Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Indacaterol maleate -Glycopyrronium bromide

Trial Indication(s)

Chronic obstructive pulmonary disease

Protocol Number

CQVA149A2318

Protocol Title

A 52-week treatment, multi-center, randomized, double-blind, double dummy, parallel-group, active controlled study to compare the effect of QVA149 (indacaterol maleate / glycopyrronium bromide) with salmeterol/fluticasone on the rate of exacerbations in subjects with moderate to very severe COPD. (FLAME).

Clinical Trial Phase

Phase 3

Phase of Drug Development

IIIb

Study Start/End Dates

Study Start Date: July 2013 (Actual)
Study Completion Date: September 2015 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a 52-week treatment, multi-center, randomized, double-blind, double-dummy, parallel-group, non-inferiority, active controlled study to evaluate the effect of QVA149 (110/50 µg o.d.) compared to salmeterol/fluticasone (50/500 µg b.i.d.) on exacerbations (mild/moderate/severe) in patients with moderate to very severe chronic obstructive pulmonary disease (COPD).
The study consisted of a screening epoch, a run-in epoch, a 52 week blinded treatment epoch and a 30-day follow-up epoch.

Centers

528 centers in 43 countries: South Africa(11), Turkey(8), Netherlands(9), Austria(10), Germany(71), Italy(20), Romania(20), Iceland(1), Denmark(9), Norway(8), Lithuania(10), Slovakia (Slovak Republic)(17), Poland(7), Canada(13), Colombia(4), Belgium(20), Finland(6), Sweden(6), Estonia(3), Bulgaria(11), Thailand(4), India(19), Spain(26), Hungary(8), Latvia(3), Guatemala(5), United Kingdom(20), Croatia(3), Czech Republic(18), Greece(11), Portugal(11), Korea, Republic of(10), France(13), Philippines(3), Japan(30), Russia(10), Taiwan(8), Hong Kong(2), Argentina(25), Chile(3), China(21), Mexico(7), Serbia(4)

Objectives:

Primary objective: To demonstrate that QVA149 (110/50 µg o.d.) was at least non-inferior to salmeterol/fluticasone (50/500 µg b.i.d.) in terms of rate of Chronic Obstructive Pulmonary Disease (COPD) exacerbations (mild/moderate/severe) during 52 weeks of treatment.

Secondary Objectives:

- To demonstrate that QVA149 (110/50 µg o.d.) was superior to salmeterol/fluticasone (50/500 µg b.i.d.) in terms of rate of all COPD exacerbations (mild/moderate/severe) during 52 weeks of treatment.

- To evaluate the effect of QVA149 compared to salmeterol/fluticasone during 52 weeks of treatment in terms of:
- Time to first COPD exacerbation (mild/moderate/severe).
- Rate and time to first moderate/severe COPD exacerbations.
- Rate and time to first moderate to severe COPD exacerbation requiring systemic glucocorticosteroids, antibiotics, hospitalizations and re-hospitalization within 30 days during the treatment period
- To evaluate the effect of QVA149 compared to salmeterol/fluticasone in terms of:
    - FEV1 and FVC on Day 1 and after 4, 12, 26, 38, and 52 weeks of treatment.
    - Lung function in terms of standardized FEV1 AUC (0 – 12h), in a subset of patients.
    - Total score of the St. George's Respiratory Questionnaire (SGRQ-C) after 4, 12, 26, 38, and 52 weeks of treatment
- Mean use of rescue therapy over the 52 weeks treatment period.
- To assess the safety (particularly with regard to ECG, laboratory tests, vital signs and adverse events) and tolerability of QVA149 (110/50 µg o.d.) vs salmeterol/fluticasone (50/500 µg bid) over the 52 weeks of treatment.
- To assess the safety of QVA149 ((110/50 µg o.d.) vs salmeterol/fluticasone (50/500 µg bid) in terms of hypothalamic pituitary adrenal (HPA) axis function, as determined by 24-hour weighted mean urine cortisol, in a sub-set of patients.

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

QVA149 110/50 µg capsules for inhalation were supplied in blisters delivered via Novartis single dose dry powder inhaler (SDDPI) and salmeterol/fluticasone dry inhalation powder was delivered via Accuhaler® device.

Statistical Methods

Primary analysis of the primary endpoint was performed on the per-protocol set; analysis of the full analysis set was supportive. Analyses of all other efficacy endpoints were performed on the full analysis set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Written informed consent must be obtained before any assessment is performed
- Male or female adults aged ≥40 years

- Patients with stable Chronic Obstructive Pulmonary Disease (COPD) according to the current GOLD strategy (GOLD 2011)
- Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years)
-Patients with a post-bronchodilator Forced Expiratory Volume in one second (FEV1) ≥25 and < 60% of the predicted normal value, and post-bronchodilator FEV1/FVC (Forced Vital Capacity) < 0.70 at day -28. (Post refers to 1 hour after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol)
-A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics
-Patients taking stable COPD medication (at least 60 days) prior to day 28
-Patients with an mMRC grade of at least 2 at day 28

Exclusion Criteria:
-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 (human Chorionic Gonadotropin) laboratory test
- 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. 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
- Patients with Type I or uncontrolled Type II diabetes
- Patients with a history of long QT syndrome or whose QTc measured at day 28 (Fridericia method) is prolonged (>450 ms for males and females) and confirmed by a central assessor. These patients should not be re-screened
-Patients who have a clinically significant ECG abnormality prior to randomization. (These patients should not be re-screened)
-Patients who have a clinically significant laboratory abnormality at screening
-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 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., selective 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 both pre-randomization visits, with a resting ventricular rate < 100/min. At screening the atrial fibrillation must be confirmed by central reading
-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: anticholinergic agents, long and short acting beta-2 agonists, sympathomimetic amines, lactose or any of the other excipients of trial medication
-Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
-Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered
-Patients who have not achieved an acceptable spirometry results at screening in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria)
-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 screening
-Patients who develop a COPD exacerbation of any severity (mild/moderate/severe) between screening and treatment 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 who have had a respiratory tract infection within 4 weeks prior to screening
-Patients who develop a respiratory tract infection between screening and prior to treatment will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection
-Patients requiring long term oxygen therapy prescribed for >12 hours per day
-Patients with any history of asthma
-Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years
-Patients with a blood eosinophil count > 600/mm3 at screening
-Patients with allergic rhinitis who use a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen is permitted)
-Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension)
-Patients with clinically significant bronchiectasis
-Patients with a diagnosis of α-1 anti-trypsin deficiency
-Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active
-Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation
-Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. (Maintenance program is permitted.)
-Patients receiving any medications in the classes listed in the protocol
-Patients receiving any COPD related medications in the classes specified in the protocol must undergo the required washout period prior to screening and follow the adjustment to treatment program
-Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of screening, whichever is longer
-Patients unable to use an electronic patient diary and EXACT pro diary

-Patients unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication) or comply with the study regimen.

Participant Flow Table

Planned treatment epoch

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Started	1680	1682
Full analysis set (FAS)	1675	1679
Per-protocol set (PPS)	1528	1556
Serial spirometry set	280	279
Safety Set (SAF)	1678	1680
Urine cortisol set	266	269
Completed	1478	1474
Not Completed	202	208
Subject/guardian decision	149	151
Death	29	30
Physician Decision	18	16
Protocol deviation	2	3
Lost to Follow-	4	4

up		
Technical problems	0	4

Double-blind treatment

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Started	1678	1680
Completed	1400	1360
Not Completed	278	320
Adverse Event	129	145
Subject/guardian decision	111	125
Lack of Efficacy	17	22
Physician Decision	13	16
Protocol deviation	8	7
Technical problems	0	5

Baseline Characteristics

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)	Total
Number of Participants [units: participants]	1680	1682	3362
Age Continuous (units: Years) Mean ± Standard Deviation	64.6±7.89	64.5±7.70	64.6±7.79
Gender, Male/Female (units: Participants)			
Female	381	424	805
Male	1299	1258	2557

Summary of Efficacy

Primary Outcome Result(s)

Rate of COPD exacerbations

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)

Number of Participants Analyzed [units: participants]	1528	1556
Rate of COPD exacerbations (units: COPD Exacerbations/year) Least Squares Mean (95% Confidence Interval)	3.59 (3.28 to 3.94)	4.03 (3.68 to 4.41)

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)	
Non-Inferiority/Equivalence Test	Yes	Study was designed to have >95% power to rule out a 1.15-fold increase in the rate exacerbations for QVA149 vs. salmeterol/fluticasone.
P Value		
Method	Other Generalized linear model	
Other Rate Ratio	0.89	If the upper limit of the confidence interval was <1.15 then non-inferiority of QVA149 compared to SFC could be claimed
95 % Confidence Interval 2-Sided	0.83 to 0.96	

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)	
Non-Inferiority/Equivalence Test	No	
P Value	0.003	
Method	Other Generalized linear method	
Other Rate Ratio	0.89	If non-inferiority was demonstrated, superiority of QVA149A compared to SFC in reducing exacerbation rate could be claimed if the upper limit of the same CI was less than 1.
95 % Confidence Interval 2-Sided	0.83 to 0.96	

Secondary Outcome Result(s)

Time to first COPD exacerbation.

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Time to first COPD exacerbation. (units: Days) Median (95% Confidence Interval)	71.0 (60.0 to 82.0)	51.0 (46.0 to 57.0)

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	<0.001
Method	Regression, Cox
Hazard Ratio (HR)	0.84
95 % Confidence Interval 2-Sided	0.78 to 0.91

Rate of moderate to severe COPD exacerbations.

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1651	1656
Rate of moderate to severe COPD exacerbations. (units: COPD Exacerbation/year) Least Squares Mean (95% Confidence Interval)	0.98 (0.88 to 1.10)	1.19 (1.07 to 1.32)

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	<0.001
Method	Other Generalized linear model
Other Rate Ratio	0.83
95 % Confidence Interval 2-Sided	0.75 to 0.91

Time to first moderate to severe COPD exacerbation.

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Time to first moderate to severe COPD exacerbation. (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[1]	308.0 (283.0 to 352.0)

[1] NA -Parameters not estimated since less than 50% of the patients had an event, the median could not be calculated

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	<0.001
Method	Regression, Cox
Hazard Ratio (HR)	0.78
95 % Confidence Interval 2-Sided	0.70 to 0.86

Rate of moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1651	1656
Rate of moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids (units: COPD Exacerbation/year) Least Squares Mean (95% Confidence Interval)	0.18 (0.14 to 0.22)	0.18 (0.14 to 0.23)

Rate of moderate to severe COPD exacerbations requiring treatment with antibiotics

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1651	1656
Rate of moderate to severe COPD exacerbations requiring treatment with antibiotics (units: COPD Exacerbation/year)	0.17 (0.13 to 0.22)	0.22 (0.17 to 0.28)

Least Squares Mean (95% Confidence Interval)

Rate of moderate to severe COPD exacerbations requiring hospitalization. COPD exacerbations starting between first dose and one day after last treatment are included.

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1651	1656
Rate of moderate to severe COPD exacerbations requiring hospitalization. COPD exacerbations starting between first dose and one day after last treatment are included. (units: COPD Exacerbation/year) Least Squares Mean (95% Confidence Interval)	0.15 (0.11 to 0.19)	0.17 (0.13 to 0.22)

Rate of moderate to severe COPD exacerbations requiring re-hospitalization within 30 days

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units:	1675	1679

participants]		
Rate of moderate to severe COPD exacerbations requiring re-hospitalization within 30 days (units: COPD Exacerbation/year) Mean ± Standard Deviation	0.0 ± 0.15	0.0 ± 0.12

Time to first moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Time to first moderate to severe COPD exacerbations requiring treatment with systemic corticosteroids (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] NA- Parameters not estimated since less than 50% of the patients had an event, the median could not be calculated

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)

Non-Inferiority/Equivalence Test	No
P Value	0.256
Method	Regression, Cox
Hazard Ratio (HR)	0.90
95 % Confidence Interval 2-Sided	0.74 to 1.08

Time to first moderate to severe COPD exacerbations requiring treatment with antibiotics

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Time to first moderate to severe COPD exacerbations requiring treatment with antibiotics (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] NA- Parameters not estimated, data did not reach median

Statistical Analysis

Groups	QVA149, Long acting B2 agonist

	(LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	0.008
Method	Regression, Cox
Hazard Ratio (HR)	0.81
95 % Confidence Interval 2-Sided	0.69 to 0.95

Time to first moderate to severe COPD exacerbations requiring hospitalization

	QVA149	**Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)**
Number of Participants Analyzed [units: participants]	1675	1679
Time to first moderate to severe COPD exacerbations requiring hospitalization (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[1]	NA (NA to NA)[2]

[1] NA- Parameters not estimated since less than 50% of the patients had an event, the median could not be calculated
[2] NA- Parameters not estimated since less than 50% of the patients had an event, the median could not be calculated

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	0.046
Method	Regression, Cox
Hazard Ratio (HR)	0.81
95 % Confidence Interval 2-Sided	0.66 to 1.00

Time to first moderate to severe COPD exacerbations requiring re-hospitalization within 30 days

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Time to first moderate to severe COPD exacerbations requiring re-hospitalization within 30 days (units: Days) Median (95% Confidence Interval)	NA (NA to NA)[]	NA (NA to NA)[]

[1] NA- Parameters not estimated since less than 50% of the patients had an event, the median could not be calculated

Statistical Analysis

Groups	QVA149, Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Non-Inferiority/Equivalence Test	No
P Value	0.790
Method	Regression, Cox
Hazard Ratio (HR)	0.89
95 % Confidence Interval 2-Sided	0.38 to 2.10

Forced expiratory volume in 1 second

	QVA149	**Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)**
Number of Participants Analyzed [units: participants]	1675	1679
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error		
Day 1, 30 min post-dose (n=1659, 1663)	0.121 ± 0.0049	0.076 ± 0.0049

Day 1, one hour post-dose (n=1657, 1664)	0.147 ± 0.0054	0.092 ± 0.0054

Forced expiratory volume in 1 second

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error	0.079 ± 0.0070	0.006 ± 0.0070

Forced expiratory volume in 1 second

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error	0.070 ± 0.0072	-0.008 ± 0.0072

Forced expiratory volume in 1 second

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error	0.049 ± 0.0073	-0.037 ± 0.0074

Forced expiratory volume in 1 second

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error	0.034 ± 0.0074	-0.039 ± 0.0075

Forced expiratory volume in 1 second

	QVA149	Long acting B2 agonist (LABA) and

		inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Forced expiratory volume in 1 second (units: Liters) Least Squares Mean ± Standard Error	0.015 ± 0.0075	-0.048 ± 0.0076

Change from baseline in Forced expiratory volume in 1 second AUC (0-12h)

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	279	277
Change from baseline in Forced expiratory volume in 1 second AUC (0-12h) (units: Liters) Least Squares Mean ± Standard Error	0.078 ± 0.0174	-0.032 ± 0.0176

Change from baseline in total St. George's Respiratory Questionnaire score

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid

		(ICS)
Number of Participants Analyzed [units: participants]	1602	1593
Change from baseline in total St. George's Respiratory Questionnaire score (units: Score on a scale) Least Squares Mean ± Standard Error	-2.3 ± 0.36	-2.3 ± 0.36

Change from baseline in total St. George's Respiratory Questionnaire score

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1602	1593
Change from baseline in total St. George's Respiratory Questionnaire score (units: Score on a scale) Least Squares Mean ± Standard Error	-3.2 ± 0.38	-1.9 ± 0.38

Change from baseline in total St. George's Respiratory Questionnaire score

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid

		(ICS)
Number of Participants Analyzed [units: participants]	1602	1593
Change from baseline in total St. George's Respiratory Questionnaire score (units: Score on a scale) Least Squares Mean ± Standard Error	-3.5 ± 0.39	-2.3 ± 0.39

Change from baseline in total St. George's Respiratory Questionnaire score

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1602	1593
Change from baseline in total St. George's Respiratory Questionnaire score (units: Score on a scale) Least Squares Mean ± Standard Error	-3.5 ± 0.40	-1.7 ± 0.40

Change from baseline in total St. George's Respiratory Questionnaire score

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid

		(ICS)
Number of Participants Analyzed [units: participants]	1602	1593
Change from baseline in total St. George's Respiratory Questionnaire score (units: Score on a scale) Least Squares Mean ± Standard Error	-3.1 ± 0.41	-1.9 ± 0.41

Change from baseline in the number of puffs of rescue medication

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1675	1679
Change from baseline in the number of puffs of rescue medication (units: Number of puffs per day) Least Squares Mean ± Standard Error	-1.01 ± 0.097	-0.76 ± 0.097

Change from baseline in the safety of QVA149 ((110/50 µg o.d.) vs fluticasone/salmeterol (500/50µg bid) in terms of HPA axis function, as determined by collection of 24-hour urine cortisol.

	QVA149	Long acting B2 agonist (LABA) and inhaled

		corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	162	154
Change from baseline in the safety of QVA149 ((110/50 µg o.d.) vs fluticasone/salmeterol (500/50µg bid) in terms of HPA axis function, as determined by collection of 24-hour urine cortisol. (units: ng/mL) Median (Full Range)	5.615 (-96.93 to 509.17)	-10.390 (-97.76 to 4444.65)

Change From Baseline in Forced Vital Capacity

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1597	1595
Change From Baseline in Forced Vital Capacity (units: Liters) Least Squares Mean ± Standard Error		
4 weeks	0.146 ± 0.0127	-0.032 ± 0.0128
12 weeks	0.134 ± 0.0131	-0.071 ± 0.0131
26 weeks	0.088 ± 0.0135	-0.121 ± 0.0136

38 weeks	0.071 ± 0.0137	-0.111 ± 0.0137
52 weeks	0.022 ± 0.0139	-0.138 ± 0.0140

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

	QVA149	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS)
Number of Participants Analyzed [units: participants]	1678	1680
Number of patients with adverse events, serious adverse events, and death (units: Number of participants)		
Patients with at least one SAEs	308	334
Patients with at least one AE	1459	1498
Death	24	24

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	QVA149 N = 1678	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS) N = 1680
Total participants affected	308 (18.36%)	334 (19.88%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA[1, †]	1 (0.06%)	0 (0.00%)
HEPARIN-INDUCED THROMBOCYTOPENIA[1, †]	1 (0.06%)	0 (0.00%)
HYPOCHROMIC ANAEMIA[1, †]	0 (0.00%)	1 (0.06%)
CARDIAC DISORDERS		
ACUTE CORONARY SYNDROME[1, †]	1 (0.06%)	2 (0.12%)
ACUTE MYOCARDIAL INFARCTION[1, †]	4 (0.24%)	2 (0.12%)
ANGINA PECTORIS[1, †]	0 (0.00%)	1 (0.06%)
ANGINA UNSTABLE[1, †]	0 (0.00%)	1 (0.06%)
ARRHYTHMIA[1, †]	1 (0.06%)	1 (0.06%)
ATRIAL FIBRILLATION[1, †]	5 (0.30%)	7 (0.42%)
ATRIAL FLUTTER[1, †]	2 (0.12%)	3 (0.18%)
ATRIAL TACHYCARDIA[1, †]	2 (0.12%)	0 (0.00%)
BRADYCARDIA[1, †]	1 (0.06%)	0 (0.00%)
CARDIAC ARREST[1, †]	5 (0.30%)	1 (0.06%)
CARDIAC FAILURE[1, †]	5 (0.30%)	7 (0.42%)

CARDIAC FAILURE ACUTE[1, †]	0 (0.00%)	2 (0.12%)
CARDIAC FAILURE CONGESTIVE[1, †]	1 (0.06%)	3 (0.18%)
CARDIAC TAMPONADE[1, †]	0 (0.00%)	1 (0.06%)
CARDIO-RESPIRATORY ARREST[1, †]	1 (0.06%)	3 (0.18%)
CARDIOVASCULAR DISORDER[1, †]	1 (0.06%)	0 (0.00%)
CONGESTIVE CARDIOMYOPATHY[1, †]	1 (0.06%)	0 (0.00%)
COR PULMONALE[1, †]	0 (0.00%)	2 (0.12%)
COR PULMONALE CHRONIC[1, †]	0 (0.00%)	2 (0.12%)
CORONARY ARTERY DISEASE[1, †]	2 (0.12%)	1 (0.06%)
CORONARY ARTERY STENOSIS[1, †]	1 (0.06%)	2 (0.12%)
ISCHAEMIC CARDIOMYOPATHY[1, †]	1 (0.06%)	0 (0.00%)
LEFT VENTRICULAR DYSFUNCTION[1, †]	0 (0.00%)	1 (0.06%)
LEFT VENTRICULAR FAILURE[1, †]	1 (0.06%)	0 (0.00%)
MYOCARDIAL INFARCTION[1, †]	6 (0.36%)	5 (0.30%)
MYOCARDIAL ISCHAEMIA[1, †]	1 (0.06%)	2 (0.12%)
MYOCARDIAL RUPTURE[1, †]	0 (0.00%)	1 (0.06%)
PERICARDIAL	0 (0.00%)	1 (0.06%)

EFFUSION[1, †]		
PERICARDIAL HAEMORRHAGE[1, †]	1 (0.06%)	0 (0.00%)
RIGHT VENTRICULAR FAILURE[1, †]	0 (0.00%)	1 (0.06%)
SINUS TACHYCARDIA[1, †]	1 (0.06%)	0 (0.00%)
VENTRICULAR ARRHYTHMIA[1, †]	1 (0.06%)	0 (0.00%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		
PROGRESSIVE CEREBELLAR DEGENERATION[1, †]	1 (0.06%)	0 (0.00%)
ENDOCRINE DISORDERS		
GOITRE[1, †]	1 (0.06%)	1 (0.06%)
EYE DISORDERS		
ANGLE CLOSURE GLAUCOMA[1, †]	0 (0.00%)	1 (0.06%)
OPHTHALMOPLEGIA[1, †]	1 (0.06%)	0 (0.00%)
OPTIC ISCHAEMIC NEUROPATHY[1, †]	0 (0.00%)	1 (0.06%)
RETINAL DETACHMENT[1, †]	1 (0.06%)	1 (0.06%)
GASTROINTESTINAL DISORDERS		
ABDOMINAL DISTENSION[1, †]	0 (0.00%)	1 (0.06%)
ABDOMINAL HERNIA[1, †]	1 (0.06%)	0 (0.00%)
ABDOMINAL PAIN	1 (0.06%)	0 (0.00%)

UPPER[1, †]		
ACID PEPTIC DISEASE[1, †]	1 (0.06%)	0 (0.00%)
ASCITES[1, †]	1 (0.06%)	0 (0.00%)
COLITIS[1, †]	1 (0.06%)	0 (0.00%)
CONSTIPATION[1, †]	1 (0.06%)	0 (0.00%)
DIARRHOEA[1, †]	1 (0.06%)	0 (0.00%)
DUODENAL ULCER[1, †]	1 (0.06%)	0 (0.00%)
DYSPHAGIA[1, †]	0 (0.00%)	1 (0.06%)
FAECALOMA[1, †]	1 (0.06%)	0 (0.00%)
GASTRIC ULCER[1, †]	1 (0.06%)	1 (0.06%)
GASTRITIS[1, †]	0 (0.00%)	2 (0.12%)
GASTROOESOPHAGEAL REFLUX DISEASE[1, †]	0 (0.00%)	3 (0.18%)
HAEMATEMESIS[1, †]	0 (0.00%)	1 (0.06%)
ILEUS[1, †]	0 (0.00%)	1 (0.06%)
ILEUS PARALYTIC[1, †]	1 (0.06%)	0 (0.00%)
INGUINAL HERNIA[1, †]	1 (0.06%)	1 (0.06%)
INTESTINAL PERFORATION[1, †]	1 (0.06%)	0 (0.00%)
INTESTINAL STENOSIS[1, †]	0 (0.00%)	1 (0.06%)
LARGE INTESTINE POLYP[1, †]	0 (0.00%)	4 (0.24%)
NAUSEA[1, †]	0 (0.00%)	1 (0.06%)
OESOPHAGITIS[1, †]	0 (0.00%)	1 (0.06%)
PANCREATITIS[1, †]	2 (0.12%)	0 (0.00%)
PANCREATITIS ACUTE[1, †]	1 (0.06%)	3 (0.18%)

STOMATITIS[1, †]	0 (0.00%)	1 (0.06%)
UMBILICAL HERNIA[1, †]	0 (0.00%)	1 (0.06%)
VOMITING[1, †]	0 (0.00%)	1 (0.06%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
ASTHENIA[1, †]	1 (0.06%)	0 (0.00%)
FATIGUE[1, †]	1 (0.06%)	0 (0.00%)
LOCAL SWELLING[1, †]	1 (0.06%)	0 (0.00%)
MULTI-ORGAN FAILURE[1, †]	0 (0.00%)	1 (0.06%)
NON-CARDIAC CHEST PAIN[1, †]	1 (0.06%)	2 (0.12%)
OEDEMA PERIPHERAL[1, †]	1 (0.06%)	1 (0.06%)
PYREXIA[1, †]	1 (0.06%)	2 (0.12%)
SUDDEN CARDIAC DEATH[1, †]	1 (0.06%)	1 (0.06%)
SUDDEN DEATH[1, †]	1 (0.06%)	2 (0.12%)
HEPATOBILIARY DISORDERS		
CHOLECYSTITIS[1, †]	0 (0.00%)	2 (0.12%)
CHOLELITHIASIS[1, †]	1 (0.06%)	1 (0.06%)
DRUG-INDUCED LIVER INJURY[1, †]	0 (0.00%)	1 (0.06%)
HEPATIC CIRRHOSIS[1, †]	2 (0.12%)	0 (0.00%)
HEPATIC CYST RUPTURED[1, †]	0 (0.00%)	1 (0.06%)
HEPATIC FUNCTION ABNORMAL[1, †]	1 (0.06%)	0 (0.00%)

LIVER DISORDER[1, †]	1 (0.06%)	0 (0.00%)
IMMUNE SYSTEM DISORDERS		
FOOD ALLERGY[1, †]	1 (0.06%)	0 (0.00%)
INFECTIONS AND INFESTATIONS		
ABSCESS JAW[1, †]	1 (0.06%)	0 (0.00%)
ABSCESS LIMB[1, †]	0 (0.00%)	1 (0.06%)
APPENDICITIS[1, †]	1 (0.06%)	1 (0.06%)
ATYPICAL MYCOBACTERIAL INFECTION[1, †]	0 (0.00%)	1 (0.06%)
BACTERAEMIA[1, †]	1 (0.06%)	0 (0.00%)
BRONCHITIS[1, †]	0 (0.00%)	4 (0.24%)
CHOLECYSTITIS INFECTIVE[1, †]	0 (0.00%)	1 (0.06%)
CYSTITIS[1, †]	1 (0.06%)	1 (0.06%)
DEVICE RELATED INFECTION[1, †]	2 (0.12%)	0 (0.00%)
DIVERTICULITIS[1, †]	1 (0.06%)	1 (0.06%)
ECZEMA INFECTED[1, †]	0 (0.00%)	1 (0.06%)
ENTEROCOLITIS INFECTIOUS[1, †]	0 (0.00%)	1 (0.06%)
ERYSIPELAS[1, †]	0 (0.00%)	2 (0.12%)
GASTROENTERITIS[1, †]	0 (0.00%)	1 (0.06%)
GASTROENTERITIS ROTAVIRUS[1, †]	1 (0.06%)	0 (0.00%)
H1N1 INFLUENZA[1, †]	0 (0.00%)	1 (0.06%)
HERPES ZOSTER[1, †]	0 (0.00%)	1 (0.06%)

INFECTED SKIN ULCER[1, †]	1 (0.06%)	0 (0.00%)
INFECTIOUS PLEURAL EFFUSION[1, †]	2 (0.12%)	0 (0.00%)
INFECTIVE ANEURYSM[1, †]	1 (0.06%)	0 (0.00%)
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE[1, †]	1 (0.06%)	1 (0.06%)
INFLUENZA[1, †]	1 (0.06%)	1 (0.06%)
LOWER RESPIRATORY TRACT INFECTION[1, †]	8 (0.48%)	7 (0.42%)
LOWER RESPIRATORY TRACT INFECTION BACTERIAL[1, †]	1 (0.06%)	0 (0.00%)
LOWER RESPIRATORY TRACT INFECTION VIRAL[1, †]	1 (0.06%)	0 (0.00%)
LUNG INFECTION[1, †]	0 (0.00%)	3 (0.18%)
MENINGITIS VIRAL[1, †]	0 (0.00%)	1 (0.06%)
NASOPHARYNGITIS[1, †]	0 (0.00%)	2 (0.12%)
ORAL VIRAL INFECTION[1, †]	1 (0.06%)	0 (0.00%)
OTITIS EXTERNA[1, †]	1 (0.06%)	0 (0.00%)
OTITIS MEDIA CHRONIC[1, †]	1 (0.06%)	0 (0.00%)
PERITONITIS[1, †]	1 (0.06%)	2 (0.12%)
PHARYNGITIS[1, †]	1 (0.06%)	0 (0.00%)
PNEUMOCOCCAL INFECTION[1, †]	0 (0.00%)	1 (0.06%)

PNEUMONIA[1, †]	34 (2.03%)	54 (3.21%)
PNEUMONIA BACTERIAL[1, †]	0 (0.00%)	1 (0.06%)
PSEUDOMONAS INFECTION[1, †]	0 (0.00%)	1 (0.06%)
PULMONARY SEPSIS[1, †]	4 (0.24%)	1 (0.06%)
PULMONARY TUBERCULOSIS[1, †]	0 (0.00%)	1 (0.06%)
PYELONEPHRITIS[1, †]	0 (0.00%)	1 (0.06%)
RESPIRATORY TRACT INFECTION[1, †]	2 (0.12%)	1 (0.06%)
RESPIRATORY TRACT INFECTION BACTERIAL[1, †]	1 (0.06%)	0 (0.00%)
SEPSIS[1, †]	1 (0.06%)	0 (0.00%)
SEPTIC SHOCK[1, †]	1 (0.06%)	1 (0.06%)
SINUSITIS[1, †]	2 (0.12%)	1 (0.06%)
SPUTUM PURULENT[1, †]	0 (0.00%)	1 (0.06%)
TUBERCULOUS PLEURISY[1, †]	1 (0.06%)	0 (0.00%)
UPPER RESPIRATORY TRACT INFECTION[1, †]	2 (0.12%)	1 (0.06%)
UPPER RESPIRATORY TRACT INFECTION BACTERIAL[1, †]	9 (0.54%)	15 (0.89%)
URETERITIS[1, †]	0 (0.00%)	1 (0.06%)
URINARY TRACT INFECTION[1, †]	1 (0.06%)	0 (0.00%)
UROSEPSIS[1, †]	1 (0.06%)	1 (0.06%)
VIRAL INFECTION[1, †]	1 (0.06%)	0 (0.00%)

VIRAL UPPER RESPIRATORY TRACT INFECTION[1, †]	1 (0.06%)	2 (0.12%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
ANAEMIA POSTOPERATIVE[1, †]	0 (0.00%)	1 (0.06%)
ANKLE FRACTURE[1, †]	1 (0.06%)	1 (0.06%)
BRAIN HERNIATION[1, †]	0 (0.00%)	1 (0.06%)
CARBON MONOXIDE POISONING[1, †]	0 (0.00%)	1 (0.06%)
CLAVICLE FRACTURE[1, †]	0 (0.00%)	1 (0.06%)
COMPRESSION FRACTURE[1, †]	0 (0.00%)	1 (0.06%)
FALL[1, †]	0 (0.00%)	1 (0.06%)
FEMORAL NECK FRACTURE[1, †]	1 (0.06%)	1 (0.06%)
FEMUR FRACTURE[1, †]	1 (0.06%)	1 (0.06%)
HEAD INJURY[1, †]	1 (0.06%)	0 (0.00%)
HIP FRACTURE[1, †]	2 (0.12%)	1 (0.06%)
HUMERUS FRACTURE[1, †]	1 (0.06%)	1 (0.06%)
LIMB INJURY[1, †]	0 (0.00%)	1 (0.06%)
MENISCUS INJURY[1, †]	0 (0.00%)	2 (0.12%)
OVERDOSE[1, †]	2 (0.12%)	1 (0.06%)
PATELLA FRACTURE[1, †]	1 (0.06%)	0 (0.00%)
PELVIC FRACTURE[1, †]	1 (0.06%)	0 (0.00%)
POSTOPERATIVE WOUND	1 (0.06%)	0 (0.00%)

COMPLICATION[1, †]		
PROCEDURAL INTESTINAL PERFORATION[1, †]	0 (0.00%)	1 (0.06%)
RIB FRACTURE[1, †]	0 (0.00%)	1 (0.06%)
SPINAL COMPRESSION FRACTURE[1, †]	1 (0.06%)	0 (0.00%)
SPINAL FRACTURE[1, †]	0 (0.00%)	1 (0.06%)
TIBIA FRACTURE[1, †]	0 (0.00%)	1 (0.06%)
WOUND DECOMPOSITION[1, †]	1 (0.06%)	0 (0.00%)
INVESTIGATIONS		
ALANINE AMINOTRANSFERASE INCREASED[1, †]	0 (0.00%)	1 (0.06%)
ASPARTATE AMINOTRANSFERASE INCREASED[1, †]	1 (0.06%)	2 (0.12%)
BLOOD POTASSIUM INCREASED[1, †]	1 (0.06%)	0 (0.00%)
WEIGHT DECREASED[1, †]	0 (0.00%)	1 (0.06%)
METABOLISM AND NUTRITION DISORDERS		
ACIDOSIS[1, †]	0 (0.00%)	1 (0.06%)
CACHEXIA[1, †]	1 (0.06%)	0 (0.00%)
DEHYDRATION[1, †]	1 (0.06%)	0 (0.00%)
DIABETES MELLITUS[1, †]	1 (0.06%)	3 (0.18%)
DIET REFUSAL[1, †]	1 (0.06%)	0 (0.00%)
ELECTROLYTE IMBALANCE[1, †]	1 (0.06%)	0 (0.00%)

HYPERGLYCAEMIA[1, †]	1 (0.06%)	1 (0.06%)
HYPERKALAEMIA[1, †]	0 (0.00%)	1 (0.06%)
HYPONATRAEMIA[1, †]	0 (0.00%)	1 (0.06%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA[1, †]	0 (0.00%)	1 (0.06%)
ARTHROPATHY[1, †]	1 (0.06%)	0 (0.00%)
GROIN PAIN[1, †]	1 (0.06%)	0 (0.00%)
INTERVERTEBRAL DISC PROTRUSION[1, †]	0 (0.00%)	1 (0.06%)
MUSCLE HAEMORRHAGE[1, †]	1 (0.06%)	0 (0.00%)
OSTEOARTHRITIS[1, †]	1 (0.06%)	0 (0.00%)
OSTEOLYSIS[1, †]	0 (0.00%)	1 (0.06%)
OSTEOPOROTIC FRACTURE[1, †]	1 (0.06%)	0 (0.00%)
POLYMYALGIA RHEUMATICA[1, †]	2 (0.12%)	0 (0.00%)
SPINAL PAIN[1, †]	0 (0.00%)	1 (0.06%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
ACUTE MYELOID LEUKAEMIA[1, †]	0 (0.00%)	1 (0.06%)
ADENOCARCINOMA GASTRIC[1, †]	0 (0.00%)	1 (0.06%)
ADENOCARCINOMA OF COLON[1, †]	1 (0.06%)	1 (0.06%)
ADRENAL GLAND	0 (0.00%)	1 (0.06%)

CANCER[1, †]		
BASAL CELL CARCINOMA[1, †]	2 (0.12%)	0 (0.00%)
B-CELL LYMPHOMA[1, †]	0 (0.00%)	1 (0.06%)
BREAST CANCER[1, †]	0 (0.00%)	1 (0.06%)
BRONCHIAL CARCINOMA[1, †]	1 (0.06%)	1 (0.06%)
CHRONIC MYELOID LEUKAEMIA[1, †]	1 (0.06%)	0 (0.00%)
COLON CANCER[1, †]	1 (0.06%)	2 (0.12%)
DIFFUSE LARGE B-CELL LYMPHOMA[1, †]	1 (0.06%)	0 (0.00%)
GASTRIC CANCER[1, †]	1 (0.06%)	0 (0.00%)
HEPATIC CANCER[1, †]	1 (0.06%)	0 (0.00%)
HYPOPHARYNGEAL CANCER[1, †]	0 (0.00%)	1 (0.06%)
LARGE INTESTINE BENIGN NEOPLASM[1, †]	1 (0.06%)	0 (0.00%)
LARYNGEAL CANCER[1, †]	1 (0.06%)	1 (0.06%)
LARYNGEAL SQUAMOUS CELL CARCINOMA[1, †]	0 (0.00%)	1 (0.06%)
LUNG ADENOCARCINOMA METASTATIC[1, †]	1 (0.06%)	0 (0.00%)
LUNG NEOPLASM MALIGNANT[1, †]	3 (0.18%)	6 (0.36%)
MALIGNANT MESENCHYMOMA[1, †]	1 (0.06%)	0 (0.00%)
METASTASES TO LIVER[1, †]	1 (0.06%)	0 (0.00%)

MYELOID LEUKAEMIA[1, †]	0 (0.00%)	1 (0.06%)
NEOPLASM MALIGNANT[1, †]	1 (0.06%)	0 (0.00%)
NON-HODGKIN'S LYMPHOMA[1, †]	1 (0.06%)	0 (0.00%)
NON-SMALL CELL LUNG CANCER[1, †]	1 (0.06%)	0 (0.00%)
OESOPHAGEAL CARCINOMA[1, †]	1 (0.06%)	0 (0.00%)
PENILE NEOPLASM[1, †]	0 (0.00%)	1 (0.06%)
PLASMA CELL MYELOMA[1, †]	0 (0.00%)	1 (0.06%)
PROSTATE CANCER[1, †]	4 (0.24%)	2 (0.12%)
RECTAL ADENOCARCINOMA[1, †]	1 (0.06%)	0 (0.00%)
RECTAL CANCER[1, †]	1 (0.06%)	1 (0.06%)
RENAL CANCER[1, †]	0 (0.00%)	1 (0.06%)
SMALL CELL CARCINOMA[1, †]	1 (0.06%)	0 (0.00%)
SMALL CELL LUNG CANCER[1, †]	1 (0.06%)	0 (0.00%)
SQUAMOUS CELL CARCINOMA[1, †]	1 (0.06%)	0 (0.00%)
SQUAMOUS CELL CARCINOMA OF LUNG[1, †]	1 (0.06%)	1 (0.06%)
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED[1, †]	1 (0.06%)	0 (0.00%)
URETHRAL CANCER[1, †]	1 (0.06%)	0 (0.00%)

NERVOUS SYSTEM

DISORDERS		
BASAL GANGLIA STROKE[1, †]	0 (0.00%)	1 (0.06%)
BRAIN INJURY[1, †]	1 (0.06%)	0 (0.00%)
BRAIN STEM HAEMORRHAGE[1, †]	0 (0.00%)	1 (0.06%)
CAROTID ARTERIOSCLEROSIS[1, †]	1 (0.06%)	0 (0.00%)
CAROTID ARTERY OCCLUSION[1, †]	0 (0.00%)	1 (0.06%)
CENTRAL NERVOUS SYSTEM LESION[1, †]	0 (0.00%)	1 (0.06%)
CEREBELLAR INFARCTION[1, †]	0 (0.00%)	1 (0.06%)
CEREBRAL INFARCTION[1, †]	2 (0.12%)	0 (0.00%)
CEREBRAL ISCHAEMIA[1, †]	1 (0.06%)	0 (0.00%)
CEREBRAL THROMBOSIS[1, †]	1 (0.06%)	0 (0.00%)
CEREBROVASCULAR ACCIDENT[1, †]	0 (0.00%)	2 (0.12%)
CLUSTER HEADACHE[1, †]	0 (0.00%)	1 (0.06%)
DEPRESSED LEVEL OF CONSCIOUSNESS[1, †]	1 (0.06%)	0 (0.00%)
DIZZINESS[1, †]	1 (0.06%)	1 (0.06%)
EPILEPSY[1, †]	1 (0.06%)	0 (0.00%)
HEADACHE[1, †]	0 (0.00%)	1 (0.06%)
HEMIPARESIS[1, †]	0 (0.00%)	1 (0.06%)
HYDROCEPHALUS[1, †]	0 (0.00%)	1 (0.06%)

ISCHAEMIC STROKE[1, †]	2 (0.12%)	0 (0.00%)
LACUNAR INFARCTION[1, †]	0 (0.00%)	1 (0.06%)
SYNCOPE[1, †]	2 (0.12%)	0 (0.00%)
TRANSIENT ISCHAEMIC ATTACK[1, †]	1 (0.06%)	1 (0.06%)
VIITH NERVE PARALYSIS[1, †]	0 (0.00%)	1 (0.06%)
PSYCHIATRIC DISORDERS		
ANXIETY[1, †]	1 (0.06%)	0 (0.00%)
COMPLETED SUICIDE[1, †]	0 (0.00%)	1 (0.06%)
DELIRIUM TREMENS[1, †]	1 (0.06%)	0 (0.00%)
DEPRESSION[1, †]	1 (0.06%)	0 (0.00%)
HALLUCINATION[1, †]	1 (0.06%)	0 (0.00%)
SLEEP DISORDER[1, †]	0 (0.00%)	1 (0.06%)
RENAL AND URINARY DISORDERS		
ACUTE KIDNEY INJURY[1, †]	1 (0.06%)	0 (0.00%)
CALCULUS URINARY[1, †]	0 (0.00%)	1 (0.06%)
CHRONIC KIDNEY DISEASE[1, †]	0 (0.00%)	1 (0.06%)
NEPHROLITHIASIS[1, †]	0 (0.00%)	1 (0.06%)
RENAL FAILURE[1, †]	0 (0.00%)	1 (0.06%)
URETHRAL STENOSIS[1, †]	2 (0.12%)	0 (0.00%)
URINARY RETENTION[1, †]	1 (0.06%)	1 (0.06%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		

BENIGN PROSTATIC HYPERPLASIA[1, †]	0 (0.00%)	2 (0.12%)
TESTICULAR TORSION[1, †]	1 (0.06%)	0 (0.00%)
UTERINE POLYP[1, †]	0 (0.00%)	1 (0.06%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
ACUTE PULMONARY OEDEMA[1, †]	0 (0.00%)	1 (0.06%)
ACUTE RESPIRATORY FAILURE[1, †]	5 (0.30%)	4 (0.24%)
ASTHMA[1, †]	0 (0.00%)	1 (0.06%)
BRONCHITIS CHRONIC[1, †]	0 (0.00%)	1 (0.06%)
BRONCHOPLEURAL FISTULA[1, †]	0 (0.00%)	1 (0.06%)
BRONCHOSPASM[1, †]	1 (0.06%)	0 (0.00%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE[1, †]	182 (10.85%)	207 (12.32%)
CHRONIC RESPIRATORY FAILURE[1, †]	4 (0.24%)	1 (0.06%)
COUGH[1, †]	0 (0.00%)	2 (0.12%)
DYSPNOEA[1, †]	8 (0.48%)	4 (0.24%)
EMPHYSEMA[1, †]	1 (0.06%)	0 (0.00%)
EPISTAXIS[1, †]	1 (0.06%)	0 (0.00%)
HAEMOPTYSIS[1, †]	1 (0.06%)	0 (0.00%)

HAEMOTHORAX[1, †]	0 (0.00%)	1 (0.06%)
HYPERCAPNIA[1, †]	0 (0.00%)	1 (0.06%)
HYPOXIA[1, †]	0 (0.00%)	1 (0.06%)
LARYNGEAL OEDEMA[1, †]	1 (0.06%)	0 (0.00%)
LUNG CONSOLIDATION[1, †]	1 (0.06%)	0 (0.00%)
PLEURAL EFFUSION[1, †]	0 (0.00%)	1 (0.06%)
PLEURISY[1, †]	2 (0.12%)	1 (0.06%)
PNEUMONITIS[1, †]	0 (0.00%)	1 (0.06%)
PNEUMOTHORAX[1, †]	2 (0.12%)	5 (0.30%)
PNEUMOTHORAX SPONTANEOUS[1, †]	0 (0.00%)	1 (0.06%)
PULMONARY EMBOLISM[1, †]	4 (0.24%)	2 (0.12%)
PULMONARY HAEMORRHAGE[1, †]	0 (0.00%)	1 (0.06%)
PULMONARY HILAR ENLARGEMENT[1, †]	0 (0.00%)	1 (0.06%)
PULMONARY HYPERTENSION[1, †]	1 (0.06%)	0 (0.00%)
PULMONARY OEDEMA[1, †]	0 (0.00%)	1 (0.06%)
RESPIRATORY ACIDOSIS[1, †]	2 (0.12%)	0 (0.00%)
RESPIRATORY FAILURE[1, †]	11 (0.66%)	6 (0.36%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
LINEAR IGA DISEASE[1, †]	0 (0.00%)	1 (0.06%)

PARAPSORIASIS[1, †]	0 (0.00%)	1 (0.06%)
SWELLING FACE[1, †]	0 (0.00%)	1 (0.06%)
URTICARIA[1, †]	1 (0.06%)	0 (0.00%)
VASCULAR DISORDERS		
AORTIC ANEURYSM[1, †]	2 (0.12%)	3 (0.18%)
AORTIC ANEURYSM RUPTURE[1, †]	0 (0.00%)	1 (0.06%)
AORTIC CALCIFICATION[1, †]	0 (0.00%)	1 (0.06%)
ARTERIOSCLEROSIS[1, †]	0 (0.00%)	1 (0.06%)
CIRCULATORY COLLAPSE[1, †]	1 (0.06%)	0 (0.00%)
DEEP VEIN THROMBOSIS[1, †]	2 (0.12%)	0 (0.00%)
EMBOLISM ARTERIAL[1, †]	0 (0.00%)	1 (0.06%)
HYPERTENSION[1, †]	3 (0.18%)	2 (0.12%)
HYPERTENSIVE CRISIS[1, †]	1 (0.06%)	0 (0.00%)
HYPOTENSION[1, †]	2 (0.12%)	0 (0.00%)
LERICHE SYNDROME[1, †]	1 (0.06%)	0 (0.00%)
ORTHOSTATIC HYPOTENSION[1, †]	1 (0.06%)	0 (0.00%)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE[1, †]	4 (0.24%)	0 (0.00%)
PERIPHERAL EMBOLISM[1, †]	0 (0.00%)	1 (0.06%)
TEMPORAL ARTERITIS[1, †]	1 (0.06%)	0 (0.00%)
THROMBOPHLEBITIS[1, †]	1 (0.06%)	0 (0.00%)

THROMBOSIS[1, †]	0 (0.00%)	1 (0.06%)
VARICOSE ULCERATION[1, †]	0 (0.00%)	1 (0.06%)
VENOUS THROMBOSIS[1, †]	1 (0.06%)	0 (0.00%)

† Systematic Assessment
1 MedDRA

Other Adverse Events by System Organ Class

Frequent Event Reporting Threshold 1%

	QVA149 N = 1678	Long acting B2 agonist (LABA) and inhaled corticosteroid (ICS) N = 1680
Total participants affected	1363 (81.23%)	1424 (84.76%)
GASTROINTESTINAL DISORDERS		
CONSTIPATION[1, †]	19 (1.13%)	17 (1.01%)
DIARRHOEA[1, †]	19 (1.13%)	24 (1.43%)
DYSPEPSIA[1, †]	18 (1.07%)	9 (0.54%)
GASTRITIS[1, †]	10 (0.60%)	20 (1.19%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
NON-CARDIAC CHEST PAIN[1, †]	20 (1.19%)	11 (0.65%)
OEDEMA PERIPHERAL[1, †]	26 (1.55%)	13 (0.77%)
PYREXIA[1, †]	17 (1.01%)	27 (1.61%)
INFECTIONS AND INFESTATIONS		
BRONCHITIS[1, †]	29 (1.73%)	41 (2.44%)
GASTROENTERITIS[1, †]	10 (0.60%)	18 (1.07%)
INFLUENZA[1, †]	34 (2.03%)	55 (3.27%)
LOWER RESPIRATORY TRACT INFECTION[1, †]	76 (4.53%)	91 (5.42%)
NASOPHARYNGITIS[1, †]	197 (11.74%)	194 (11.55%)
ORAL CANDIDIASIS[1, †]	20 (1.19%)	71 (4.23%)
OROPHARYNGEAL CANDIDIASIS[1, †]	2 (0.12%)	17 (1.01%)
PNEUMONIA[1, †]	19 (1.13%)	27 (1.61%)
RESPIRATORY TRACT INFECTION VIRAL[1, †]	17 (1.01%)	8 (0.48%)
RHINITIS[1, †]	27 (1.61%)	28 (1.67%)
SINUSITIS[1, †]	16 (0.95%)	20 (1.19%)
UPPER RESPIRATORY TRACT INFECTION[1, †]	79 (4.71%)	82 (4.88%)
UPPER RESPIRATORY TRACT INFECTION BACTERIAL[1, †]	121 (7.21%)	157 (9.35%)
URINARY TRACT	14 (0.83%)	22 (1.31%)

INFECTION[1, †]		
VIRAL UPPER RESPIRATORY TRACT INFECTION[1, †]	131 (7.81%)	136 (8.10%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA[1, †]	20 (1.19%)	23 (1.37%)
BACK PAIN[1, †]	35 (2.09%)	34 (2.02%)
MUSCULOSKELETAL PAIN[1, †]	17 (1.01%)	13 (0.77%)
NERVOUS SYSTEM DISORDERS		
DIZZINESS[1, †]	6 (0.36%)	27 (1.61%)
HEADACHE[1, †]	38 (2.26%)	34 (2.02%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
CHRONIC OBSTRUCTIVE PULMONARY DISEASE[1, †]	1262 (75.21%)	1331 (79.23%)
COUGH[1, †]	50 (2.98%)	49 (2.92%)
DYSPHONIA[1, †]	7 (0.42%)	30 (1.79%)
DYSPNOEA[1, †]	41 (2.44%)	47 (2.80%)
OROPHARYNGEAL PAIN[1, †]	35 (2.09%)	33 (1.96%)
SPUTUM INCREASED[1, †]	10 (0.60%)	23 (1.37%)
VASCULAR DISORDERS		

HYPERTENSION[1, †]	44 (2.62%)	40 (2.38%)

† Systematic Assessment
1 MedDRA

Other Relevant Findings

None

Conclusion:

In conclusion, in patients at risk of COPD exacerbations QVA149, a steroid free combination of 2 bronchodilators, was shown to be more effective than an established standard of care of a LABA/ICS such as salmeterol/fluticasone in preventing exacerbations.
Overall QVA149 was generally well tolerated in this study and the safety results were balanced between the 2 treatment arms with no new safety concerns

Date of Clinical Trial Report

. 10-Feb-2016