Sponsor

Novartis

Generic Drug Name

Indacaterol/glycopyrronium

Therapeutic Area of Trial

Chronic obstructive pulmonary disease (COPD)

Approved Indication

Investigational

Protocol Number

CQVA149A2304

Title

A 64-week treatment, multi-center, randomized, double-blind, parallel-group, active controlled study to evaluate the effect of QVA149 (110/50 µg q.d.) vs NVA237 (50 µg q.d.) and open-label tiotropium (18 µg q.d.) on COPD exacerbations in patients with severe to very severe chronic obstructive pulmonary disease

Study Phase

Phase III

Study Start/End Dates

27 Apr 2010 to 11 Jul 2012

Study Design/Methodology

Multi-center, double-blind, parallel-group, active controlled study to evaluate the efficacy and safety of QVA149 (110/50 µg q.d.), NVA237 (50 µg q.d.) or open-label (OL) tiotropium (18 µg q.d.) in patients with severe to very severe Chronic obstructive pulmonary disease (COPD). The study's primary objective was to demonstrate that QVA149 was superior to NVA237 with regard to the rate of moderate to severe COPD exacerbations over the treatment period. At the end of a 2 week run-in period patients were randomized to 52 weeks of double blind treatment with a study continuation period up to 64 weeks. The study consisted of 3 periods: pre-randomization, double-blind treatment, and the variable double-blind treatment period. There was a 30 day follow-up period at the end of the trial to assess survival. All study treatments were given in addition to permitted COPD background therapy.

Centers

362 centers in 27 countries. Argentina (35), Austria (5), Canada (9), Colombia (8), Czech Republic (18), Denmark (7), Estonia (3), Finland (3), France (5), Germany (50), United Kingdom (18), Greece (11), Hungary (11), India (14), Ireland (5), Israel (9), Italy (16), Mexico

(6), Netherlands (13), Peru (7), Philippines (6), Poland (7), Russia (18), Slovakia (10), South Africa (5), Spain (5), United States (58).

Publication

Jadwiga A Wedzicha, Marc Decramer, Joachim H Ficker, Dennis E Niewoehner, Thomas Sandström, Angel Fowler Taylor, Peter D'Andrea, Christie Arrasate, Hungta Chen, Donald Banerji. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. The Lancet Respiratory Medicine, Published online, 23 April 2013.

http://dx.doi.org/10.1016/S2213-2600(13)70052-3

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

QVA149 was administered at a dose of 110/50 µg daily delivered via the Novartis single dose dry powder inhaler (SDDPI). NVA237 was delivered at a dose of 50 µg daily via the Novartis SDDPI device. Tiotropium was administered daily and provided open-label in the manufacturer device.

Statistical Methods

This study was designed to demonstrate that QVA149 (110/50 µg q.d.) is superior to NVA237 (50 µg q.d.) with regard to the rate of moderate to severe COPD exacerbations during the treatment period, in patients with severe to very severe COPD. Data were analyzed by Novartis Integrated Information Sciences (IIS) associates according to a data analysis plan included in the protocol and study report.

Analysis sets:

- The Randomized (RAN) Set was comprised of all randomized patients, regardless of whether or not they actually received study medication. Patients in RAN were analyzed according to the treatment they were randomized to receive.
- The Full Analysis Set (FAS) included all randomized patients who received at least one dose of study drug. Following the intention-to-treat principle, patients in the FAS were analyzed according to the treatment they were randomized to receive.
- Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from site 820, which had major issues with GCP compliance; site was terminated, health authorities notified and data from these nine patients have been excluded from certain analyses due to concerns with validity. All efficacy endpoints, unless otherwise stated were analyzed using mFAS. The FAS was used only for sensitivity analysis of the primary variable.
- Per-protocol Set (PPS) included all patients in the mFAS without any major protocol deviations. Patients were analyzed according to the treatment they were randomized to receive. If a patient incorrectly took more than one treatment, he/she was deemed to have a non-protocol deviation and was excluded from the PP set. Major protocol deviations were defined prior to database lock and unblinding of the study.
- Safety Set (SAF) included all patients who received at least one dose of study drug whether or not they were randomized. Patients were analyzed according to the treatment they received,

regardless of whether or not this was the treatment they were randomized to receive. However, if patients switched treatment during the study, they were analyzed according to the treatment they were randomized to receive.

- Modified Safety Set (mSAF) included all patients in the Safety set except patients from site 820 who had major GCP compliance issues. The modified safety set was used in the analysis of all safety endpoints.

The numbers of patients screened, randomized, completed and discontinued are summarized for all patients, by country and center. The overall numbers of patients who were screened, randomized, completed the treatment phase and discontinued from the treatment phase were also summarized with reasons for discontinuation. A listing is provided with patient randomization number and completion status, with date of last dose and primary reason for discontinuation, including unblinding date if applicable. Misrandomized patients and forced randomizations are flagged.

Protocol deviations are tabulated by category and deviation. Protocol deviations are listed with date and study day of occurrence, deviation and severity codes.

The number of patients included in each analysis set is tabulated. Reasons for exclusion from analysis sets are tabulated for all patients. A listing of patients excluded from the analysis sets is provided with reasons for exclusion (i.e. including both protocol and non-protocol deviations). Moreover, patients who discontinued the post treatment follow-up are summarized by reason of discontinuation.

Patient demographics and other baseline characteristics were summarized, treatments (study drug, rescue medication, other concomitant therapies and compliance) were summarized using the modified safety set.

Analysis of primary variable

Moderate or severe COPD exacerbations were adjudicated by an independent adjudication committee of three pulmonologists. These events were adjudicated as to whether they were true independent moderate or severe COPD exacerbations or relapses/continuation of the previous events.

The primary analysis variable was the number of adjudicated moderate or severe COPD exacerbations during the treatment period, (period between the first day of the study drug administration to the last day of the study drug administration). In this study, the cause of mortality was adjudicated for patients who died during the study. If the adjudicated cause of death was COPD exacerbation, and this event was not captured in the eCRF page (e.g. patient died before reaching hospital) as severe or moderate COPD exacerbation then one event was added to the total number of moderate or severe COPD exacerbations counts of the patient who died.

The number of moderate or severe COPD exacerbations prior-to-adjudication i.e. number of moderate or severe COPD exacerbation as reported in the eCRF was analyzed as sensitivity analysis.

The primary efficacy analysis was performed on the mFAS.

The model included terms for treatment, smoking status at baseline, medication history of inhaled corticosteroid (ICS) use, and country as fixed effects. The model also contained the baseline daily total symptom score, baseline COPD exacerbation history (the number of COPD exacerbations in the year prior to screening), FEV_1 prior to inhalation and FEV_1 60 min post inhalation of two short acting bronchodilators (components of reversibility at Visit 2) as covariates.

The primary analysis was done without imputation. Patients who discontinued prematurely were followed-up till the end of the study (i.e. 64-weeks period). During the post treatment follow-up, adverse events including COPD exacerbations were collected. For these patients, moderate or severe COPD exacerbations that occurred within 14 days of the last treatment date were added to the number of COPD exacerbations (adjudicated events) that occurred prior to discontinuation from the study. As a sensitivity analysis, this augmented count of exacerbations was re-analyzed using a generalized linear model the same way as the primary analysis.

Safety

The assessment of safety included all safety measurements including adverse events and COPD exacerbations, however, particular attention was paid to the key safety variables for this class of drug, namely increased heart rate, increased blood pressure, cardio- and cerebrovascular events (major cerebrovascular events, cardiac arrhythmias, atrial fibrillation/flutter), diabetes and hyperglycemia, QTc prolongation, paradoxical bronchospasm, dry mouth, glaucoma/increased intraocular pressure, urinary outflow obstruction, urinary retention, constipation and gastrointestinal hypomotility and tachyarrhythmias.

All safety endpoints were summarized by treatment for patients in the modified safety set (mSAF).

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Male or female adults aged ≥40 years, who had signed an informed consent form prior to initiation of any study-related procedure.
2. Patients with severe to very severe Chronic Obstructive Pulmonary Disease COPD (Stage III or IV) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines 2008.
3. Current or ex-smokers with a smoking history of at least 10 pack years (Ten pack-years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years).
4. Patients with a post-bronchodilator Forced Expiratory Volume in one second (FEV1) <50% of the predicted normal value, and post-bronchodilator FEV1/ Forced Vital Capacity (FVC) <0.70 at Visit 2 (day -14). (Post refers to 1 h after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol).

5. A documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics.

Exclusion Criteria:

1. Pregnant women or nursing mothers (pregnancy confirmed by positive urine pregnancy test).
2. Women of child-bearing potential
3. Patients requiring long term oxygen therapy (> 15 h a day) on a daily basis for chronic hypoxemia.
4. Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the 6 weeks prior to visit 1 or between visit 1 (Day -21) and Visit 3 (Day 1).
5. Patients who developed a COPD exacerbation during a period between visit 1 and 3 were ineligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
6. Patients who had a respiratory tract infection within 4 weeks prior to visit 1 (Day -21)

   • Patients who developed an upper or lower respiratory tract infection during the screening period (up to visit 3 (Day 1) were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection
7. Patients with concomitant pulmonary disease, e.g. pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), clinically significant bronchiectasis, sarcoidosis, interstitial lung disorder or pulmonary hypertension.
8. Patients with lung lobectomy, or lung volume reduction or lung transplantation.
9. Patients who, in the judgment of the investigator, have a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to):
   - Unstable ischemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable Atrial Fibrillation (AF). Patients with such events not considered clinically significant by the investigator may be considered for inclusion in the study
   - history of malignancy of any organ system (including lung cancer), 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
   - uncontrolled hypo- or hyperthyroidism, hypokalemia or hyper adrenergic state
   - narrow-angle glaucoma
   - Symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. (Patients with a Transurethral Resection of Prostate (TURP) were excluded from the study. Patients who underwent full re-section of the prostate could be considered

for the study, as well as patients who were asymptomatic and stable on pharmacological treatment for the condition).

- any condition which might have compromised patient safety or compliance, interfered with evaluation, or precluded completion of the study

10. Patients with any history of asthma indicated by (but not limited to) a blood eosinophil count > 600/mm3 (at visit 2), or onset of symptoms prior to 40 years. Patients without asthma were excluded if their eosinophil count was >600/mm3 at visit 2.
11. Patients with allergic rhinitis who used H1 antagonists or intranasal corticosteroids intermittently (treatment with a constant dose was permitted).
12. Patients with eczema (atopic), known high IgE levels or a known positive skin prick test in the last 5 years.
13. Patients with known history and diagnosis of alpha-1 antitrypsin deficiency.
14. Patients who were participating in the active phase of a supervised pulmonary rehabilitation program.
15. Patients with Type I or uncontrolled Type II diabetes.
16. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs or drugs of a similar class or any component thereof:
    - anticholinergic agents
    - long and short acting beta-2 agonists
    - sympathomimetic amines.
17. Patients with a history of long QT syndrome or whose QTc measured at visit 2 (Day -14) (Fridericia method) was prolonged (>450 ms for males and females) as confirmed by the central ECG assessor.
18. Patients with a clinically significant abnormality on the screening or baseline ECG who in the judgment of the investigator would be at potential risk if enrolled into the study. (These patients could not be re-screened).
19. Patients who needed treatments for COPD and allied conditions after the start of the study (visit 1)
20. Patients who needed treatments for COPD and allied conditions (e.g. allergic rhinitis) unless they had been stabilized
21. Patients taking other prohibited medications
22. Patients unable to use a dry powder inhaler (e.g. single dose dry powder inhaler (SDDPI), HandiHaler® device, or pressurized Metered Dose Inhaler MDI (rescue medication).
23. Patients unable to use an electronic patient diary.
24. Patients who were, in the opinion of the investigator known to be unreliable or non-compliant.

25. Patients who used other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of visit 1 (day -21), whichever was longer.
26. Patients who had live attenuated vaccination within 30 days prior to the screening visit or during the run-in period. Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine was acceptable provided it was not administered within 48 hours prior to screening and randomization visits.

No additional exclusions were applied by the investigator, in order to ensure that the study population was representative of all eligible patients.

Participant Flow

Patient disposition (All patients)

Disposition Reason	QVA149 n (%)	NVA237 n (%)	Tio n (%)	Total n (%)
Screened				3865
Randomized	741 (100)	741 (100)	742 (100)	2224 (100)
Completed	570 (76.9)	538 (72.6)	559 (75.3)	1667 (75.0)
Discontinued	171 (23.1)	203 (27.4)	183 (24.7)	557 (25.0)
Primary reason for premature discontinuation				
Adverse event(s)	59 (8.0)	67 (9.0)	47 (6.3)	173 (7.8)
Subject withdrew consent	33 (4.5)	50 (6.7)	44 (5.9)	127 (5.7)
Death	21 (2.8)	22 (3.0)	24 (3.2)	67 (3.0)
Unsatisfactory therapeutic effect	18 (2.4)	32 (4.3)	38 (5.1)	88 (4.0)
Administrative problems	15 (2.0)	8 (1.1)	9 (1.2)	32 (1.4)
Protocol deviation	13 (1.8)	12 (1.6)	12 (1.6)	37 (1.7)
Lost to follow-up	5 (0.7)	6 (0.8)	4 (0.5)	15 (0.7)
Abnormal test procedure result(s)	3 (0.4)	2 (0.3)	1 (0.1)	6 (0.3)
Patient's inability to use the device	3 (0.4)	1 (0.1)	0	4 (0.2)
Abnormal laboratory value(s)	1 (0.1)	3 (0.4)	4 (0.5)	8 (0.4)

Patient disposition during the post treatment follow-up (All patients)

Disposition Reason	QVA149 n (%)	NVA237 n (%)	Tio n (%)	Total n (%)
Randomized	741 (100)	741 (100)	742 (100)	2224 (100)
Completed post treatment follow-up	642 (86.6)	626 (84.5)	626 (84.4)	1894 (85.2)
Discontinued post treatment follow-up	98 (13.2)	115 (15.5)	115 (15.5)	328 (14.7)
Primary reason for premature discontinuation				
Subject withdrew consent	45 (6.1)	50 (6.7)	52 (7.0)	147 (6.6)
Deaths (total)*	30 (4.0)	28 (3.8)	29 (3.9)	87 (3.9)
Deaths during treatment period	23 (3.2)	22 (3.0)	25 (3.4)	70 (3.1)
Deaths during post-treatment follow-up period#	7 (1.0)	6 (0.8)	4 (0.5)	17 (0.8)
Administrative problems	14 (1.9)	23 (3.1)	19 (2.6)	56 (2.5)
Lost to follow-up	8 (1.1)	14 (1.9)	15 (2.0)	37 (1.7)

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Baseline Characteristics

Demographics (mSAF set)

Variable	Statistic	QVA149 N=729	NVA237 N=740	Tio N=737	Total N=2206
Age (years)	n	729	740	737	2206
	Mean (SD)	63.1 (8.07)	63.1 (7.98)	63.6 (7.79)	63.3 (7.95)
	Median	63.0	63.0	64.0	63.0
	Min - Max	42 - 83	40 - 90	42 - 88	40 - 90
Age					
<65 years	n (%)	417 (57.2)	415 (56.1)	387 (52.5)	1219 (55.3)
65 - <75 years	n (%)	249 (34.2)	274 (37.0)	296 (40.2)	819 (37.1)
≥ 75 years	n (%)	63 (8.6)	51 (6.9)	54 (7.3)	168 (7.6)
Gender					
Male	n (%)	556 (76.3)	542 (73.2)	553 (75.0)	1651 (74.8)
Female	n (%)	173 (23.7)	198 (26.8)	184 (25.0)	555 (25.2)
Race					
Caucasian	n (%)	594 (81.5)	605 (81.8)	613 (83.2)	1812 (82.1)
Black	n (%)	4 (0.5)	5 (0.7)	7 (0.9)	16 (0.7)
Asian	n (%)	89 (12.2)	92 (12.4)	79 (10.7)	260 (11.8)
Native American	n (%)	8 (1.1)	4 (0.5)	7 (0.9)	19 (0.9)
Pacific Islander	n (%)	0	0	0	0
Other	n (%)	34 (4.7)	34 (4.6)	31 (4.2)	99 (4.5)
Ethnicity					
Hispanic/Latino	n (%)	136 (18.7)	145 (19.6)	139 (18.9)	420 (19.0)
Chinese	n (%)	0	1 (0.1)	0	1 (0.0)
Indian (Indian subcontinent)	n (%)	50 (6.9)	55 (7.4)	47 (6.4)	152 (6.9)
Japanese	n (%)	2 (0.3)	0	0	2 (0.1)
Mixed Ethnicity	n (%)	8 (1.1)	7 (0.9)	7 (0.9)	22 (1.0)
Other	n (%)	533 (73.1)	532 (71.9)	544 (73.8)	1609 (72.9)
Weight (kg)	n	729	739	737	2205
	Mean (SD)	72.2 (17.41)	72.4 (18.24)	72.7 (18.95)	72.4 (18.20)
	Median	72.0	70.2	70.0	71.0
	Min - Max	36.0 - 132.7	33.0 - 135.0	33.4 - 154.0	33.0 - 154.0
Height (cm)	n	729	739	737	2205
	Mean (SD)	169.0 (8.88)	168.8 (8.85)	168.5 (8.87)	168.8 (8.86)
	Median	169.0	169.0	169.0	169.0
	Min - Max	145.0 - 195.0	143.0 - 196.0	143.0 - 195.0	143.0 - 196.0
Body mass index (kg/m^2)	n	729	739	737	2205
	Mean (SD)	25.1 (5.14)	25.3 (5.43)	25.4 (5.77)	25.3 (5.45)
	Median	25.0	24.6	24.7	24.8
	Min - Max	13.7 - 41.9	12.9 - 44.3	13.7 - 56.2	12.9 - 56.2
Body mass index					
≤ 30.0 kg/m^2	n (%)	616 (84.5)	599 (80.9)	600 (81.4)	1815 (82.3)
> 30.0 kg/m^2	n (%)	113 (15.5)	140 (18.9)	137 (18.6)	390 (17.7)
Missing	n (%)	0	1 (0.1)	0	1 (0.0)

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Outcome Measures

Primary Outcome Result(s)

Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and NVA237 Treatment Arms during the Treatment Period

	QVA149 N=729	NVA237 N=739	Tio N=737
Number of moderate or severe exacerbations per patient - n (%)			
None	310 (42.5)	313 (42.4)	335 (45.5)
1	202 (27.7)	192 (26.0)	186 (25.2)
2	120 (16.5)	108 (14.6)	88 (11.9)
3	53 (7.3)	61 (8.3)	55 (7.5)
≥ 4	44 (6.0)	65 (8.8)	73 (9.9)
Mean (SD)	1.11 (1.345)	1.22 (1.483)	1.22 (1.659)
Median	1	1	1
Min - Max	0 - 8	0 - 9	0 - 11
Total number of exacerbations	812	900	898
Total number of treatment years	866.93	840.98	848.78
Rate of exacerbations per year	0.94	1.07	1.06
Model based estimates			
Rate (95% CI)	0.84 (0.75, 0.94)	0.95 (0.85, 1.06)	0.93 (0.83, 1.04)
Treatment comparisons	**QVA149 vs. NVA237**	**QVA149 vs. Tio**	**NVA237 vs. Tio**
Ratio of rates	0.88	0.90	1.03
95% CI	(0.77, 0.99)	(0.79, 1.02)	(0.91, 1.16)
p - value	0.038	0.096	0.676

Treatment group comparisons are based on a Negative Binomial model: log (exacerbation rate) = treatment + smoking status + ICS use + baseline COPD exacerbation history + country + baseline total symptom score + FEV_1 reversibility components.
Ratio of rates <1 favors the treatment group in the numerator of the ratio.

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Secondary Outcome Result(s)

Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and Open-label Tiotropium Treatment Arms during the Treatment Period.

	QVA149 N=729	NVA237 N=739	Tio N=737
Summary statistics			
Patients with moderate or severe COPD exacerbation, n (%)	419 (57.5)	426 (57.6)	402 (54.5)
Time-to event (Days)			
25- percentile	83	83	83
95% CI of the 25-percentile	(69, 102)	(67, 97)	(71, 102)
Event-free rates (%)			
at Month 6	60.6	58.9	60.3
95% CI of rate at Month 6	(57.0, 64.2)	(55.3, 62.6)	(56.6, 63.9)
at Month 12	45.6	44.1	47.1
95% CI of rate at Month 12	(41.9, 49.3)	(40.4, 47.9)	(43.3, 50.9)
at Month 15	42.0	38.5	42.9
95% CI of rate at Month 15	(38.3, 45.7)	(34.8, 42.3)	(39.1, 46.7)
at Month 18	36.1	36.0	38.3
95% CI of rate at Month 18	(32.0, 40.2)	(32.1, 39.8)	(34.2, 42.4)
Cox regression analysis	**QVA149 vs. NVA237**	**QVA149 vs. Tio**	**NVA237 vs. Tio**
Hazard ratio	0.93	1.00	1.07
95% CI of hazard ratio	(0.813, 1.070)	(0.870, 1.151)	(0.934, 1.232)
p-value	0.319	0.995	0.319

Patients without COPD exacerbation were censored at the date of the last medication intake.
Event free rates are calculated by the Life Table (LT) method.
The Cox regression model was stratified by country and included the terms for treatment, ICS use, smoking status, baseline COPD exacerbation history, baseline total symptom score, and FEV_1 reversibility components.
A hazard ratio <1 favors the treatment group in the numerator of the ratio.

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Time to First Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbation between QVA149, NVA237 and Open Label Tiotropium during the Treatment Period.

	QVA149 N=729	NVA237 N=739	Tio N=737
Patients with a moderate or severe COPD exacerbation, n/N(%)	419/729 (57.5)	426/739 (57.6)	402/737 (54.5)
Maximum follow-up time (days)	558	550	577
Median follow-up time (days)	260	211	240
Time-to event (days), Percentiles			
25% (95% CI)	83(69, 102)	83(67, 97)	83(71, 102)
Median (95% CI)	296(267, 358)	287(255, 325)	331(280, 390)
75% (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)

Rate of moderate or severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Requiring the Use of both Systemic Glucocorticosteroids and Antibiotics

	QVA149 N=729	NVA237 N=739	Tio N=737
Number of moderate or severe exacerbations per patient - n (%)			
None	466 (63.9)	451 (61.0)	469 (63.6)
1	173 (23.7)	166 (22.5)	160 (21.7)
2	59 (8.1)	69 (9.3)	61 (8.3)
3	18 (2.5)	34 (4.6)	25 (3.4)
≥ 4	13 (1.8)	19 (2.6)	22 (3.0)
Mean (SD)	0.55 (0.919)	0.66 (1.048)	0.63 (1.081)
Median	0	0	0
Min - Max	0 - 6	0 - 6	0 - 8
Total number of exacerbations	403	491	461
Total number of treatment years	866.93	840.98	848.78
Rate of exacerbations per year	0.46	0.58	0.54
Model based estimates			
Rate (95% CI)	0.35 (0.30, 0.41)	0.45 (0.38, 0.52)	0.41 (0.35, 0.47)
Treatment comparisons	**QVA149 vs. NVA237**	**QVA149 vs. Tio**	**NVA237 vs. Tio**
Ratio of rates	0.79	0.87	1.10
95% CI	(0.67, 0.93)	(0.74, 1.02)	(0.94, 1.29)
p - value	0.005	0.094	0.255

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Number of Days With moderate or severe Exacerbation That Required Treatment With Systemic Corticosteroids and Antibiotics

Event	Statistic	QVA149 N=729	NVA237 N=739	Tio N=737
Number of patients with exacerbation that required treatment with systemic corticosteroids	n/N (%)	97/729 (13.3)	108/739 (14.6)	109/737 (14.8)
Number of days with exacerbation that required treatment with systemic corticosteroids	Mean	20.49	25.22	17.57
	SD	25.426	42.674	17.797
	Min	1	1	1
	Q25	7.00	8.00	7.00
	Median	12.00	12.00	11.00
	Q75	22.00	25.00	22.00
	Max	165	363	98

Event	Statistic	QVA149 N=729	NVA237 N=739	Tio N=737
Number of patients with exacerbation that required treatment with antibiotics	n/N (%)	195/729 (26.7)	177/739 (24.0)	177/737 (24.0)
Number of days with exacerbation that required treatment with antibiotics	Mean	25.08	18.10	25.94
	SD	47.035	21.790	50.007
	Min	1	1	1
	Q25	8.00	7.00	7.00
	Median	13.00	11.00	13.00
	Q75	26.00	19.00	23.00
	Max	532	130	406

Event	Statistic	QVA149 N=729	NVA237 N=739	Tio N=737
Number of patients with exacerbation that required treatment with both systemic corticosteroids and antibiotics	n/N (%)	266/729 (36.5)	290/739 (39.2)	270/737 (36.6)
Number of days with exacerbation that required treatment with both systemic corticosteroids and antibiotics	Mean	22.10	26.18	22.03
	SD	49.999	52.336	42.513
	Min	0	0	0
	Q25	0.00	0.00	0.00
	Median	9.00	11.00	11.00
	Q75	23.50	29.00	25.50
	Max	533	514	491

Time to Study Withdrawal or Premature Discontinuation for Any Reason between QVA149 (110/50 µg q.d.), NVA237 (50 µg q.d.) and Open Label Tiotropium (18 µg q.d.) during the Treatment Period.

	QVA149 N=729	NVA237 N=740	Tio N=737
Discontinued patients, n/N(%)	159/729 (21.8)	202/740 (27.3)	178/737 (24.2)
Maximum follow-up time (days)	558	550	587
Time before discontinuation (days)			
25-percentile	541	439	538
95% CI of the 25-percentile	(495,n.e.)	(362,n.e.)	(423,n.e.)
Rate of patients in the study, (%)			
At Month 6	90.0	86.4	87.5
95% CI of rate at Month 6	(87.8-92.2)	(83.9-88.8)	(85.1-89.9)
At Month 12	83.1	77.6	80.3
95% CI of rate at Month 12	(80.4-85.8)	(74.6-80.6)	(77.5-83.2)
At Month 15	80.0	74.3	77.1
95% CI of rate at Month 15	(77.1-82.9)	(71.1-77.4)	(74.0-80.1)
At the end of the study	73.4	58.5	73.4
95% CI of rate at the end of study	(66.0-80.8)	(37.1-79.8)	(68.7-78.1)
Log-rank test			
P-value compared to QVA		0.012	0.222

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Percentage of Patients with Study Withdrawal or Premature Discontinuation for Any Reason Between QVA149 (110/50 µg q.d.), NVA237 (50 µg q.d.) and Open Label Tiotropium (18 µg q.d.) during the Treatment Period

	QVA149 N=729	NVA237 N=740	Tio N=737
Discontinued patients, n/N(%)	159/729 (21.8)	202/740 (27.3)	178/737 (24.2)
Maximum follow-up time (days)	558	550	587
Time before discontinuation (days)			
25-percentile	541	439	538
95% CI of the 25-percentile	(495,n.e.)	(362,n.e.)	(423,n.e.)
Rate of patients in the study, (%)			
At Month 6	90.0	86.4	87.5
95% CI of rate at Month 6	(87.8-92.2)	(83.9-88.8)	(85.1-89.9)
At Month 12	83.1	77.6	80.3
95% CI of rate at Month 12	(80.4-85.8)	(74.6-80.6)	(77.5-83.2)
At Month 15	80.0	74.3	77.1
95% CI of rate at Month 15	(77.1-82.9)	(71.1-77.4)	(74.0-80.1)
At the end of the study	73.4	58.5	73.4
95% CI of rate at the end of study	(66.0-80.8)	(37.1-79.8)	(68.7-78.1)
Log-rank test			
P-value compared to QVA		0.012	0.222

Cumulative Rates of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations for Multiple COPD Exacerbation at Different Time Points

	QVA149 N=729	NVA237 N=739	Tio N=737
Number of moderate or severe COPD exacerbations, n	831	926	897
Total exposure time (years)	866.9	841.0	848.8
Cumulative rates, (95% CI)			
26 weeks	0.57(0.51, 0.62)	0.65(0.58, 0.71)	0.63(0.56, 0.70)
52 weeks	0.99(0.91, 1.09)	1.13(1.03, 1.25)	1.11(1.00, 1.23)
64 weeks	1.19(1.08, 1.30)	1.36(1.24, 1.49)	1.32(1.19, 1.46)
76 weeks	1.39(1.27, 1.53)	1.59(1.45, 1.74)	1.55(1.40, 1.71)
Treatment comparison at the end of study			
vs. NVA237, Rate ratio (95%ci)	0.88(0.78, 1.00)		
p-value	0.049		
vs. Tio, Rate ratio (95%ci)	0.90(0.79, 1.03)	1.02(0.90, 1.16)	
p-value	0.122	0.738	

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Forced Expiratory Volume in 1 Second (FEV-1) After 4, 12, 26, 38, 52 and 64 Weeks of Treatment Between QVA149, NVA237 and Open Label Tiotropium

		Treatment				Treatment difference			
Treatment	n	Baseline Mean	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Visit: Week 4									
QVA149 (N=729)	656	0.90	1.08	0.009	QVA149 - NVA237	0.08	0.009	(0.07, 0.10)	<0.001
					QVA149 - Tio	0.07	0.009	(0.06, 0.09)	<0.001
NVA237 (N=739)	654	0.90	0.99	0.009	NVA237 - Tio	-0.01	0.009	(-0.03, 0.01)	0.260
Tio (N=737)	630	0.91	1.00	0.009					
Visit: Week 12									
QVA149 (N=729)	666	0.91	1.08	0.010	QVA149 - NVA237	0.07	0.010	(0.05, 0.09)	<0.001
					QVA149 - Tio	0.07	0.010	(0.05, 0.09)	<0.001
NVA237 (N=739)	663	0.90	1.01	0.009	NVA237 - Tio	-0.01	0.010	(-0.03, 0.01)	0.466
Tio (N=737)	653	0.90	1.01	0.009					
Visit: Week 26									
QVA149 (N=729)	604	0.92	1.07	0.010	QVA149 - NVA237	0.07	0.011	(0.05, 0.10)	<0.001
					QVA149 - Tio	0.07	0.011	(0.05, 0.09)	<0.001
NVA237 (N=739)	577	0.91	0.99	0.010	NVA237 - Tio	-0.01	0.011	(-0.03, 0.01)	0.469
Tio (N=737)	599	0.91	1.00	0.010					
Visit: Week 38									
QVA149 (N=729)	593	0.92	1.08	0.011	QVA149 - NVA237	0.07	0.012	(0.05, 0.10)	<0.001
					QVA149 - Tio	0.08	0.011	(0.05, 0.10)	<0.001
NVA237 (N=739)	549	0.91	1.00	0.011	NVA237 - Tio	0.00	0.012	(-0.02, 0.02)	0.906
Tio (N=737)	583	0.92	1.00	0.011					
Visit: Week 52									
QVA149 (N=729)	557	0.93	1.05	0.011	QVA149 - NVA237	0.07	0.012	(0.05, 0.09)	<0.001
					QVA149 - Tio	0.06	0.012	(0.04, 0.08)	<0.001
NVA237 (N=739)	538	0.92	0.98	0.011	NVA237 - Tio	-0.01	0.012	(-0.03, 0.02)	0.528
Tio (N=737)	548	0.91	0.99	0.011					
Visit: Week 64									
QVA149 (N=729)	549	0.93	1.05	0.011	QVA149 - NVA237	0.07	0.012	(0.05, 0.10)	<0.001
					QVA149 - Tio	0.06	0.012	(0.03, 0.08)	<0.001
NVA237 (N=739)	504	0.93	0.98	0.011	NVA237 - Tio	-0.02	0.012	(-0.04, 0.01)	0.179
Tio (N=737)	530	0.92	0.99	0.011					

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Forced Vital Capacity (FVC) after 4, 12, 26, 38, 52 and 64 weeks of treatment between QVA149, NVA237 and Open Label Tiotropium

				Treatment			Treatment difference			
Visit	Treatment	n	Baseline Mean	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 4	QVA149 (N=729)	656	2.41	2.74	0.020	QVA149 - NVA237	0.14	0.020	(0.10, 0.18)	<0.001
						QVA149 - Tio	0.13	0.020	(0.10, 0.17)	<0.001
	NVA237 (N=739)	654	2.38	2.59	0.019	NVA237 - Tio	-0.01	0.020	(-0.05, 0.03)	0.757
	Tio (N=737)	630	2.40	2.60	0.019					
Week 12	QVA149 (N=729)	623	2.43	2.77	0.021	QVA149 - NVA237	0.14	0.021	(0.10, 0.18)	<0.001
						QVA149 - Tio	0.12	0.021	(0.08, 0.16)	<0.001
	NVA237 (N=739)	621	2.40	2.63	0.021	NVA237 - Tio	-0.02	0.021	(-0.06, 0.02)	0.384
	Tio (N=737)	619	2.40	2.65	0.021					
Week 26	QVA149 (N=729)	604	2.43	2.73	0.023	QVA149 - NVA237	0.13	0.023	(0.08, 0.17)	<0.001
						QVA149 - Tio	0.11	0.023	(0.07, 0.16)	<0.001
	NVA237 (N=739)	577	2.40	2.60	0.022	NVA237 - Tio	-0.01	0.023	(-0.06, 0.03)	0.567
	Tio (N=737)	599	2.41	2.61	0.022					
Week 38	QVA149 (N=729)	592	2.43	2.76	0.025	QVA149 - NVA237	0.11	0.024	(0.06, 0.16)	<0.001
						QVA149 - Tio	0.12	0.024	(0.08, 0.17)	<0.001
	NVA237 (N=739)	548	2.41	2.65	0.025	NVA237 - Tio	0.02	0.024	(-0.03, 0.06)	0.521
	Tio (N=737)	580	2.41	2.63	0.025					
Week 52	QVA149 (N=729)	557	2.44	2.68	0.025	QVA149 - NVA237	0.09	0.024	(0.04, 0.14)	<0.001
						QVA149 - Tio	0.10	0.024	(0.05, 0.14)	<0.001
	NVA237 (N=739)	538	2.40	2.58	0.025	NVA237 - Tio	0.01	0.024	(-0.04, 0.05)	0.836

ANCOVA model: Pre-dose FVC = treatment + baseline FVC + baseline ICS + FEV1 reversibility components + smoking status + country + center (country). Center is included as a random effect nested within country.
Pre-dose FVC is defined as the average of the -15 min and the -45 min FVC values.
Baseline is defined as the average of the -45 min and -15 min FVC values taken on Day 1 prior to first dose.
FVC data taken within 6h of rescue medication or within 7 days of systemic corticosteroid is excluded from this analysis.

Mean Daily use (# of puffs) of rescue therapy between QVA149, NVA237 and Open Label Tiotropium over the 64 week treatment period

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Analysis of the change from baseline in mean daily, daytime and nighttime number of puffs of rescue medication used ove (mFAS)

Disease severity: Severe or less

Timepoint	Treatment	n	Baseline Mean	-Treatment- LS Mean	SE	Comparison	--------Treatment Difference -------- LS Mean	SE	95% CI	p-value
'TOT_RESC'	QVA149 (N=579)	565	5.40	-2.3	0.137	QVA149 - NVA237	-0.78	0.145	(-1.07,-0.50)	<0.001
						QVA149 - Tio	-0.68	0.146	(-0.97,-0.40)	<0.001
	NVA237 (N=584)	575	5.41	-1.5	0.135	NVA237 - Tio	0.099	0.145	(-0.19,0.38)	0.495
	Tio (N=581)	561	5.24	-1.6	0.136					

Disease severity: Very severe

Timepoint	Treatment	n	Baseline Mean	-Treatment- LS Mean	SE	Comparison	--------Treatment Difference -------- LS Mean	SE	95% CI	p-value
'TOT_RESC'	QVA149 (N=150)	143	6.98	-2.1	0.234	QVA149 - NVA237	-0.94	0.287	(-1.5,-0.37)	0.001
						QVA149 - Tio	-1.05	0.287	(-1.61,-0.48)	<0.001
	NVA237 (N=155)	149	6.89	-1.1	0.228	NVA237 - Tio	-0.11	0.283	(-0.67,0.44)	0.695
	Tio (N=156)	148	6.60	-1.0	0.228					

Percentage of days without rescue therapy use between QVA149,NVA237 and Open Label Tiotropium over the 64 week treatment period

Treatment	n	Baseline Mean	Treatment LS Mean	SE	Comparison	Treatment difference LS Mean	SE	95% CI	p-value
QVA149 (N=729)	701	11.99	29.36	1.445	QVA149 - NVA237	7.71	1.486	(4.79, 10.62)	<0.001
					QVA149 - Tio	5.50	1.491	(2.58, 8.42)	<0.001
NVA237 (N=739)	720	11.90	21.65	1.410	NVA237 - Tio	-2.21	1.484	(-5.12, 0.70)	0.137
Tio (N=737)	703	12.75	23.86	1.422					

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St. George's Respiratory Questionnaire (SGRQ) scores between QVA149, NVA237 and Open Label Tiotropium over 12, 26, 38, 52 and 64 weeks of treatment

		Treatment				Treatment difference			
Treatment	n	Baseline Mean	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Visit: Week 12									
QVA149 (N=729)	694	52.82	44.69	0.612	QVA149 - NVA237	-2.45	0.637	(-3.69, -1.20)	<0.001
					QVA149 - Tio	-2.94	0.639	(-4.19, -1.68)	<0.001
NVA237 (N=739)	694	52.04	47.13	0.603	NVA237 - Tio	-0.49	0.640	(-1.75, 0.76)	0.443
Tio (N=737)	676	52.22	47.62	0.607					
Visit: Week 26									
QVA149 (N=729)	684	52.69	44.06	0.655	QVA149 - NVA237	-1.88	0.667	(-3.19, -0.57)	0.005
					QVA149 - Tio	-1.71	0.669	(-3.02, -0.40)	0.011
NVA237 (N=739)	677	51.73	45.93	0.647	NVA237 - Tio	0.17	0.672	(-1.15, 1.49)	0.803
Tio (N=737)	658	52.11	45.77	0.651					
Visit: Week 38									
QVA149 (N=729)	648	52.42	42.72	0.667	QVA149 - NVA237	-2.81	0.695	(-4.17, -1.44)	<0.001
					QVA149 - Tio	-3.14	0.690	(-4.50, -1.79)	<0.001
NVA237 (N=739)	626	51.27	45.53	0.663	NVA237 - Tio	-0.33	0.697	(-1.70, 1.03)	0.632
Tio (N=737)	635	51.89	45.86	0.660					
Visit: Week 52									
QVA149 (N=729)	625	52.30	43.38	0.722	QVA149 - NVA237	-2.58	0.731	(-4.01, -1.15)	<0.001
					QVA149 - Tio	-2.83	0.721	(-4.25, -1.42)	<0.001
NVA237 (N=739)	593	50.99	45.96	0.723	NVA237 - Tio	-0.25	0.732	(-1.69, 1.18)	0.732
Tio (N=737)	613	51.62	46.21	0.714					
Visit: Week 64									
QVA149 (N=729)	600	52.09	43.39	0.778	QVA149 - NVA237	-2.07	0.762	(-3.57, -0.58)	0.007
					QVA149 - Tio	-2.69	0.754	(-4.17, -1.21)	<0.001
NVA237 (N=739)	564	50.46	45.46	0.780	NVA237 - Tio	-0.62	0.767	(-2.12, 0.89)	0.421
Tio (N=737)	579	51.30	46.08	0.778					

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Safety Results

Adverse events (including COPD exacerbations) overall and by primary system organ class - n (%) of patients (mSAF)

Primary MedDRA system organ class	QVA149 N=729 n (%)	NVA237 N=740 n (%)	Tio N=737 n (%)
Any primary system organ class	**678 (93.0)**	**694 (93.8)**	**686 (93.1)**
Respiratory, thoracic and mediastinal disorders	643 (88.2)	662 (89.5)	653 (88.6)
Infections and infestations	398 (54.6)	402 (54.3)	374 (50.7)
Gastrointestinal disorders	114 (15.6)	89 (12.0)	108 (14.7)
Musculoskeletal and connective tissue disorders	98 (13.4)	82 (11.1)	78 (10.6)
General disorders and administration site conditions	82 (11.2)	86 (11.6)	72 (9.8)
Nervous system disorders	68 (9.3)	72 (9.7)	72 (9.8)
Metabolism and nutrition disorders	53 (7.3)	51 (6.9)	49 (6.6)
Vascular disorders	52 (7.1)	38 (5.1)	44 (6.0)
Injury, poisoning and procedural complications	48 (6.6)	37 (5.0)	44 (6.0)
Cardiac disorders	44 (6.0)	62 (8.4)	50 (6.8)
Skin and subcutaneous tissue disorders	34 (4.7)	31 (4.2)	28 (3.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (3.0)	22 (3.0)	25 (3.4)
Psychiatric disorders	22 (3.0)	20 (2.7)	27 (3.7)
Eye disorders	19 (2.6)	22 (3.0)	24 (3.3)
Renal and urinary disorders	18 (2.5)	24 (3.2)	19 (2.6)
Investigations	16 (2.2)	25 (3.4)	15 (2.0)
Ear and labyrinth disorders	15 (2.1)	12 (1.6)	7 (0.9)
Reproductive system and breast disorders	15 (2.1)	14 (1.9)	9 (1.2)
Blood and lymphatic system disorders	13 (1.8)	11 (1.5)	13 (1.8)
Hepatobiliary disorders	12 (1.6)	5 (0.7)	10 (1.4)
Immune system disorders	6 (0.8)	3 (0.4)	2 (0.3)
Endocrine disorders	5 (0.7)	5 (0.7)	7 (0.9)
Social circumstances	2 (0.3)	0	1 (0.1)
Congenital, familial and genetic disorders	1 (0.1)	0	2 (0.3)
Surgical and medical procedures	0	1 (0.1)	0

Primary system organ classes in descending order of percentage according to the QVA149 group.
A patient with multiple AEs within a primary system organ class is counted only once in the total row. A patient with multiple AEs within multiple primary system organ classes is counted multiple times.
All adverse events starting on or after the time of first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included in the summaries. Adverse events after the last study visit are not included.

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Most frequent AEs, including COPD exacerbations, (at least 1.0% in QVA149 treatment group) by preferred term - n (%) of patients (mSAF)

MedDRA preferred term	QVA149 N=729 n (%)	NVA237 N=740 n (%)	Tio N=737 n (%)
Any preferred term (Total)	**678 (93.0)**	**694 (93.8)**	**686 (93.1)**
Chronic obstructive pulmonary disease	636 (87.2)	651 (88.0)	642 (87.1)
Upper respiratory tract infection bacterial	132 (18.1)	133 (18.0)	115 (15.6)
Nasopharyngitis	98 (13.4)	81 (10.9)	90 (12.2)
Viral upper respiratory tract infection	74 (10.2)	77 (10.4)	75 (10.2)
Lower respiratory tract infection	58 (8.0)	83 (11.2)	77 (10.4)
Cough	41 (5.6)	39 (5.3)	25 (3.4)
Bronchitis	35 (4.8)	38 (5.1)	30 (4.1)
Pneumonia	33 (4.5)	36 (4.9)	34 (4.6)
Hypertension	32 (4.4)	22 (3.0)	26 (3.5)
Headache	30 (4.1)	33 (4.5)	40 (5.4)
Upper respiratory tract infection	28 (3.8)	25 (3.4)	28 (3.8)
Pyrexia	27 (3.7)	25 (3.4)	24 (3.3)
Urinary tract infection	27 (3.7)	20 (2.7)	15 (2.0)
Oropharyngeal pain	26 (3.6)	32 (4.3)	29 (3.9)
Back pain	25 (3.4)	34 (4.6)	36 (4.9)
Dyspnoea	25 (3.4)	44 (5.9)	35 (4.7)
Influenza	23 (3.2)	22 (3.0)	19 (2.6)
Oedema peripheral	23 (3.2)	18 (2.4)	17 (2.3)
Diarrhoea	21 (2.9)	11 (1.5)	15 (2.0)
Pharyngitis	17 (2.3)	11 (1.5)	10 (1.4)
Non-cardiac chest pain	16 (2.2)	13 (1.8)	10 (1.4)
Hypercholesterolaemia	14 (1.9)	11 (1.5)	11 (1.5)
Dizziness	13 (1.8)	12 (1.6)	8 (1.1)
Dyspepsia	13 (1.8)	10 (1.4)	15 (2.0)
Gastritis	13 (1.8)	5 (0.7)	12 (1.6)
Musculoskeletal pain	13 (1.8)	9 (1.2)	7 (0.9)
Type 2 diabetes mellitus	13 (1.8)	9 (1.2)	6 (0.8)
Arthralgia	12 (1.6)	11 (1.5)	10 (1.4)
Sinusitis	12 (1.6)	20 (2.7)	21 (2.8)
Atrial fibrillation	11 (1.5)	10 (1.4)	8 (1.1)
Oral candidiasis	11 (1.5)	10 (1.4)	12 (1.6)
Nausea	10 (1.4)	12 (1.6)	4 (0.5)
Contusion	9 (1.2)	5 (0.7)	5 (0.7)
Gastrooesophageal reflux disease	9 (1.2)	5 (0.7)	9 (1.2)
Hyperlipidaemia	9 (1.2)	4 (0.5)	7 (0.9)
Pain in extremity	9 (1.2)	8 (1.1)	5 (0.7)
Rhinitis	9 (1.2)	10 (1.4)	6 (0.8)
Toothache	9 (1.2)	4 (0.5)	6 (0.8)

MedDRA preferred term	QVA149 N=729 n (%)	NVA237 N=740 n (%)	Tio N=737 n (%)
Abdominal pain upper	8 (1.1)	7 (0.9)	9 (1.2)
Benign prostatic hyperplasia	8 (1.1)	7 (0.9)	6 (0.8)
Constipation	8 (1.1)	13 (1.8)	4 (0.5)
Lower respiratory tract infection bacterial	8 (1.1)	12 (1.6)	4 (0.5)
Abdominal pain	7 (1.0)	12 (1.6)	10 (1.4)
Acute respiratory failure	7 (1.0)	7 (0.9)	1 (0.1)
Insomnia	7 (1.0)	6 (0.8)	7 (0.9)
Sputum increased	7 (1.0)	13 (1.8)	9 (1.2)

Preferred terms are sorted within preferred term in descending order of percentage according to the QVA149 group.
A patient with multiple occurrences of an AE is counted only once in the AE category.
All AEs starting on or after the time of first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included in the summaries.
Adverse events after the last study visit are not included.

Deaths, other serious adverse events, including COPD exacerbations, and adverse events leading to permanent discontinuation of study drug – n (%) of patients (mSAF)

	QVA149 N=729 n (%)	NVA237 N=740 n (%)	Tio N=737 n (%)
Patients with any AE(s)	678 (93.0)	694 (93.8)	686 (93.1)
Patients with any SAEs (including death)	167 (22.9)	179 (24.2)	165 (22.4)
Death*	23 (3.2)	22 (3.0)	25 (3.4)
SAE(s)	167 (22.9)	179 (24.2)	165 (22.4)
Patients with AEs leading to discontinuation (SAEs and non SAEs)	79 (10.8)	86 (11.6)	67 (9.1)
Discontinued due to SAE(s)	61 (8.4)	57 (7.7)	50 (6.8)
Discontinued due to non-SAE(s)	18 (2.5)	29 (3.9)	17 (2.3)

Death*= number of patients who died between the first treatment day and 30 days of the last treatment.
All AEs starting on or after the time of first administration of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration are included in the summaries.

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Other Relevant Findings

Cardio-cerebrovascular SAEs by primary system organ class and preferred term (mSAF)

	QVA149 N=729 n (%)	NVA237 N=740 n (%)	Tio N=737 n (%)
Patients with ≥ 1 CCV serious adverse event	**23 (3.2)**	**24 (3.2)**	**25 (3.4)**
Cardiac disorders	19 (2.6)	19 (2.6)	20 (2.7)
Atrial fibrillation	6 (0.8)	3 (0.4)	4 (0.5)
Coronary artery disease	3 (0.4)	2 (0.3)	1 (0.1)
Myocardial infarction	2 (0.3)	3 (0.4)	4 (0.5)
Acute myocardial infarction	1 (0.1)	4 (0.5)	2 (0.3)
Angina pectoris	1 (0.1)	3 (0.4)	1 (0.1)
Angina unstable	1 (0.1)	2 (0.3)	0
Acute coronary syndrome	1 (0.1)	1 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	1 (0.1)	0
Cardiac failure	1 (0.1)	1 (0.1)	4 (0.5)
Myocardial ischaemia	1 (0.1)	1 (0.1)	0
Cardiac failure chronic	1 (0.1)	0	0
Cardiopulmonary failure	1 (0.1)	0	0
Cor pulmonale chronic	1 (0.1)	0	0
Ischaemic cardiomyopathy	1 (0.1)	0	0
Cor pulmonale	0	3 (0.4)	0
Atrial flutter	0	2 (0.3)	1 (0.1)
Cardiac failure acute	0	0	1 (0.1)
Cardiac failure congestive	0	0	1 (0.1)
Right ventricular failure	0	0	1 (0.1)
Supraventricular tachyarrhythmia	0	0	1 (0.1)
Nervous system disorders	5 (0.7)	5 (0.7)	5 (0.7)
Cerebral ischaemia	2 (0.3)	0	0
Cerebrovascular accident	1 (0.1)	1 (0.1)	3 (0.4)
Transient ischaemic attack	1 (0.1)	1 (0.1)	0
Cerebral infarction	1 (0.1)	0	1 (0.1)
Cerebral haemorrhage	0	1 (0.1)	0
Cerebrovascular insufficiency	0	1 (0.1)	0
Ischaemic stroke	0	1 (0.1)	0
Cerebrovascular disorder	0	0	1 (0.1)
Surgical and medical procedures	0	1 (0.1)	0
Coronary arterial stent insertion	0	1 (0.1)	0

Preferred terms are sorted in descending order of frequency in the QVA149 treatment group.
All CCV serious adverse events starting on or after the time of first administration of study drug but not later than 30 days after the last administration are included in the summaries.

Date of Clinical Trial Report

28 August 2012

Date Inclusion on Novartis Clinical Trial Results Database

09 July 2013

Date of Latest Update