NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

indacaterol maleate/glycopyrronium bromide

Trial Indication(s)

Moderate to severe COPD.

Protocol Number

CQVA149A2316

Protocol Title

A 26-week, randomized, double blind, parallel-group multicenter study to assess the efficacy and safety of QVA149 (110/50 µg o.d.) vs tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in patients with moderate to severe COPD

Clinical Trial Phase

Phase 4

Phase of Drug Development

IV

Study Start/End Dates

Study Start Date: November 2015 (Actual)
Primary Completion Date: July 2017 (Actual)
Study Completion Date: July 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multicenter, randomized, parallel-group, double-blind, triple-dummy study to assess the efficacy of the 2 active treatment groups in patients with moderate to severe COPD.
The study consisted of 4 epochs: Screening (1 week), Run-in (4 weeks), Treatment (26 weeks, double-blind, triple-dummy), and Follow-up (4 weeks).

Centers

192 centers in 21 countries: Belgium(6), Estonia(4), Lithuania(6), Hungary(8), Canada(12), Austria(7), Denmark(2), United Kingdom(11), Latvia(8), Germany(45), Netherlands(4), Spain(9), Poland(16), Slovakia (Slovak Republic)(5), Croatia(4), Czech Republic(5), Argentina(11), Romania(12), Bulgaria(5), Greece(4), Serbia(8)

Objectives:

Primary objective
To demonstrate the non-inferiority of QVA149 (110/50 µg o.d.) on post-dose trough forced expiratory volume in 1 second (FEV1) versus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) after 26 weeks of treatment in moderate-to-severe COPD patients.

Secondary objectives

- To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over 26 weeks of treatment in terms of:
    - Rate of moderate or severe COPD exacerbations requiring:
- Systemic glucocorticosteroids and/or antibiotics during the Treatment Epoch (moderate exacerbations only)
- Hospitalizations during the Treatment Epoch and re-hospitalization within 30 days during the

  - Treatment Epoch (severe exacerbations only)
- To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of:
  - Trough FEV1 and forced vital capacity (FVC) over 26 weeks of treatment
- Total score of the St. George's respiratory questionnaire for COPD (SGRQ-C) after 12 and 26 weeks of treatment
  - Total score of the transitional dyspnea index (TDI) after 12 and 26 weeks of treatment
  - Mean use of rescue medication (number of puffs/day) and the percentage of days without rescue medication over the 26-week Treatment Epoch
- To assess the safety (particularly with regard to electrocardiogram (ECG), laboratory tests,
- vital signs, and adverse events [AEs]) and tolerability (discontinuations due to AEs) of QVA149 (110/50 µg o.d.) versus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over the 26 weeks of treatment
- To assess the safety of QVA149 (110/50 µg o.d.) versus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of function of the hypothalamic-pituitary-adrenal axis as determined by 24-hour weighted mean urine cortisol in a subset of patients

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

- QVA149 110/50 µg capsules o.d. for inhalation, supplied in blisters delivered via Novartis single-dose dry-powder inhaler
- Salmeterol/fluticasone propionate FDC 50/500 µg placebo b.i.d. provided as dry inhalation powder via Accuhaler™
- Tiotropium 18 µg placebo o.d. provided as inhalation capsules delivered via HandiHaler®

QVA149 110/50 µg o.d. was provided as inhalation capsules. Placebo inhalation capsules were equally matched in size, shape and color to QVA149 110/50 µg o.d. inhalation capsules

Statistical Methods

Analysis of the primary variable

The primary variable was the mean change from baseline in post-dose trough FEV1 after 26 weeks of treatment. It was analyzed using a mixed-effect model for repeated measures (MMRM), which included fixed, categorical effects of treatment and visit, country/region, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction.

Analysis of the secondary variables

COPD exacerbations

The number of moderate or severe COPD exacerbations during the Treatment Epoch was summarized by treatment group, as continuous variables and as categorical variables classified into 0, 1, 2, 3, ≥ 4 events.

The rate of moderate or severe COPD exacerbations during the Treatment Epoch was analyzed using a generalized linear model that assumed a negative binomial distribution. The time at risk for a patient was the length of time exposed to study treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Patients who have signed Informed Consent Form prior to initiation of any study-related procedure.
- Male and female adults aged ≥ 40 years.
- Patients with moderate to severe airflow obstruction with stable COPD (Stage 2 or Stage 3) according to the 2014 GOLD Guidelines.
- Patients with a post-bronchodilator FEV1 ≥40 and < 80% of the predicted normal value, and post-bronchodilator FEV1/FVC < 0.70 at run-in Visit 101. (Post refers to 15 min after inhalation of 400 µg of salbutamol).
- Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at screening.
- Patients who are on triple treatment at least for the last 6 months (LAMA +LABA/ICS).

Exclusion Criteria:
- Patients who have not achieved acceptable spirometry results at Visit 101 in accordance with ATS (American Thoracic Society)/ERS (European Respiratory Society) criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria) .
- Patients who have had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or

hospitalization in the last year prior to Visit 1.
- Patients who developed a COPD exacerbation of any severity either 6 weeks before the screening (Visit 1) or between screening (Visit 1) and treatment (Visit 201) 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.

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	QVA149	Tiotropium + salmeterol/fluticasone
Started	527	526
Completed	456	472
Not Completed	71	54
Patient/guardian decision	32	18
Adverse Event	17	15
Technical problems	4	7
Lack of Efficacy	7	2
Death	3	4
Physician Decision	3	3
Protocol deviation	2	3
Lost to Follow-up	1	2
Non-compliance with study treatment	1	0

Sponsor decision	1	0

Baseline Characteristics

	QVA149	Tiotropium + salmeterol/fluticasone	Total
Number of Participants [units: participants]	527	526	1053
Age Continuous (units: Years) Mean ± Standard Deviation			
	65.4±7.99	65.2±7.62	65.3±7.80
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	149	161	310
Male	378	365	743
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)			
American Indian or Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	526	523	1049
More than one race	0	0	0

Unknown or Not Reported	1	0	1

Summary of Efficacy

Primary Outcome Result(s)

Mean change from baseline in post-dose trough FEV1

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Mean change from baseline in post-dose trough FEV1 (units: Liters) Least Squares Mean ± Standard Error		
	-0.029 ± 0.0119	-0.003 ± 0.0115

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
Non-Inferiority/Equivalence Test		Non-inferiority will be demonstrated if the 95% confidence interval of the treatment difference lies entirely to the right of (higher than) –50 mL.

P Value	0.0404	1 sided
Method	Other Mixed Model for Repeated Measures Analys	
Mean Difference (Final Values)	-0.026	
95 % Confidence Interval	-0.053 to 0.001	

Secondary Outcome Result(s)

Annualized rate of moderate or severe COPD exacerbations

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Annualized rate of moderate or severe COPD exacerbations (units: COPD exacerbations/year) Number (95% Confidence Interval)		
	0.52 (0.43 to 0.63)	0.48 (0.40 to 0.58)

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone

P Value	0.5802	2 sided
Method	Other Generalized Linear Model Analysis	
Other Ratio of rates	1.08	
95 % Confidence Interval	0.83 to 1.40	

Annualized Rate of COPD exacerbations requiring treatment with systemic glucocorticosteroids and/or antibiotics, moderate exacerbations only

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Annualized Rate of COPD exacerbations requiring treatment with systemic glucocorticosteroids and/or antibiotics, moderate exacerbations only (units: COPD Exacerbations/year) Number (95% Confidence Interval)		
	0.47 (0.39 to 0.58)	0.44 (0.36 to 0.53)

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone

P Value	0.5651	2-sided
Method	Other Generalized Linear Model Analysis	
Other Ratio of rates	1.08	
95 % Confidence Interval 2-Sided	0.82 to 1.43	

Annualized Rate of COPD exacerbations requiring hospitalisation

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Annualized Rate of COPD exacerbations requiring hospitalisation (units: COPD Exacerbations/year) Number (95% Confidence Interval)		
	0.001 (0.0 to NA)[1]	0.001 (0.00 to NA)[1]

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.9665	2-sided
Method	Other Generalized Linear Model Analysis	

Other Ratio of rates	1.02
95 % Confidence Interval 2-Sided	0.44 to 2.34

Mean change from baseline in pre-dose trough FEV1

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Mean change from baseline in pre-dose trough FEV1 (units: Liters) Least Squares Mean ± Standard Error		
	-0.029 ± 0.0119	-0.003 ± 0.0115

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.0573	2-Sided
Method	Other Mixed Model for Repeated Measures Analys	
Mean Difference (Final Values)	-0.026	

95 % Confidence Interval	-0.053 to 0.001

Mean change from baseline in St. George's Respiratory Questionnaire

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Mean change from baseline in St. George's Respiratory Questionnaire (units: Score on a scale) Least Squares Mean ± Standard Error		
	-0.7 ± 0.53	-2.5 ± 0.51

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.0022	2-Sided
Method	Other Mixed Model for Repeated Measures Analys	
Mean Difference (Final Values)	1.8	
95 % Confidence Interval	0.7 to 3.0	

Mean change from baseline in St. George's Respiratory Questionnaire

	QVA149	Tiotropium + salmeterol/fluticasone
Number of Participants Analyzed [units: participants]	527	526
Mean change from baseline in St. George's Respiratory Questionnaire (units: Score on a scale) Least Squares Mean ± Standard Error		
	-1.0 ± 0.54	-2.5 ± 0.52

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.0221	2-Sided
Method	Other Mixed Model for Repeated measures Analys	
Mean Difference (Final Values)	1.4	
95 % Confidence Interval 2-Sided	0.2 to 2.6	

Transition Dyspnea Index (TDI) score

	QVA149	Tiotropium + salmeterol/fluticasone

Number of Participants Analyzed [units: participants]	527	526
Transition Dyspnea Index (TDI) score (units: Score on a scale) Least Squares Mean ± Standard Error		
	1.177 ± 0.1558	1.418 ± 0.1508

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone
P Value	0.1724
Method	Other Mixed Model for Repeated Measures Analys
Mean Difference (Final Values)	-0.241
95 % Confidence Interval	-0.587 to 0.105

Transition Dyspnea Index (TDI) score

	QVA149	**Tiotropium + salmeterol/fluticasone**
Number of Participants Analyzed [units: participants]	527	526
Transition Dyspnea Index (TDI) score		

(units: Score on a scale) Least Squares Mean ± Standard Error		
	1.382 ± 0.1567	1.671 ± 0.1519

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.1055	2-Sided
Method	Other Mixed Model for Repated Measures Analysi	
Mean Difference (Final Values)	-0.288	
95 % Confidence Interval	-0.638 to 0.061	

Change from baseline in the mean daily number of puffs of rescue medication

	QVA149	**Tiotropium + salmeterol/fluticasone**
Number of Participants Analyzed [units: participants]	527	526
Change from baseline in the mean daily number of puffs of rescue medication (units: Number of puffs per day) Least Squares Mean ± Standard Error		

	-0.307 ± 0.1006	-0.484 ± 0.0983

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.0641	2-Sided
Method	Other Linear Mixed Model Analysis	
Mean Difference (Final Values)	0.177	
95 % Confidence Interval	-0.010 to 0.365	

Mean change From baseline in Forced Vital Capacity (FVC)

	QVA149	**Tiotropium + salmeterol/fluticasone**
Number of Participants Analyzed [units: participants]	527	526
Mean change From baseline in Forced Vital Capacity (FVC) (units: Liters) Least Squares Mean ± Standard Error		
	-0.030 ± 0.0192	-0.048 ± 0.0186

Statistical Analysis

Groups	QVA149, Tiotropium + salmeterol/fluticasone	
P Value	0.4107	2-Sided
Method	Other Mixed Model for Repeated Measures Analys	
Mean Difference (Final Values)	0.018	
95 % Confidence Interval 2-Sided	-0.025 to 0.061	

Summary of Safety

Safety Results

All-Cause Mortality

	QVA149 N = 527	Tio+Salm/flut N = 526
Total participants affected	4 (0.76%)	5 (0.95%)

Serious Adverse Events by System Organ Class

Time Frame The study consists of four epochs: screening (1 week), run-in (4 weeks), blinded treatment (26 weeks) and follow-up (4 weeks).

Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment

	QVA149 N = 527	Tio+Salm/flut N = 526
Total participants affected	32 (6.07%)	34 (6.46%)
Blood and lymphatic system disorders		
Haemorrhagic anaemia	0 (0.00%)	1 (0.19%)
Cardiac disorders		
Acute myocardial infarction	2 (0.38%)	0 (0.00%)
Angina unstable	1 (0.19%)	0 (0.00%)
Atrial fibrillation	1 (0.19%)	1 (0.19%)
Cardiac arrest	0 (0.00%)	1 (0.19%)
Cardiac failure	1 (0.19%)	0 (0.00%)
Cardiac failure acute	0 (0.00%)	1 (0.19%)
Cardiac tamponade	1 (0.19%)	0 (0.00%)
Myocardial infarction	2 (0.38%)	2 (0.38%)
Myocardial ischaemia	1 (0.19%)	0 (0.00%)
Endocrine disorders		
Inappropriate antidiuretic hormone secretion	1 (0.19%)	0 (0.00%)
Gastrointestinal disorders		

Anal fissure	0 (0.00%)	1 (0.19%)
Duodenal ulcer	0 (0.00%)	1 (0.19%)
Haemorrhoids	0 (0.00%)	1 (0.19%)
Inguinal hernia	1 (0.19%)	0 (0.00%)
General disorders and administration site conditions		
Non-cardiac chest pain	1 (0.19%)	0 (0.00%)
Pyrexia	0 (0.00%)	1 (0.19%)
Hepatobiliary disorders		
Cholelithiasis	1 (0.19%)	0 (0.00%)
Drug-induced liver injury	1 (0.19%)	0 (0.00%)
Infections and infestations		
Appendicitis	1 (0.19%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	1 (0.19%)
Ophthalmic herpes zoster	0 (0.00%)	1 (0.19%)
Pneumonia	4 (0.76%)	3 (0.57%)
Soft tissue infection	1 (0.19%)	0 (0.00%)
Upper respiratory tract infection	1 (0.19%)	0 (0.00%)
Injury, poisoning and procedural complications		
Femoral neck fracture	1 (0.19%)	0 (0.00%)
Multiple injuries	1 (0.19%)	0 (0.00%)

Musculoskeletal and connective tissue disorders		
Systemic lupus erythematosus	0 (0.00%)	1 (0.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder neoplasm	0 (0.00%)	1 (0.19%)
Cholesteatoma	0 (0.00%)	1 (0.19%)
Colon cancer	1 (0.19%)	0 (0.00%)
Colon neoplasm	1 (0.19%)	0 (0.00%)
Lung neoplasm	0 (0.00%)	1 (0.19%)
Lung neoplasm malignant	0 (0.00%)	2 (0.38%)
Metastases to central nervous system	0 (0.00%)	1 (0.19%)
Pituitary tumour benign	1 (0.19%)	0 (0.00%)
Prostate cancer	0 (0.00%)	1 (0.19%)
Renal neoplasm	0 (0.00%)	1 (0.19%)
Nervous system disorders		
Cerebral haemorrhage	1 (0.19%)	0 (0.00%)
Ischaemic stroke	0 (0.00%)	1 (0.19%)
Syncope	0 (0.00%)	1 (0.19%)
Renal and urinary disorders		
Renal failure	1 (0.19%)	0 (0.00%)

Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	1 (0.19%)	0 (0.00%)
Chronic obstructive pulmonary disease	12 (2.28%)	13 (2.47%)
Dyspnoea	0 (0.00%)	1 (0.19%)
Hypoxia	1 (0.19%)	0 (0.00%)
Pneumothorax	0 (0.00%)	1 (0.19%)
Pulmonary embolism	0 (0.00%)	1 (0.19%)
Skin and subcutaneous tissue disorders		
Erythema multiforme	1 (0.19%)	0 (0.00%)
Vascular disorders		
Aortic aneurysm	0 (0.00%)	1 (0.19%)
Aortic aneurysm rupture	0 (0.00%)	1 (0.19%)
Aortic dissection	0 (0.00%)	1 (0.19%)
Deep vein thrombosis	0 (0.00%)	1 (0.19%)
Orthostatic hypotension	1 (0.19%)	0 (0.00%)
Peripheral arterial occlusive disease	0 (0.00%)	1 (0.19%)
Peripheral artery occlusion	0 (0.00%)	1 (0.19%)
Peripheral artery stenosis	1 (0.19%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	The study consists of four epochs: screening (1 week), run-in (4 weeks), blinded treatment (26 weeks) and follow-up (4 weeks).
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	1%

	QVA149 N = 527	Tio+Salm/flut N = 526
Total participants affected	398 (75.52%)	392 (74.52%)
Cardiac disorders		
Atrioventricular block first degree	1 (0.19%)	6 (1.14%)
Gastrointestinal disorders		
Diarrhoea	3 (0.57%)	6 (1.14%)
General disorders and administration site conditions		
Non-cardiac chest pain	3 (0.57%)	6 (1.14%)
Oedema peripheral	7 (1.33%)	3 (0.57%)
Infections and infestations		
Bronchitis	13 (2.47%)	5 (0.95%)
Influenza	6 (1.14%)	6 (1.14%)
Oral candidiasis	12 (2.28%)	18 (3.42%)
Oropharyngeal candidiasis	6 (1.14%)	7 (1.33%)
Pneumonia	2 (0.38%)	6 (1.14%)

Respiratory tract infection viral	1 (0.19%)	6 (1.14%)
Upper respiratory tract infection bacterial	2 (0.38%)	6 (1.14%)
Urinary tract infection	7 (1.33%)	1 (0.19%)
Viral upper respiratory tract infection	57 (10.82%)	59 (11.22%)
Investigations		
Blood creatinine increased	26 (4.93%)	24 (4.56%)
Musculoskeletal and connective tissue disorders		
Back pain	8 (1.52%)	9 (1.71%)
Pain in extremity	2 (0.38%)	6 (1.14%)
Nervous system disorders		
Headache	7 (1.33%)	13 (2.47%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	370 (70.21%)	353 (67.11%)
Cough	24 (4.55%)	15 (2.85%)
Oropharyngeal pain	7 (1.33%)	7 (1.33%)
Vascular disorders		
Hypertension	7 (1.33%)	10 (1.90%)

Other Relevant Findings

None

Conclusion:

Non-inferiority of QVA149 o.d. versus tiotropium o.d. + salmeterol/fluticasone propionate FDC b.i.d. on post-dose trough FEV1 after 26 weeks of treatment in moderate-to-severe COPD patients on long term triple therapy and up to 1 exacerbation in the previous year could not be demonstrated

- The effect of QVA149 was similar to that of tiotropium o.d. + salmeterol/fluticasone propionate FDC b.i.d. over 26 weeks of treatment in terms of annualized rate of moderate and severe COPD exacerbations including those requiring systemic glucocorticosteroids and/or antibiotics and hospitalizations
- Patients with high blood eosinophil cell count at baseline (≥ 300 cells/µL) may benefit the most from treatment with tiotropium o.d. + salmeterol/fluticasone propionate FDC b.i.d. as judged by the differences observed between groups in the changes from baseline in pre-dose trough FEV1 over 26 weeks of treatment
- Both treatments elicited an improvement in the health status of patients with no clinically meaningful differences as judged by the decrease from baseline in SGRQ-C scores
- The effects of QVA149 o.d. and tiotropium o.d. + salmeterol/fluticasone propionate FDC b.i.d. over 26 weeks of treatment were similar in terms of:

- Trough FVC
- Total TDI score
- Mean use of rescue medication and percentage of days without rescue medication

- Treatment with QVA149 o.d. or tiotropium o.d. + salmeterol/fluticasone propionate FDC during 26 weeks was safe and well tolerated, as judged by the low number of AEs and SAEs reported
- Treatment with QVA149 or tiotropium o.d. + salmeterol/fluticasone propionate FDC b.i.d. resulted in preservation of the hypothalamic-pituitary-adrenal axis function in a subset of randomly selected patients

Date of Clinical Trial Report

12Apr2018