within region as a random effect. For all of treatment contrasts 95% confidence intervals were provided together with the associated p-value for a difference. This analysis was repeated for average pre-dose FVC, and FEV1 and FVC taken at the 60 minute post-dose time point.

The change from baseline in total and component (namely, symptoms, activity and impacts) SGRQ-C score were analyzed using the same MMRM model as specified for the statistical analysis of FEV1 with the baseline SGRQ-C score as a covariate. The estimated treatment difference (QVA149–Placebo and QVA149-Tiotropium) together with the associated 95% confidence interval and 2-sided p value was displayed. A decrease from baseline of at least 4 units in the SGRQ total score was defined a clinically important improvement. The proportion of patients with change in total SGRQ-C ≤ -4 and ≤ -8 units was summarized by visit and treatment with numbers and percentages.

The CAT score was summarized and analyzed similarly to SGRQ total score, with baseline SGRQ total score being replaced by baseline CAT score in the MMRM model. A clinically improvement was defined as at least 2 units decrease.

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

- all COPD exacerbations (including mild, moderate and severe)
- only moderate or severe COPD exacerbations
- only moderate COPD exacerbations
- only severe COPD exacerbations.
- COPD exacerbation requiring the use of systemic glucocorticosteroids
- COPD exacerbation requiring the use of antibiotics
- COPD exacerbation requiring hospitalization

The time to first COPD exacerbation was analyzed using Cox regression model for the FAS. The model included treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during 12 months prior to study), smoking status at baseline, history of ICS use, region and COPD disease severity 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.

Symptom variables were summarized by treatment and analyzed using a linear mixed model (LMM) having same covariates used for the analysis of SGRQ total score, with the baseline SGRQ total score term being replaced by the respective baseline symptom variables as below:

- The mean change from baseline in the daily, morning and evening symptom scores
- The percentage of nights with ‘no nighttime awakenings’
- The percentage of days with ‘no daytime symptoms’
- The percentage of ‘days able to perform usual daily activities’
- The change from baseline in the mean number of puffs (daily, daytime, nighttime) over Weeks 1 – 52

were summarized by treatment using descriptive statistics. The change from baseline in mean daily, daytime, and nighttime number of puffs of rescue medication over treatment periods were analyzed using a linear mixed model.

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 haematological abnormalities which could interfere with the assessment of safety.

Participant Flow Table

All Patients

	QVA149	Tiotropium	Placebo
Started	407	405	404
Randomized set (RAN)	407	405	404
Full analysis set (FAS)	407	405	403
Completed	348	354	320
Not Completed	59	51	84
Adverse Event	27	22	26
Withdrawal by Subject	12	10	20
Unsatisfactory therapeutic effect	9	8	27
Death	4	2	1
Protocol deviation	4	3	3

Abnormal laboratory value	1	1	0
Administrative problems	1	4	4
Lost to Follow-up	1	0	0
Abnormal test procedure result(s)	0	1	3

Follow up period

	QVA149	Tiotropium	Placebo
Started	407	405	404
Completed	382	377	378
Not Completed	25	28	26
Subject withdrew consent	13	14	16
Death	10	5	4
Administrative problems	1	3	2
Lost to Follow-up	1	6	4

Baseline Characteristics

	QVA149	Tiotropium	Placebo	Total
Number of Participants [units: participants]	407	405	404	1216
Age Continuous (units: Years) Mean ± Standard Deviation	64.6±7.89	64.1±8.57	64.9±7.95	64.5±8.14
Gender, Male/Female (units: Participants)				
Female	119	105	94	318
Male	288	300	310	898

Summary of Efficacy

Primary Outcome Result(s)

Number of patients with serious adverse events

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Number of patients with serious adverse events (units: Participants)	55	55	50

Secondary Outcome Result(s)

Percentage of patients with composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular (CCV) events.

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Percentage of patients with composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular (CCV) events. (units: Percentage of participants)	3.9	2	1

Post Hoc Analysis: Percentage of patients with composite endpoint of cardiovascular death and MACE

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Percentage of patients with composite endpoint of cardiovascular death and MACE (units: Percentage of	1	0.7	0.7

participants)

Change from baseline in Pre-Dose forced expiratory volume over in second (FEV1)

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	379
Change from baseline in Pre-Dose forced expiratory volume over in second (FEV1) (units: Liters) Least Squares Mean ± Standard Error			
Day 22 (n=378, 383, 361)	0.1733 ± 0.18537	0.1018 ± 0.18389	-0.0148 ± 0.16758
Day 43 (n=380, 375, 345)	0.1751 ± 0.20800	0.0961 ± 0.18261	-0.0196 ± 0.18178
Day 85 (n=373, 373, 340)	0.1752 ± 0.20198	0.0785 ± 0.19606	-0.0506 ± 0.19369
Day 183 (n=356, 358, 314)	0.1557 ± 0.21754	0.0714 ± 0.20358	-0.0583 ± 0.20305
Day 274 (n=343, 351, 303)	0.1463 ± 0.21424	0.0750 ± 0.21489	-0.0601 ± 0.20936
Day 364 (n=333, 346, 297)	0.1468 ± 0.22933	0.0559 ± 0.22433	-0.0826 ± 0.21443

Change from baseline in health status as measured by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	383	378	353

Change from baseline in health status as measured by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) (units: Score) Least Squares Mean ± Standard Error	-6.2 ± 0.74	-5.5 ± 0.74	-1.5 ± 0.77

Change from baseline in Daily, morning and evening symptom scores

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Change from baseline in Daily, morning and evening symptom scores (units: Score) Least Squares Mean ± Standard Error			
Daily total symptom score (n=395, 395, 385)	-1.31 ± 0.094	-1.16 ± 0.093	-0.77 ± 0.095
Daytime total symptom score (n= 380, 385, 374)	-1.14 ± 0.095	-1.00 ± 0.094	-0.59 ± 0.095
Nighttime total symptom score (n= 387, 388, 375)	-0.95 ± 0.092	-0.92 ± 0.091	-0.61 ± 0.093

Change from baseline in percentage of nights with ‘no nighttime awakenings, no daytime symptoms, and days able to perform usual daily activities.

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Change from baseline in percentage of nights with ‘no nighttime			

awakenings, no daytime symptoms, and days able to perform usual daily activities.
(units: Percentage)
Least Squares Mean ± Standard Error

No night time awakenings (n=387, 388, 375)	11.9 ± 1.43	11.8 ± 1.42	9.1 ± 1.45
No daytime symptoms (n= 380, 385, 374)	5.4 ± 0.98	4.4 ± 0.97	1.8 ± 0.99
Days able to perform activities(n=380, 385, 374)	9.9 ± 1.58	5.6 ± 1.56	1.1 ± 1.59

Change from baseline in 1 hour post-dose FVC measurements

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Change from baseline in 1 hour post-dose FVC measurements (units: Liters) Mean ± Standard Deviation			
Day 1(n=403, 402, 399)	0.3331 ± 0.30312	0.2806 ± 0.28293	0.0630 ± 0.22884
Day 22 (n=384, 381, 362)	0.3971 ± 0.40009	0.3123 ± 0.36755	0.0178 ± 0.33624
Day 43 (n=380, 373, 351)	0.4021 ± 0.42797	0.2966 ± 0.37124	0.0274 ± 0.35681
Day 85 (376, 371, 345)	0.4169 ± 0.42175	0.2867 ± 0.40131	0.0035 ± 0.36897
Day 183 (n=364, 359, 317)	0.3880 ± 0.45342	0.2822 ± 0.39781	-0.0283 ± 0.36919
Day 274 (n=349, 352,	0.3582 ± 0.43072	0.2821 ± 0.40546	-0.0404 ± 0.37777
Day 364 (n= 336, 347,	0.3153 ±	0.2224 ±	-0.0498 ±

	0.46560	0.40778	0.39908

Change from baseline in 1 hour post-dose FEV1 measurements

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403
Change from baseline in 1 hour post-dose FEV1 measurements (units: Liters) Mean ± Standard Deviation			
Day 1 (n=403, 402, 399)	0.2064 ± 0.14248	0.1567 ± 0.13349	0.0281 ± 0.11123
Day 22 (n=384, 381, 362)	0.2883 ± 0.21074	0.2077 ± 0.20027	1.5827 ± 15.69990
Day 43 (n=380, 373, 351)	0.2904 ± 0.23377	0.2008 ± 0.20752	1.6209 ± 16.89209
Day 85 (n=376, 371, 345)	0.3026 ± 0.23260	0.1913 ± 0.23274	-0.0217 ± 0.20195
Day 183 (n=364, 359, 317)	0.2860 ± 0.24351	0.1842 ± 0.22851	-0.0253 ± 0.21129
Day 274 (n=349, 352, 306)	0.2749 ± 0.24314	0.1681 ± 0.23626	-0.0360 ± 0.21854
Day 364 (n= 336, 347, 302)	0.2619 ± 0.25967	0.1621 ± 0.23922	-0.0533 ± 0.21560

Time to premature discontinuation

	QVA149	Tiotropium 18 µg o.d	Placebo
Number of Participants Analyzed [units: participants]	407	405	403

Time to premature discontinuation (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (378 to NA)[1]	NA (NA to NA)[1]

[1] NA - not estimable

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Source Vocabulary for Table Default	MedDRA 15.1
Assessment Type for Table Default	Systematic Assessment

	QVA 149 N = 407	Tiotropium N = 405	Placebo N = 403
Total participants affected	55 (13.51%)	55 (13.58%)	50 (12.41%)
Blood and lymphatic system disorders			
Anaemia[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Cardiac disorders			
Acute myocardial infarction[1]	1 (0.25%)	1 (0.25%)	0 (0.00%)
Angina unstable[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Atrial fibrillation[1]	3 (0.74%)	0 (0.00%)	0 (0.00%)
Cardiac arrest[1]	2 (0.49%)	0 (0.00%)	1 (0.25%)
Cardiac failure[1]	1 (0.25%)	1 (0.25%)	1 (0.25%)
Cardiac failure acute[1]	2 (0.49%)	0 (0.00%)	0 (0.00%)
Cardiopulmonary failure[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Cardio-respiratory arrest[1]	1 (0.25%)	3 (0.74%)	0 (0.00%)
Cor pulmonale[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)

Mitral valve incompetence[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Myocardial infarction[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Ventricular extrasystoles[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders			
Sudden hearing loss[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Eye disorders			
Cataract[1]	0 (0.00%)	2 (0.49%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal mass[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Abdominal pain[1]	1 (0.25%)	1 (0.25%)	0 (0.00%)
Gastrointestinal inflammation[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Inguinal hernia[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Intestinal obstruction[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Mesenteric artery thrombosis[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Pancreatitis haemorrhagic[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Small intestinal obstruction[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Umbilical hernia[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
General disorders and administration site conditions			
Chest pain[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)

Hypothermia[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders			
Bile duct stone[1]	1 (0.25%)	1 (0.25%)	1 (0.25%)
Cholangitis[1]	0 (0.00%)	0 (0.00%)	2 (0.50%)
Cholecystitis acute[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hepatic mass[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Liver injury[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Infections and infestations			
Acute sinusitis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Arthritis bacterial[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Breast abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Bronchitis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Bronchitis bacterial[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Bronchopneumonia[1]	0 (0.00%)	1 (0.25%)	1 (0.25%)
Cellulitis[1]	1 (0.25%)	1 (0.25%)	0 (0.00%)
Diverticulitis[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Gastroenteritis salmonella[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Influenza[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Lobar pneumonia[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection[1]	0 (0.00%)	2 (0.49%)	2 (0.50%)
Pneumonia[1]	3 (0.74%)	6 (1.48%)	2 (0.50%)
Pneumonia bacterial[1]	2 (0.49%)	0 (0.00%)	1 (0.25%)
Respiratory tract infection[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)

Skin infection[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Upper respiratory tract infection[1]	1 (0.25%)	0 (0.00%)	2 (0.50%)
Upper respiratory tract infection bacterial[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Urinary tract infection[1]	2 (0.49%)	1 (0.25%)	1 (0.25%)
Viral upper respiratory tract infection[1]	0 (0.00%)	2 (0.49%)	0 (0.00%)
Injury, poisoning and procedural complications			
Acetabulum fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Alcohol poisoning[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Concussion[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Femoral neck fracture[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Fibula fracture[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Laceration[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Ligament sprain[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Lower limb fracture[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Pneumothorax traumatic[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Rib fracture[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Road traffic accident[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Thoracic vertebral fracture[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Tibia fracture[1]	0 (0.00%)	2 (0.49%)	0 (0.00%)
Toxicity to various agents[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Traumatic haemothorax[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)

Upper limb fracture[1]	2 (0.49%)	0 (0.00%)	0 (0.00%)
Investigations			
Arteriogram coronary[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hepatic enzyme increased[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Transaminases increased[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Metabolism and nutrition disorders			
Hypokalaemia[1]	2 (0.49%)	0 (0.00%)	0 (0.00%)
Malnutrition[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Type 2 diabetes mellitus[1]	1 (0.25%)	0 (0.00%)	1 (0.25%)
Musculoskeletal and connective tissue disorders			
Synovitis[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Adenocarcinoma gastric[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Adenolipoma[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Colon cancer[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Diffuse large B-cell lymphoma[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Gastric cancer[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hepatic cancer[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)

Hepatocellular carcinoma[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Hypopharyngeal cancer[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Lung adenocarcinoma[1]	0 (0.00%)	1 (0.25%)	1 (0.25%)
Lung neoplasm malignant[1]	1 (0.25%)	1 (0.25%)	1 (0.25%)
Malignant mediastinal neoplasm[1]	0 (0.00%)	2 (0.49%)	0 (0.00%)
Mantle cell lymphoma[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Metastases to bone[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Metastases to lymph nodes[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Metastatic neoplasm[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Prostate cancer[1]	2 (0.49%)	2 (0.49%)	1 (0.25%)
Renal cell carcinoma[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Squamous cell carcinoma of lung[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Carotid artery stenosis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Cerebral haemorrhage[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident[1]	1 (0.25%)	0 (0.00%)	1 (0.25%)
Optic neuritis[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Radiculitis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Syncope[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Transient ischaemic attack[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Vertebrobasilar insufficiency[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)

VIth nerve paresis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Psychiatric disorders			
Aggression[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Alcoholism[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Depression[1]	0 (0.00%)	1 (0.25%)	1 (0.25%)
Suicide attempt[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Renal and urinary disorders			
Calculus ureteric[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Renal failure acute[1]	1 (0.25%)	0 (0.00%)	1 (0.25%)
Urinary retention[1]	1 (0.25%)	1 (0.25%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Bronchial disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Chronic obstructive pulmonary disease[1]	20 (4.91%)	18 (4.44%)	23 (5.71%)
Cough[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Dyspnoea[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Dyspnoea exertional[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Haemoptysis[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hypoxia[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Nasal polyps[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Pneumothorax[1]	0 (0.00%)	3 (0.74%)	0 (0.00%)
Pneumothorax spontaneous[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)

Pulmonary fibrosis[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Respiratory distress[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Respiratory failure[1]	3 (0.74%)	1 (0.25%)	1 (0.25%)
Skin and subcutaneous tissue disorders			
Decubitus ulcer[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Surgical and medical procedures			
Hip arthroplasty[1]	0 (0.00%)	1 (0.25%)	0 (0.00%)
Vascular disorders			
Aortic aneurysm[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Hypertension[1]	3 (0.74%)	0 (0.00%)	1 (0.25%)
Hypertensive crisis[1]	1 (0.25%)	0 (0.00%)	1 (0.25%)
Iliac artery occlusion[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Ischaemia[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)
Jugular vein distension[1]	1 (0.25%)	0 (0.00%)	0 (0.00%)
Peripheral artery thrombosis[1]	0 (0.00%)	0 (0.00%)	1 (0.25%)

1 MedDRA

Other Adverse Events by System Organ Class

Source Vocabulary for Table Default	MedDRA 15.1
Assessment Type for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 2%

	QVA 149 N = 407	Tiotropium N = 405	Placebo N = 403
Total participants affected	294 (72.24%)	294 (72.59%)	309 (76.67%)
Infections and infestations			
Influenza[1]	7 (1.72%)	11 (2.72%)	18 (4.47%)
Lower respiratory tract infection[1]	22 (5.41%)	14 (3.46%)	19 (4.71%)
Nasopharyngitis[1]	33 (8.11%)	31 (7.65%)	26 (6.45%)
Respiratory tract infection viral[1]	4 (0.98%)	11 (2.72%)	7 (1.74%)
Upper respiratory tract infection[1]	18 (4.42%)	22 (5.43%)	18 (4.47%)
Upper respiratory tract infection bacterial[1]	27 (6.63%)	28 (6.91%)	25 (6.20%)
Viral upper respiratory tract infection[1]	19 (4.67%)	13 (3.21%)	17 (4.22%)
Musculoskeletal and connective tissue disorders			
Back pain[1]	10 (2.46%)	6 (1.48%)	6 (1.49%)
Nervous system disorders			
Headache[1]	9 (2.21%)	13 (3.21%)	11 (2.73%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive	269 (66.09%)	274 (67.65%)	287 (71.22%)

pulmonary disease[1]			
Cough[1]	17 (4.18%)	21 (5.19%)	18 (4.47%)
Dyspnoea[1]	8 (1.97%)	7 (1.73%)	12 (2.98%)
Vascular disorders			
Hypertension[1]	9 (2.21%)	10 (2.47%)	13 (3.23%)

1 MedDRA

Other Relevant Findings

None

Conclusion:

Overall, this study in COPD patients with moderate to severe airflow limitation demonstrated that treatment with QVA149 110/50 µg administered once daily for 52 weeks was safe and effective. The study met its primary endpoint, demonstrating that the SAE incidence rate of QVA149 was non-inferior to placebo. QVA149 showed maintenance bronchodilation which was sustained over the 52 week period.
The safety profile of QVA149 was similar to placebo in terms of overall AE and SAE frequency, laboratory parameters, QTc prolongation and vital signs, though there was a small imbalance in the number of deaths and serious CCV events overall. Based on the individual presentation of death and non-MACE cases that drove the imbalance for the secondary endpoint of all fatal events and serious CCV events in the QVA149 treatment group, and after rigorous adjudication for MACE and events not considered MACE, it is reassuring that the individual cases did not raise a concern with regard to drug causality, and that adjudicated CV-related deaths and MACE were balanced across all treatment groups. The incidence of non-fatal MI and stroke was low overall in QVA149-treated patients and similar compared with placebo. No deaths were suspected to be related to study medication and most patients had pre-existing co-morbid conditions in addition to COPD. With regards to the increased rate for serious CCV events and mortality, the individual cases reflect the

unfortunate morbidity and mortality which is a feature of the underlying indication and were not unexpected in an aging, comorbid COPD population. In conclusion, the positive benefit/risk profile of QVA149 remains unchanged.

Date of Clinical Trial Report

02-Sept-2015