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Generic Drug Name

indacaterol and glycopyrronium

Therapeutic Area of Trial

Chronic obstructive pulmonary disease

Approved Indication

Not applicable

Protocol Number

CQVA149A2303

Title

A 26-week treatment, multi-center, randomized, double-blind, parallel-group, placebo and active controlled (open label) study to assess the efficacy, safety and tolerability of QVA149 (110/50 µg q.d.) in patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Study Phase

Phase III

Study Start/End Dates

21-Sep-2010 to 10-Feb-2012

Study Design/Methodology

This was a 26-week treatment multi-center, randomized, double-blind, parallel-group, placebo and active controlled (open label) study to assess the efficacy, safety and tolerability of indacaterol and glycopyrronium (QVA149),110/50 µg) in patients with moderate to severe COPD.

The study population consisted of 2144 male and female adults (age ≥40) with a clinical diagnosis of stable moderate to severe COPD (GOLD 2008) and a smoking history of at least 10 pack-years. It was estimated that at least 2743 patients were to be screened in order to randomize approximately 2138 patients into 5 treatment arms of the study with a randomization ratio of 2:2:2:2:1 : QVA149 (n=475), indacaterol (QAB149) (n=475), glycopyrronium (NVA237) (n=475), open label tiotropium (n=475), placebo (n=238).

Patients were randomized into the study with the intention that 1710 patients would complete the study. Dropouts were not replaced. The study was multi-national.

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Centers

301 sites participated in 27 countries (Argentina (23), Australia (5), Bulgaria (9), Canada (14), China (15), Finland (3), France (4), Germany (7), Guatemala (5), Hungary (7), India (14), Japan (54), Mexico (4), Netherlands (11), Panama (3), Philippines (7), Poland (5), Romania (3), Russia (7), Slovakia (14), South Africa (3), Spain (23), Switzerland (4), Taiwan (8), Turkey (4), United Kingdom (10), United States (35)

Publication

Not applicable.

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

Investigational therapy

Indacaterol and glycopyrronium (QVA149) 110/50 µg capsules q.d. for inhalation, single dose, delivered via dry powder inhaler (SDDPI)

Reference therapies

- Open label tiotropium 18 µg capsules q.d., delivered via the HandiHaler® device
- Indacaterol (QAB149) 150 µg capsules q.d. for inhalation, delivered via dry powder inhaler (SDDPI)
- Glycopyrronium (NVA237) 50 µg capsules q.d. for inhalation delivered via dry powder inhaler (SDDPI)
- Matching placebo inhalation capsules for inhalation delivered via dry powder inhaler (SDDPI)

Statistical Methods

The primary efficacy variable, trough Forced Expiratory Volume in 1 second (FEV1) (mean of 23 h 15 min and 23 h 45 min values) following 26 weeks of treatment imputed with last observation carried forward (LOCF), was analyzed using a mixed model for the full analysis set (FAS). The model contained treatment as a fixed effect with baseline FEV1 and FEV1 prior to inhalation and FEV1 60 minutes post inhalation of two short acting bronchodilators (components of reversibility at Day -14) as covariates. The model also included baseline smoking status (current/ex-smoker), baseline ICS use (Yes/No) and region as fixed effects with center nested within region as a random effect.

Estimated adjusted treatment effects and estimated adjusted treatment differences were displayed along with the associated confidence intervals and p-values. Superiority of indacaterol and glycopyrronium (QVA149) vs. glycopyrronium (NVA237) or indacaterol and glycopyrronium (QVA149) vs. indacaterol (QAB149) was demonstrated if the adjusted one-sided p-value was less than the multiplicity adjusted significance level.

In order to demonstrate assay sensitivity, superiority of indacaterol and glycopyrronium (QVA149), indacaterol (QAB149) and glycopyrronium (NVA237) over placebo were also formally tested for the primary variable using the same model as specified above. This was an

important secondary objective. Superiority of indacaterol and glycopyrronium (QVA149), indacaterol (QAB149) or glycopyrronium (NVA237) over placebo was demonstrated if the adjusted one-sided p-value was less than the multiplicity adjusted significance level.

Key secondary efficacy variables: The transitional dyspnea index TDI focal score at week 26 (imputed with last observation carried forward - LOCF) was analyzed for the full analysis set (FAS) using the same mixed model as specified for the primary analysis except with baseline FEV1 replaced by the baseline dyspnea index (BDI) focal score.

The total score of the St. George's Respiratory Questionnaire (SGRQ) after 26 weeks of treatment (imputed with LOCF) was analyzed for the FAS using the same mixed model as specified for the primary analysis except with baseline FEV1 replaced by the baseline SGRQ total score.

The mean change from baseline in the daily number of puffs of rescue medication used over 26 weeks of treatment was analyzed for the FAS using the same mixed model as specified for the primary analysis with baseline FEV1 replaced by the baseline daily rescue use.

For each key secondary variable, estimated adjusted treatment effects and estimated adjusted treatment differences were displayed along with the associated confidence intervals and p-values. Superiority of indacaterol and glycopyrronium (QVA149) vs. placebo was demonstrated if the adjusted one-sided p-value was less than the multiplicity adjusted significance level.

Important secondary efficacy variables: An important secondary objective was to compare indacaterol and glycopyrronium (QVA149) against open label tiotropium 18 µg, delivered via the HandiHaler® device in terms of trough FEV1 after 26 weeks of treatment (imputed with LOCF) using a non-inferiority margin of 40mL. The same mixed model as specified for the primary objective for the per-protocol set was used and QVA149 was considered as non-inferior to tiotropium if the adjusted one-sided p-value was less than the multiplicity adjusted significance level.

The other important secondary objective to demonstrate superiority of indacaterol and glycopyrronium (QVA149), indacaterol (QAB149) and glycopyrronium (NVA237) over placebo is described above.

To handle the issue of multiplicity, a statistical gate-keeping procedure was applied to hierarchical families of hypotheses for the primary, key and important secondary comparisons: To insure a family-wise false positive error rate at an overall level of < 5%, a flexible gate-keeping procedure allowing type-one error rate associated with a rejected hypothesis to be reallocated according to a set of pre-specified rules, was employed.

Family 1 consisted of hypotheses to demonstrate assay sensitivity of indacaterol and glycopyrronium (QVA149), indacaterol (QAB149) and glycopyrronium (NVA237) for trough FEV1 at week 26 and was tested first since these were considered the low-risk hypotheses. The primary set of endpoints defined as superior improvement between indacaterol and glycopyrronium (QVA149) and the single components indacaterol (QAB149) and glycopyrronium (NVA237) for trough FEV1 at Week 26 were contained in Family 2 in the hierarchical structure using the combination rule. The third endpoint formally tested, concerned showing non-inferiority of indacaterol and glycopyrronium (QVA149) from open label tiotropium in 26 week trough FEV1 (Family 3-A). Family 3-B consisted of three hypothesis tests, i.e., the set of key secondary endpoints, and at this stage a Hochberg adjustment was used to control the type one error rate (Family 3-B).

Other secondary efficacy variables were analyzed for the FAS only and treatment comparisons were displayed without an adjustment for multiplicity.

The assessment of safety was based on the incidence of AEs (with maximum severity and suspected relationship to study drug) and SAEs. All AEs including COPD exacerbations were summarized and listed, AEs starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a SAE) after the last inhalation of study drug were classified as a treatment emergent AE. In addition, newly occurring or worsening clinically notable laboratory values were summarized and statistical analysis of vital signs and ECG measurements was performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female adults aged ≥40 years
- Smoking history of at least 10 pack years
- Diagnosis of COPD (moderate-to-severe as classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, 2008)
- Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC (forced vital capacity) <70%

Exclusion Criteria:

- Patients who have had a respiratory tract infection within 4 weeks prior to Visit 1
- Patients with concomitant pulmonary disease
- Patients with a history of asthma
- Any patient with lung cancer or a history of lung cancer
- Patients with a history of certain cardiovascular co-morbid conditions
- Patients with a known history and diagnosis of alpha-1 antitrypsin deficiency
- Patients in the active phase of a supervised pulmonary rehabilitation program
- Patients contraindicated for inhaled anticholinergic agents and β2 agonists
- Other protocol-defined inclusion/exclusion criteria may apply

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Participant Flow

	QVA149 n (%)	QAB149 n (%)	NVA237 n (%)	Tio n (%)	Pbo n (%)	Total n (%)
Screened						3625
Randomized	475 (100)	477 (100)	475 (100)	483 (100)	234 (100)	2144 (100)
Completed	437 (92.0)	421 (88.3)	422 (88.8)	441 (91.3)	189 (80.8)	1910 (89.1)
Discontinued	38 (8.0)	56 (11.7)	53 (11.2)	42 (8.7)	45 (19.2)	234 (10.9)
Primary reason for premature discontinuation						
Protocol deviation	14 (2.9)	8 (1.7)	12 (2.5)	10 (2.1)	11 (4.7)	55 (2.6)
Subject withdrew consent	12 (2.5)	13 (2.7)	22 (4.6)	11 (2.3)	13 (5.6)	71 (3.3)
Adverse Event (s)	5 (1.1)	23 (4.8)	13 (2.7)	10 (2.1)	10 (4.3)	61 (2.8)
Administrative problems	3 (0.6)	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.9)	9 (0.4)
Unsatisfactory therapeutic effect	2 (0.4)	8 (1.7)	2 (0.4)	5 (1.0)	8 (3.4)	25 (1.2)
Lost to follow-up	1 (0.2)	1 (0.2)	0	4 (0.8)	1 (0.4)	7 (0.3)
Death	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	4 (0.2)
Abnormal test procedure result (s)	0	0	2 (0.4)	0	0	2 (0.1)

Patients who screen failed and re-screened under a new patient number were counted more than once in the number of screening.

Baseline Characteristics

Variable Statistic	QVA149 N=474	QAB149 N=476	NVA237 N=473	Tio N=480	Pbo N=232	Total N=2135
Age (years)						
Mean (SD)	64.0 (8.88)	63.6 (8.78)	64.3 (9.04)	63.5 (8.73)	64.4 (8.58)	63.9 (8.83)
Median	64.0	64.0	65.0	63.0	65.0	64.0
Min - Max	43 - 87	41 - 85	41 - 91	40 - 86	41 - 84	40 - 91
Age group - n (%)						
< 65 years	250 (52.7)	249 (52.3)	233 (49.3)	262 (54.6)	110 (47.4)	1104 (51.7)
65 - < 75 years	158 (33.3)	173 (36.3)	173 (36.6)	158 (32.9)	95 (40.9)	757 (35.5)
≥ 75 years	66 (13.9)	54 (11.3)	67 (14.2)	60 (12.5)	27 (11.6)	274 (12.8)
Gender – n (%)						
Male	362 (76.4)	354 (74.4)	365 (77.2)	360 (75.0)	169 (72.8)	1610 (75.4)
Female	112 (23.6)	122 (25.6)	108 (22.8)	120 (25.0)	63 (27.2)	525 (24.6)
Race – n (%)						
Caucasian	321 (67.7)	332 (69.7)	315 (66.6)	322 (67.1)	155 (66.8)	1445 (67.7)
Black	1 (0.2)	5 (1.1)	5 (1.1)	5 (1.0)	2 (0.9)	18 (0.8)
Asian	140 (29.5)	131 (27.5)	137 (29.0)	135 (28.1)	71 (30.6)	614 (28.8)
Native American	5 (1.1)	2 (0.4)	12 (2.5)	8 (1.7)	3 (1.3)	30 (1.4)
Pacific Islander	0	0	0	0	0	0
Other	7 (1.5)	6 (1.3)	4 (0.8)	10 (2.1)	1 (0.4)	28 (1.3)

Variable Statistic	QVA149 N=474	QAB149 N=476	NVA237 N=473	Tio N=480	Pbo N=232	Total N=2135
Ethnicity – n (%)						
Hispanic/Latino	55 (11.6)	59 (12.4)	62 (13.1)	69 (14.4)	28 (12.1)	273 (12.8)
Chinese	38 (8.0)	35 (7.4)	43 (9.1)	36 (7.5)	25 (10.8)	177 (8.3)
Indian (subcontinent)	35 (7.4)	33 (6.9)	38 (8.0)	44 (9.2)	18 (7.8)	168 (7.9)
Japanese	42 (8.9)	41 (8.6)	40 (8.5)	40 (8.3)	19 (8.2)	182 (8.5)
Mixed Ethnicity	2 (0.4)	4 (0.8)	3 (0.6)	7 (1.5)	1 (0.4)	17 (0.8)
Other	302 (63.7)	304 (63.9)	287 (60.7)	284 (59.2)	141 (60.8)	1318 (61.7)
Weight (kg)	n=474	n=476	n=473	n=479	n=232	n=2134
Mean (SD)	73.1 (17.44)	73.2 (17.80)	72.7 (18.14)	73.3 (17.89)	72.0 (19.43)	73.0 (17.99)
Median	71.0	71.0	70.0	72.0	70.0	70.9
Min - Max	33.7 - 133.3	38.0 - 135.9	36.0 - 170.0	37.0 - 147.7	38.6 - 136.0	33.7 - 170.0
Height (cm)	n=474	n=476	n=473	n=480	n=232	n=2135
Mean (SD)	167.4 (9.21)	167.6 (8.91)	167.3 (8.51)	167.3 (8.89)	166.6 (8.64)	167.3 (8.85)
Median	167.5	167.0	167.0	167.0	166.5	167.0
Min - Max	140.0 -188.0	146.0-193.0	137.0-196.0	137.0 -196.0	148.0-189.0	137.0-196.0
BMI (kg/m²)	n=474	n=476	n=473	n=479	n=232	n=2134
Mean (SD)	26.0 (5.33)	25.9 (5.51)	25.9 (5.68)	26.0 (5.26)	25.8 (6.02)	25.9 (5.51)
Median	25.3	25.1	24.9	25.8	24.8	25.2
Min - Max	14.8 - 45.1	14.2 - 49.2	14.5 - 60.8	15.6 - 48.2	14.8 - 48.1	14.2 - 60.8
BMI group – n (%)						
≤ 30.0 kg/m^2	381 (80.4)	374 (78.6)	380 (80.3)	376 (78.3)	192 (82.8)	1703 (79.8)
> 30.0 kg/m^2	93 (19.6)	102 (21.4)	93 (19.7)	103 (21.5)	40 (17.2)	431 (20.2)
Missing	0	0	0	1 (0.2)	0	1 (0.05)

BMI = Body mass index (= weight [kg] / height [m]²)

Outcome Measures

Primary Outcome Result(s)

Trough Forced Expiratory Volume in One Second (FEV1) After 26 Weeks of Treatment with QVA149 110/50 µg compared to both QAB149 150 µg and NVA237 50 µg, in patients with moderate to severe COPD.

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
FAS										
									One-sided	
QVA149 (N=474)	442	1.28 (0.023)	1.45	0.010	QVA149 - QAB149	0.07	0.014	(0.05, 0.10)	<0.001	<0.001*
					QVA149 - NVA237	0.09	0.014	(0.06, 0.11)	<0.001	<0.001*

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		Treatment			Treatment difference					
Treatment	n	Baseline mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	Unadjusted 95% CI	Unadjusted p-value	Adjusted p-value (one-sided)
QAB149 (N=476)	435	1.29 (0.022)	1.38	0.010						
NVA237 (N=473)	424	1.28 (0.022)	1.36	0.010						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Data within 6h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

Key Secondary Outcome Result(s)

Transitional Dyspnea Index (TDI) focal score following 26 weeks of treatment with QVA149 compared to placebo.

		Treatment			Treatment difference					
Treatment	n	Baseline mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	Unadjusted 95% CI	Unadjusted p-value	Adjusted p-value (one-sided)
									One-sided	
QVA149 (N=474)	439	6.45 (0.101)	2.72	0.170	QVA149 - Pbo	1.09	0.244	(0.61,1.57)	<0.001	<0.001*
Pbo (N=232)	193	6.56 (0.157)	1.63	0.230						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
BDI = Baseline Dyspnea Index, TDI = Transition Dyspnea Index.
Mixed model: TDI focal score = treatment + BDI focal score + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

St. George's Respiratory Questionnaire (SGRQ) total score following 26 weeks of treatment with QVA149 compared to placebo.

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
									One-sided	
QVA149 (N=474)	441	46.83 (0.898)	37.01	0.679	QVA149 - Pbo	-3.01	1.041	(-5.05, -0.97)	0.002	0.002*
Placebo (N=232)	196	46.07 (1.201)	40.02	0.941						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: SGRQ total score= treatment + baseline SGRQ total score + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

Change from baseline in mean daily number of puffs of rescue medication use over 26 weeks of treatment with QVA149 110/50 µg compared to placebo.

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
									One-sided	
QVA149 (N=474)	419	4.21 (0.195)	-1.88	0.105	QVA149- Pbo	-0.96	0.171	(-1.29,-0.62)	<0.001	<0.001*
Pbo (N=232)	199	3.88 (0.290)	-0.92	0.147						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Change from baseline = treatment + baseline number of puffs + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.
* denotes a statistically significant one-sided comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

Important Secondary Outcome Result(s)

Trough Forced Expiratory Volume In One Second ($FEV_{1)}$ following 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg and QAB149 150 µg compared to placebo (mean of 23 hours 15 minutes and 23 hour 45 minute post-dose time points for 26 Weeks)

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
FAS										
									One-sided	
QVA149 (N=474)	442	1.28 (0.023)	1.45	0.010	QVA149 - Pbo	0.20	0.017	(0.17, 0.24)	<0.001	<0.001*
QAB149 (N=476)	435	1.29 (0.022)	1.38	0.010	QAB149 - Pbo	0.13	0.017	(0.10, 0.16)	<0.001	<0.001*
NVA237 (N=473)	424	1.28 (0.022)	1.36	0.010	NVA237 - Pbo	0.12	0.017	(0.08, 0.15)	<0.001	<0.001*
Pbo (N=232)	191	1.29 (0.035)	1.25	0.015						

Trough Forced Expiratory Volume In One Second FEV_1 following 26 weeks of treatment with QVA149 110/50 µg compared to open label tiotropium (18 µg). (Mean of 23 hours 15 minutes and 23 hour 45 minute post-dose time points at Week 26)

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value (one-sided)**	**Adjusted p-value**
QVA149 (N=412)	387	1.30 (0.025)	1.46	0.011	QVA149 - Tio	0.07	0.015	(0.04, 0.10)	<0.001	
Tiotropium (N=405)	382	1.29 (0.040)	1.25	0.017						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Data within 6h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.
Non-inferiority was evaluated by testing the following null hypothesis (H_6) :
H_6: When allowing for a 40ml non-inferiority margin, the difference in the mean trough FEV_1, following 26 weeks of treatment, for QVA149 110/50 µg is 40 ml lower than that for open label Tiotropium.

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Secondary Outcome Result(s)

Baseline Transitional Dyspnea Index (BDI/TDI) focal score following 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

			Treatment		Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
									One-sided	
QVA149 (N=474)	439	6.45 (0.101)	2.72	0.170	QVA149 - Pbo	1.09	0.244	(0.61,1.57)	<0.001	<0.001*
									Two-sided	
					QVA149 - QAB149	0.26	0.189	(-0.11,0.63)	0.175	
					QVA149 - NVA237	0.21	0.191	(-0.17,0.58)	0.283	
					QVA149 - Tio	0.51	0.190	(0.14, 0.88)	0.007	
QAB149 (N=476)	440	6.28 (0.097)	2.47	0.171	QAB149 - Pbo	0.84	0.244	(0.36, 1.31)	<0.001	
NVA237 (N=473)	424	6.22 (0.097)	2.52	0.172	NVA237 - Pbo	0.89	0.244	(0.41,1.36)	<0.001	
Tio (N=480)	441	6.46 (0.095)	2.21	0.171	Tio - Pbo	0.58	0.244	(0.10,1.06)	0.017	
Pbo (N=232)	193	6.56 (0.157)	1.63	0.230						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
BDI = Baseline Dyspnea Index, TDI = Transition Dyspnea Index.
Mixed model: TDI focal score = treatment + BDI focal score + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

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Baseline Transitional Dyspnea Index (BDI/TDI) focal score following 12 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

Baseline Timepoint	Treatment	n	Mean (SE)	Treatment difference LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 12 LOCF	QVA149 (N=474)	442	6.45 (0.100)	2.44	0.158	QVA149 - Pbo	1.22	0.236	(0.76, 1.69)	<0.001
						QVA149 - QAB149	0.26	0.185	(-0.11, 0.62)	0.164
						QVA149 - NVA237	0.41	0.186	(0.04, 0.77)	0.030
						QVA149 - Tio	0.63	0.186	(0.26, 0.99)	<0.001
	QAB149 (N=476)	443	6.28 (0.096)	2.18	0.157	QAB149 - Pbo	0.96	0.237	(0.50, 1.43)	<0.001
						QAB149 - NVA237	0.15	0.186	(-0.22, 0.51)	0.429
						QAB149 - Tio	0.37	0.185	(0.01, 0.73)	0.046
	NVA237 (N=473)	435	6.21 (0.097)	2.04	0.158	NVA237 - Pbo	0.82	0.236	(0.35, 1.28)	<0.001
						NVA237 - Tio	0.22	0.186	(-0.14, 0.59)	0.232
	Tio (N=480)	445	6.43 (0.094)	1.81	0.158	Tio - Pbo	0.59	0.236	(0.13, 1.06)	0.012
	Pbo (N=232)	200	6.53 (0.154)	1.22	0.215					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval
Mixed model: TDI focal score = treatment + BDI focal score + FEV1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
The BDI was measured at day 1 prior to first dose. The TDI (transition dyspnea index) captures changes from baseline.
For LOCF analyses missing data were imputed with LOCF but not by more than 14 weeks and data within 4 weeks of day 1 were not carried forward.

Proportion of patients with a clinically important improvement of at least 1 point in TDI focal score at Week 26.

Treatment	n/N' (%)	Comparison	Odds Ratio	95% CI	p-value
QVA149 (N=474)	299 / 439 (68.1)	QVA149 / Pbo	1.86	(1.22, 2.83)	0.004
		QVA149 / QAB149	1.13	(0.81, 1.58)	0.458
		QVA149 / NVA237	1.12	(0.81, 1.57)	0.489
		QVA149 / Tio	1.51	(1.08, 2.10)	0.016
QAB149 (N=476)	284 / 440 (64.6)	QAB149 / Pbo	1.64	(1.08, 2.49)	0.020
		QAB149 / NVA237	0.99	(0.71, 1.38)	0.961
		QAB149 / Tio	1.33	(0.96, 1.85)	0.091
NVA237 (N=473)	270 / 424 (63.7)	NVA237 / Pbo	1.65	(1.09, 2.51)	0.018
		NVA237 / Tio	1.34	(0.96, 1.86)	0.083
Tiotropium (N=480)	261 / 441 (59.2)	Tio / Pbo	1.24	(0.82, 1.87)	0.318
Placebo (N=232)	111 / 193 (57.5)				

n = number of patients with improvement of ≥ 1. N=no. patients included in the analysis. CI = confidence interval.
Logistic regression model: Logit (proportion) = treatment + BDI focal score + FEV_1 reversibility components +baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.
The BDI was measured at day 1 prior to first dose. The TDI (transition dyspnea index) captures changes from baseline. Missing data were imputed with LOCF but not by more than14 weeks and data within 4 weeks of day 1 were not carried forward.
An odds ratio > 1 favors the treatment in the numerator of the ratio.

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St. George's Respiratory Questionnaire (SGRQ) total score following 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

		Treatment			Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
									One-sided	
QVA149 (N=474)	441	46.83 (0.898)	37.01	0.679	QVA149 - Pbo	-3.01	1.041	(-5.05, -0.97)	0.002	0.002*
									Two-sided	
					QVA149 - QAB149	-1.09	0.810	(-2.68, 0.50)	0.179	
					QVA149 - NVA237	-1.18	0.817	(-2.78, 0.42)	0.149	
					QVA149 - Tio	-2.13	0.811	(-3.72, -0.54)	0.009	
QAB149 (N=476)	443	46.82 (0.828)	38.10	0.680	QAB149 - Pbo	-1.92	1.042	(-3.97, 0.12)	0.065	
NVA237 (N=473)	430	47.80 (0.894)	38.19	0.686	NVA237 - Pbo	-1.83	1.039	(-3.87, 0.21)	0.078	
Tiotropium (N=480)	450	46.48 (0.862)	39.14	0.677	Tio - Pbo	-0.88	1.038	(-2.92, 1.16)	0.397	
Placebo (N=232)	196	46.07 (1.201)	40.02	0.941						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: SGRQ total score= treatment + baseline SGRQ total score + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.
* denotes a statistically significant comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

NOVARTIS

St. George's Respiratory Questionnaire (SGRQ) total score following 12 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

Baseline Timepoint	Treatment	n	Mean (SE)	LS Mean	SE	Treatment difference Comparison	LS Mean	SE	95% CI	p-value
Week 12 LOCF	QVA149 (N=474)	448	46.96 (0.889)	37.56	0.659	QVA149 - Pbo	-3.99	0.997	(-5.94, -2.03)	<0.001
						QVA149 - QAB149	-0.98	0.785	(-2.52, 0.56)	0.211
						QVA149 - NVA237	-1.84	0.788	(-3.38, -0.29)	0.020
						QVA149 - Tio	-2.37	0.785	(-3.91, -0.83)	0.003
	QAB149 (N=476)	446	46.66 (0.827)	38.55	0.662	QAB149 - Pbo	-3.00	0.999	(-4.96, -1.05)	0.003
						QAB149 - NVA237	-0.86	0.789	(-2.40, 0.69)	0.279
						QAB149 - Tio	-1.39	0.782	(-2.93, 0.14)	0.075
	NVA237 (N=473)	441	47.84 (0.879)	39.40	0.663	NVA237 - Pbo	-2.15	0.994	(-4.10, -0.20)	0.031
						NVA237 - Tio	-0.54	0.787	(-2.08, 1.01)	0.495
	Tio (N=480)	454	46.63 (0.851)	39.94	0.658	Tio - Pbo	-1.61	0.995	(-3.56, 0.34)	0.105
	Pbo (N=232)	205	46.61 (1.188)	41.55	0.900					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval
Mixed model: SGRQ total score = treatment + baseline SGRQ total score + FEV1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Baseline SGRQ total score was completed at day 1 prior to first dose.
For LOCF analyses, missing data were imputed with LOCF but not by more than 14 weeks and data within 4 weeks of day 1 were not carried forward.

Percentage of patients with a clinically important improvement from baseline of >=4 in SGRQ total score at Week 26

Treatment	n/N' (%)	Comparison	Odds Ratio	95% CI	p-value
QVA149 (N=474)	281 / 441 (63.7)	QVA149 / Pbo	1.39	(0.95, 2.02)	0.088
		QVA149 / QAB149	1.03	(0.76, 1.38)	0.853
		QVA149 / NVA237	1.18	(0.88, 1.60)	0.276
		QVA149 / Tio	1.35	(1.00, 1.82)	0.047
QAB149 (N=476)	279 / 443 (63.0)	QAB149 / Pbo	1.35	(0.93, 1.96)	0.117
		QAB149 / NVA237	1.15	(0.85, 1.55)	0.360
		QAB149 / Tio	1.31	(0.98, 1.76)	0.068
NVA237 (N=473)	260 / 430 (60.5)	NVA237 / Pbo	1.17	(0.81, 1.70)	0.403
		NVA237 / Tio	1.14	(0.85, 1.54)	0.377
Tio (N=480)	254 / 450 (56.4)	Tio / Pbo	1.03	(0.71, 1.49)	0.890
Pbo (N=232)	111 / 196 (56.6)				

n = number of patients who achieved an improvement of >= 4. N' = number of patients included in the analysis.
CI = confidence interval.
Logistic regression model: Logit (proportion) = treatment + baseline SGRQ total score + FEV1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Baseline SGRQ total score was completed at day 1 prior to first dose.
Missing data were imputed with LOCF but not by more than 14 weeks and data within 4 weeks of day 1 were not carried forward.
An odds ratio > 1 favors the treatment in the numerator of the ratio.

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Percentage of nights with 'no nighttime awakenings', days with 'no daytime symptoms', and 'days able to perform usual daily activities' following 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Percent of nights with 'no nighttime awakenings'									
QVA149 (N=474)	418	43.78 (1.940)	63.68	1.473	QVA149 - Pbo	10.01	2.368	(5.37,14.66)	<0.001
					QVA149 - QAB149	1.20	1.892	(-2.51, 4.91)	0.525
					QVA149 - NVA237	5.05	1.910	(1.30, 8.79)	0.008
					QVA149 - Tio	3.68	1.891	(-0.03, 7.39)	0.052
QAB149 (N=476)	413	43.67 (1.968)	62.48	1.479	QAB149 - Pbo	8.81	2.374	(4.16, 13.47)	<0.001
NVA237 (N=473)	399	44.99 (1.974)	58.64	1.500	NVA237 - Pbo	4.97	2.374	(0.31, 9.62)	0.037
Tio (N=480)	422	45.19 (1.988)	60.00	1.469	Tio - Pbo	6.33	2.363	(1.70, 10.97)	0.007
Pbo (N=232)	198	45.58 (2.841)	53.67	2.047					
Percent of days with 'no daytime symptoms'									
QVA149 (N=474)	415	1.45 (0.361)	7.49	0.931	QVA149 - Pbo	3.05	1.485	(0.14, 5.96)	0.040
					QVA149 - QAB149	-1.68	1.180	(-3.99, 0.64)	0.155
					QVA149 - NVA237	1.09	1.191	(-1.24, 3.43)	0.359
					QVA149 - Tio	1.95	1.180	(-0.36, 4.27)	0.098
QAB149 (N=476)	410	1.76 (0.346)	9.17	0.933	QAB149 - Pbo	4.73	1.487	(1.81, 7.64)	0.001
NVA237 (N=473)	395	1.94 (0.408)	6.40	0.948	NVA237 - Pbo	1.96	1.487	(-0.96, 4.87)	0.189
Tio (N=480)	418	1.69 (0.363)	5.54	0.928	Tio - Pbo	1.10	1.481	(-1.81, 4.00)	0.459
Pbo(N=232)	195	3.30 (0.734)	4.44	1.294					
Percent of 'days able to perform usual daily activities'									
QVA149 (N=474)	415	28.63 (1.771)	45.97	1.578	QVA149 - Pbo	11.48	2.529	(6.52, 16.44)	<0.001
					QVA149 - QAB149	5.04	2.014	(1.09, 8.99)	0.012
					QVA149 - NVA237	5.87	2.034	(1.88, 9.86)	0.004
					QVA149 - Tio	8.45	2.014	(4.50, 12.40)	<0.001
QAB149 (N=476)	410	27.92 (1.729)	40.94	1.582	QAB149 - Pbo	6.44	2.534	(1.47, 11.41)	0.011
NVA237 (N=473)	395	26.69 (1.735)	40.10	1.607	NVA237 - Pbo	5.61	2.536	(0.63, 10.58)	0.027
Tio (N=480)	418	27.24 (1.693)	37.52	1.572	Tio - Pbo	3.03	2.525	(-1.92, 7.98)	0.230
Pbo(N=232)	195	29.84 (2.696)	34.49	2.197					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: %-days = treatment + baseline %-days + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.

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Change from baseline in the mean daily number of puffs of rescue medication at over 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

			Treatment		Treatment difference					
Treatment	**n**	**Baseline mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**Unadjusted 95% CI**	**Unadjusted p-value**	**Adjusted p-value (one-sided)**
									One-sided	
QVA149 (N=474)	419	4.21 (0.195)	-1.88	0.105	QVA149- Pbo	-0.96	0.171	(-1.29,-0.62)	<0.001	<0.001*
									Two-sided	
					QVA149 - QAB149	-0.30	0.137	(-0.57, -0.03)	0.027	
					QVA149 - NVA237	-0.66	0.138	(-0.93, -0.39)	<0.001	
					QVA149 - Tio	-0.54	0.137	(-0.81, -0.27)	<0.001	
QAB149 (N=476)	416	3.66 (0.164)	-1.57	0.106	QAB149- Pbo	-0.65	0.171	(-0.99, -0.32)	<0.001	
NVA237 (N=473)	403	3.70 (0.182)	-1.22	0.107	NVA237 - Pbo	-0.30	0.171	(-0.63, 0.04)	0.081	
Tio (N=480)	424	3.83 (0.170)	-1.34	0.105	Tio - Pbo	-0.41	0.171	(-0.75, -0.08)	0.015	
Pbo (N=232)	199	3.88 (0.290)	-0.92	0.147						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Change from baseline = treatment + baseline number of puffs + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.
* denotes a statistically significant one-sided comparison according to the statistical gate-keeping procedure applied to the hierarchical families of hypotheses.

NOVARTIS

Change from baseline in the mean daily number of puffs of rescue medication over 12 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

Time period	Treatment	n	Baseline Mean (SE)	Treatment LS Mean	Treatment SE	Comparison	Treatment difference LS Mean	SE	95% CI	p-value
Week 1- 12	QVA149 (N=474)	420	4.21 (0.195)	-1.82	0.102	QVA149 - Pbo	-0.99	0.165	(-1.31, -0.67)	<0.001
						QVA149 - QAB149	-0.36	0.132	(-0.62, -0.10)	0.007
						QVA149 - NVA237	-0.60	0.133	(-0.86, -0.34)	<0.001
						QVA149 - Tio	-0.53	0.132	(-0.79, -0.27)	<0.001
	QAB149 (N=476)	420	3.65 (0.163)	-1.46	0.102	QAB149 - Pbo	-0.63	0.165	(-0.95, -0.31)	<0.001
						QAB149 - NVA237	-0.24	0.133	(-0.51, 0.02)	0.066
						QAB149 - Tio	-0.17	0.131	(-0.43, 0.08)	0.184
	NVA237 (N=473)	413	3.70 (0.179)	-1.22	0.103	NVA237 - Pbo	-0.39	0.164	(-0.71, -0.06)	0.019
						NVA237 - Tio	0.07	0.132	(-0.19, 0.33)	0.599
	Tio (N=480)	427	3.85 (0.171)	-1.28	0.102	Tio - Pbo	-0.46	0.164	(-0.78, -0.13)	0.005
	Pbo (N=232)	203	3.85 (0.285)	-0.83	0.141					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval
Mixed model: change in daily number of rescue puffs = treatment + baseline daily number of rescue puffs + FEV1 reversibility components + baseline smoking status + baseline ICS use + center (region) + error. Center was included as a random effect nested within region.
Baseline was defined as the average daily number of puffs during the 14 day run-in period.

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Change from Baseline in the Daytime and Nighttime Rescue Medication Use (Number of Puffs) Over 26 Weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Change from baseline in mean daytime number of puffs									
QVA149 (N=474)	415	2.41 (0.116)	-1.11	0.061	QVA149 - Pbo	-0.52	0.099	(-0.72,-0.33)	<0.001
					QVA149 - QAB149	-0.15	0.079	(-0.31, 0.00)	0.057
					QVA149 - NVA237	-0.36	0.080	(-0.51,-0.20)	<0.001
					QVA149 - Tio	-0.28	0.079	(-0.44,-0.13)	<0.001
QAB149 (N=476)	410	2.09 (0.096)	-0.96	0.062	QAB149 - Pbo	-0.37	0.100	(-0.57,-0.18)	<0.001
NVA237 (N=473)	395	2.14 (0.109)	-0.75	0.063	NVA237 - Pbo	-0.17	0.100	(-0.36, 0.03)	0.093
Tio (N=480)	418	2.19 (0.102)	-0.83	0.061	Tio - Pbo	-0.24	0.099	(-0.44,-0.05)	0.015
Pbo (N=232)	195	2.27 (0.186)	-0.58	0.086					
Change from baseline in mean nighttime number of puffs									
QVA149 (N=474)	418	1.82 (0.089)	-0.78	0.049	QVA149 - Pbo	-0.44	0.081	(-0.60, -0.28)	<0.001
					QVA149 - QAB149	-0.15	0.065	(-0.28, -0.03)	0.018
					QVA149 - NVA237	-0.31	0.065	(-0.44, -0.18)	<0.001
					QVA149 - Tio	-0.26	0.065	(-0.39, -0.14)	<0.001
QAB149 (N=476)	413	1.57 (0.077)	-0.63	0.049	QAB149 - Pbo	-0.29	0.081	(-0.44, -0.13)	<0.001
NVA237 (N=473)	399	1.58 (0.083)	-0.48	0.050	NVA237 - Pbo	-0.13	0.081	(-0.29, 0.03)	0.105
Tio (N=480)	422	1.67 (0.078)	-0.52	0.049	Tio - Pbo	-0.17	0.081	(-0.33, -0.02)	0.031
Pbo (N=232)	198	1.66 (0.123)	-0.34	0.069					
Percentage of 'days with no rescue use'									
QVA149 (N=474)	418	19.19 (1.627)	47.09	1.752	QVA149 - Pbo	12.33	2.798	(6.84, 17.82)	<0.001
					QVA149 - QAB149	2.28	2.229	(-2.09, 6.65)	0.307
					QVA149 - NVA237	9.35	2.250	(4.94, 13.76)	<0.001
					QVA149 - Tio	10.58	2.230	(6.21, 14.96)	<0.001
QAB149 (N=476)	411	21.51 (1.754)	44.81	1.764	QAB149 - Pbo	10.05	2.804	(4.55, 15.55)	<0.001
NVA237 (N=473)	397	21.99 (1.767)	37.74	1.790	NVA237 - Pbo	2.98	2.805	(-2.52, 8.48)	0.288
Tio (N=480)	419	21.88 (1.750)	36.51	1.752	Tio - Pbo	1.75	2.795	(-3.73, 7.23)	0.532
Pbo (N=232)	196	23.55 (2.539)	34.76	2.437					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: change from baseline (or % of days) = treatment + baseline number of puffs (or baseline % of days) + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error.
Center was included as a random effect nested within region.

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Standardized FEV1 (With Respect to Length of Time) Area Under the Curve (AUC) from 5 min to 4 hours post-dose following 1 day and 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Day 1									
QVA149 (N=474)	464	1.30 (0.023)	1.52	0.006	QVA149 - Pbo	0.22	0.009	(0.20, 0.24)	<0.001
					QVA149 - QAB149	0.06	0.008	(0.05, 0.08)	<0.001
					QVA149 - NVA237	0.03	0.008	(0.02, 0.05)	<0.001
					QVA149 - Tio	0.08	0.008	(0.07, 0.10)	<0.001
QAB149 (N=476)	471	1.29 (0.021)	1.46	0.006	QAB149 - Pbo	0.16	0.009	(0.14, 0.18)	<0.001
NVA237 (N=473)	464	1.28 (0.021)	1.49	0.006	NVA237 - Pbo	0.19	0.009	(0.17, 0.20)	<0.001
Tio (N=480)	473	1.28 (0.023)	1.44	0.006	Tio - Pbo	0.14	0.009	(0.12, 0.16)	<0.001
Pbo (N=232)	228	1.28 (0.032)	1.30	0.008					
Week 26									
QVA149 (N=474)	433	1.29 (0.023)	1.57	0.010	QVA149 - Pbo	0.34	0.018	(0.30, 0.37)	<0.001
					QVA149 - QAB149	0.11	0.014	(0.08, 0.14)	<0.001
					QVA149 - NVA237	0.14	0.014	(0.11, 0.17)	<0.001
					QVA149 - Tio	0.13	0.014	(0.11, 0.16)	<0.001
QAB149 (N=476)	418	1.31 (0.022)	1.46	0.010	QAB149 - Pbo	0.23	0.018	(0.19, 0.26)	<0.001
NVA237 (N=473)	412	1.28 (0.022)	1.43	0.010	NVA237 - Pbo	0.20	0.018	(0.16, 0.23)	<0.001
Tio (N=480)	435	1.28 (0.024)	1.44	0.010	Tio - Pbo	0.20	0.018	(0.17, 0.24)	<0.001
Pbo (N=232)	186	1.29 (0.036)	1.23	0.015					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: AUC FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Data within 6 h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.

FEV_1 at all time-points following 1 day and 26 weeks of treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo, in the serial spirometry subset.

Summary table not available.

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Standardized AUC for FEV_1 on Day 1 and Week 26 (5 min – 12h), following treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo, in the serial spirometry subset.

		Treatment				Treatment difference			
Treatment	n	Baseline Mean (SE)	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Day 1									
QVA149 (N=66)	64	1.25 (0.065)	1.50	0.017	QVA149 - Pbo	0.26	0.025	(0.21, 0.31)	<0.001
					QVA149 - QAB149	0.10	0.020	(0.06, 0.14)	<0.001
					QVA149 - NVA237	0.08	0.020	(0.04, 0.12)	<0.001
					QVA149 - Tio	0.13	0.020	(0.09, 0.17)	<0.001
QAB149 (N=64)	64	1.19 (0.060)	1.40	0.017	QAB149 - Pbo	0.16	0.025	(0.11, 0.21)	<0.001
NVA237 (N=63)	63	1.20 (0.061)	1.42	0.018	NVA237 - Pbo	0.18	0.025	(0.13, 0.23)	<0.001
Tio (N=70)	70	1.34 (0.066)	1.38	0.017	Tio - Pbo	0.13	0.025	(0.08, 0.18)	<0.001
Pbo (N=31)	31	1.28 (0.102)	1.24	0.023					
Week 26									
QVA149 (N=66)	60	1.25 (0.067)	1.52	0.027	QVA149 - Pbo	0.33	0.041	(0.25, 0.42)	<0.001
					QVA149 - QAB149	0.13	0.033	(0.06, 0.19)	<0.001
					QVA149 - NVA237	0.13	0.033	(0.06, 0.19)	<0.001
					QVA149 - Tio	0.12	0.032	(0.06, 0.19)	<0.001
QAB149 (N=64)	55	1.24 (0.067)	1.39	0.027	QAB149 - Pbo	0.20	0.042	(0.12, 0.29)	<0.001
NVA237 (N=63)	58	1.18 (0.060)	1.39	0.028	NVA237 - Pbo	0.21	0.041	(0.12, 0.29)	<0.001
Tio (N=70)	67	1.33 (0.065)	1.39	0.027	Tio - Pbo	0.21	0.041	(0.13, 0.29)	<0.001
Pbo (N=31)	27	1.32 (0.112)	1.18	0.036					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: AUC FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region. Data within 6 h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.

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Standardized FEV1 (With Respect to Length of Time) Area Under the Curve (AUC) From 5 Minutes to 23 Hours 45 Minutes at Week 26 following treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo, in the serial spirometry subset.

		Treatment			Treatment difference				
Treatment	**n**	**Baseline Mean (SE)**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
QVA149 (N=66)	60	1.25 (0.067)	1.46	0.026	QVA149 - Pbo	0.32	0.041	(0.24, 0.40)	<0.001
					QVA149 - QAB149	0.11	0.032	(0.05, 0.18)	<0.001
					QVA149 - NVA237	0.11	0.032	(0.05, 0.18)	<0.001
					QVA149 - Tio	0.11	0.031	(0.04, 0.17)	<0.001
QAB149 (N=64)	55	1.24 (0.067)	1.35	0.027	QAB149 - Pbo	0.20	0.041	(0.12, 0.28)	<0.001
NVA237 (N=63)	58	1.18 (0.060)	1.35	0.027	NVA237 - Pbo	0.20	0.041	(0.12, 0.28)	<0.001
Tio (N=70)	67	1.33 (0.065)	1.36	0.026	Tio - Pbo	0.21	0.040	(0.13, 0.29)	<0.001
Pbo (N=31)	27	1.32 (0.112)	1.15	0.036					

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: AUC FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
Data within 6 h of rescue medication use or 7 days of systemic corticosteroid use is excluded from this analysis.

Forced vital capacity (FVC) at all available time points, following treatment with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg and tiotropium compared to placebo.

Summary table not available.

Percentage of patients with at least one moderate or severe COPD exacerbation over the 26 week treatment period with QVA149 110/50 µg, NVA237 50 µg, QAB149 150 µg, tiotropium and placebo.

	QVA149 (N=474)	**QAB149 (N=476)**	**NVA237 (N=473)**	**Tio (N=480)**	**Pbo (N=232)**
Summary statistics					
Patients with a moderate or severe COPD exacerbation, n (%)	85 (17.9)	103 (21.6)	89 (18.8)	85 (17.7)	60 (25.9)
Cox regression analysis					
Hazard ratio compared to placebo	0.56	0.73	0.58	0.56	
95% CI of hazard ratio	(0.399, 0.779)	(0.528, 1.003)	(0.417, 0.810)	(0.400, 0.779)	
p-value for comparison to placebo	<0.001	0.052	0.001	<0.001	

Patients without a moderate or severe COPD exacerbation are censored at the date of last study medication.
The Cox regression model was stratified by region and included terms for treatment, baseline smoking status, baseline ICS use, baseline total symptom score, baseline COPD exacerbation history and FEV1 reversibility.
A hazard ratio < 1 favors the treatment group in the numerator of the ratio (i.e.QVA149, QAB149, NVA237, Tio).

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Percentage of participants with COPD exacerbations requiring hospitalization or treatment with systemic corticosteroids and/or antibiotics but no hospitalization

Exacerbations requiring hospitalization

	QVA149 N=474	QAB149 N=476	NVA237 N=473
Patients with a COPD exacerbation, n/N(%)	10/474 (2.1)	12/476 (2.5)	9/473 (1.9)
Maximum follow-up time (days)	204	201	212
Median follow-up time (days)	183	183	183
Time-to event (days), Percentiles			
25% (95% CI)	200 (200, n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Median (95% CI)	200 (200, n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
75% (95% CI)	n.e. (200, n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Event-free rates, % (95% CI)			
26 Weeks	98.0 (96.7, 99.3)	97.2 (95.7, 98.8)	97.9 (96.6, 99.3)

n.e. = not estimable.
Patients who do not experience a COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics are censored at the date of last study medication.
Follow-up time = Time from randomization until the start of the first COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics or censoring.
Time-to event percentiles are calculated by the Kaplan Meier method and event free rates are calculated by the life-table method.
Exacerbation episodes less than 7 days apart were considered to be one continuous exacerbation.

Exacerbations requiring hospitalization

	Tio N=480	Pbo N=232
Patients with a COPD exacerbation, n/N(%)	5/480 (1.0)	7/232 (3.0)
Maximum follow-up time (days)	198	209
Median follow-up time (days)	183	183
Time-to event (days), Percentiles		
25% (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Median (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
75% (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Event-free rates, % (95% CI)		
26 Weeks	98.9 (98.0, 99.9)	96.6 (94.1, 99.1)

n.e. = not estimable.
Patients who do not experience a COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics are censored at the date of last study medication.
Follow-up time = Time from randomization until the start of the first COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics or censoring.
Time-to event percentiles are calculated by the Kaplan Meier method and event free rates are calculated by the life-table method.
Exacerbation episodes less than 7 days apart were considered to be one continuous exacerbation.

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Exacerbations requiring treatment with systemic corticosteroids and/or antibiotics but no hospitalization

	QVA149 N=474	QAB149 N=476	NVA237 N=473
Patients with a COPD exacerbation, n/N(%)	79/474 (16.7)	94/476 (19.7)	84/473 (17.8)
Maximum follow-up time (days)	204	201	212
Median follow-up time (days)	183	183	183
Time-to event (days), Percentiles			
25% (95% CI)	n.e. (n.e., n.e.)	n.e. (184, n.e.)	n.e. (n.e., n.e.)
Median (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
75% (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Event-free rates, % (95% CI)			
26 Weeks	82.7 (79.2, 86.2)	79.1 (75.3, 83.0)	81.1 (77.4, 84.7)

n.e. = not estimable.
Patients who do not experience a COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics are censored at the date of last study medication.
Follow-up time = Time from randomization until the start of the first COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics or censoring.
Time-to event percentiles are calculated by the Kaplan Meier method and event free rates are calculated by the life-table method.
Exacerbation episodes less than 7 days apart were considered to be one continuous exacerbation.

Exacerbations requiring treatment with systemic corticosteroids and/or antibiotics but no hospitalization

	Tio N=480	Pbo N=232
Patients with a COPD exacerbation, n/N(%)	81/480 (16.9)	54/232 (23.3)
Maximum follow-up time (days)	198	209
Median follow-up time (days)	183	182
Time-to event (days), Percentiles		
25% (95% CI)	n.e. (n.e., n.e.)	180 (80, n.e.)
Median (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
75% (95% CI)	n.e. (n.e., n.e.)	n.e. (n.e., n.e.)
Event-free rates, % (95% CI)		
26 Weeks	82.1 (78.6, 85.7)	74.5 (68.6, 80.4)

n.e. = not estimable.
Patients who do not experience a COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics are censored at the date of last study medication.
Follow-up time = Time from randomization until the start of the first COPD exacerbation leading to hospitalization/treatment with systemic corticosteroids and/or antibiotics or censoring.
Time-to event percentiles are calculated by the Kaplan Meier method and event free rates are calculated by the life-table method.
Exacerbation episodes less than 7 days apart were considered to be one continuous exacerbation.

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Analysis of 24-hourly mean heart rate (beats per minute) in the Holter sub-group

Visit	Treatment	n	Baseline Mean (SE)	Treatment LS Mean	Treatment SE	Comparison	Treatment difference LS Mean	SE	95% CI		p-value
Day 85	QVA149 (N=59)	35	78.3 (1.31)	80.8	1.50	QVA149 - Pbo	1.9	2.00	(-2.1,	5.8)	0.353
						QVA149 - QAB149	0.9	1.53	(-2.1,	4.0)	0.543
						QVA149 - NVA237	1.3	1.67	(-2.0,	4.7)	0.421
	QAB149 (N=52)	38	81.0 (1.66)	79.9	1.35	QAB149 - Pbo	0.9	1.98	(-3.0,	4.9)	0.638
						QAB149 - NVA237	0.4	1.66	(-2.9,	3.7)	0.803
	NVA237 (N=55)	27	82.2 (1.87)	79.4	1.57	NVA237 - Pbo	0.5	2.13	(-3.7,	4.7)	0.808
	Pbo (N=24)	15	80.9 (1.94)	78.9	1.95						
Day 183	QVA149 (N=59)	36	78.1 (1.32)	79.8	1.68	QVA149 - Pbo	2.8	2.17	(-1.5,	7.1)	0.198
						QVA149 - QAB149	1.1	1.70	(-2.2,	4.5)	0.505
						QVA149 - NVA237	-0.7	1.87	(-4.5,	3.0)	0.694
	QAB149 (N=52)	36	80.9 (1.81)	78.6	1.57	QAB149 - Pbo	1.7	2.15	(-2.6,	5.9)	0.438
Day 183	QAB149 (N=52)	36	80.9 (1.81)	78.6	1.57	QAB149 - NVA237	-1.9	1.85	(-5.6,	1.8)	0.312
	NVA237 (N=55)	26	82.2 (2.02)	80.5	1.75	NVA237 - Pbo	3.6	2.30	(-1.0,	8.1)	0.124
	Pbo (N=24)	16	80.4 (1.90)	77.0	2.09						

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: heart rate = treatment + baseline heart rate + baseline smoking status + baseline ICS use + region + center (region) + error. Center was included as a random effect nested within region.
24-hourly mean heart rate from the last assessment prior to first dose of study drug on Day 1, from either a scheduled or unscheduled visit, taken from the 24-hourly data, is used as baseline.
The post-baseline 24-hourly mean heart rate is the mean heart rate over the 24 hour period, derived using hourly mean heart rates.
If a visit has an overall Holter interpretation of 'not evaluable' then any numeric data collected at that visit are not

Rate of Moderate or Severe COPD Exacerbation

Treatment	Rate	n	Comparison	Ratio of rates	95% CI	p-value
QVA149 (N=474)	0.46	465	QVA149 / Pbo	0.57	(0.41, 0.79)	<0.001
			QVA149 / QAB149	0.73	(0.55, 0.96)	0.025
			QVA149 / NVA237	0.90	(0.68, 1.21)	0.494
			QVA149 / Tio	0.98	(0.73, 1.32)	0.904
QAB149 (N=476)	0.59	474	QAB149 / Pbo	0.78	(0.57, 1.07)	0.119
			QAB149 / NVA237	1.25	(0.95, 1.64)	0.116
			QAB149 / Tio	1.35	(1.02, 1.79)	0.034
NVA237 (N=473)	0.53	463	NVA237 / Pbo	0.63	(0.45, 0.86)	0.004
			NVA237 / Tio	1.09	(0.81, 1.45)	0.576
Tio (N=480)	0.45	476	Tio / Pbo	0.58	(0.42, 0.80)	<0.001
Pbo (N=232)	0.75	230				

CI = confidence interval. n = number of patients included in the analysis.
Exacerbation episodes less than 7 days apart were considered to be one continuous exacerbation.
Rate is the number of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years.
Negative binomial regression model: log (exacerbation rate) = treatment + baseline smoking status + baseline ICS use + baseline total symptom score + baseline COPD exacerbation history + FEV1 reversibility components + region.
Log(length of time in the study) is included in the model as an offset term.
A ratio of rates < 1 favors the treatment group in the numerator of the ratio.

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Safety Results

Adverse Events by System Organ Class

	QVA149 N = 474 n (%)	QAB149 N = 476 n (%)	NVA237 N = 473 n (%)	Tio N = 480 n (%)	Pbo N = 232 n (%)
Patients with any AE (s)	261 (55.1)	291 (61.1)	290 (61.3)	275 (57.3)	134 (57.8)
Primary system organ class					
Respiratory, thoracic and mediastinal disorders	163 (34.4)	182 (38.2)	176 (37.2)	166 (34.6)	99 (42.7)
Infections and infestations	124 (26.2)	151 (31.7)	144 (30.4)	157 (32.7)	83 (35.8)
Musculoskeletal and connective tissue disorders	37 (7.8)	37 (7.8)	37 (7.8)	35 (7.3)	18 (7.8)
Gastrointestinal disorders	35 (7.4)	45 (9.5)	49 (10.4)	45 (9.4)	25 (10.8)
Nervous system disorders	28 (5.9)	24 (5.0)	25 (5.3)	24 (5.0)	10 (4.3)
General disorders and administration site conditions	26 (5.5)	24 (5.0)	26 (5.5)	21 (4.4)	9 (3.9)
Injury, poisoning and procedural complications	17 (3.6)	15 (3.2)	20 (4.2)	14 (2.9)	5 (2.2)
Skin and subcutaneous tissue disorders	16 (3.4)	18 (3.8)	20 (4.2)	10 (2.1)	4 (1.7)
Vascular disorders	16 (3.4)	14 (2.9)	13 (2.7)	10 (2.1)	5 (2.2)
Metabolism and nutrition disorders	10 (2.1)	9 (1.9)	11 (2.3)	10 (2.1)	6 (2.6)
Cardiac disorders	8 (1.7)	12 (2.5)	16 (3.4)	10 (2.1)	10 (4.3)
Renal and urinary disorders	8 (1.7)	7 (1.5)	6 (1.3)	5 (1.0)	1 (0.4)
Eye disorders	7 (1.5)	12 (2.5)	5 (1.1)	12 (2.5)	1 (0.4)
Psychiatric disorders	7 (1.5)	10 (2.1)	3 (0.6)	3 (0.6)	4 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (1.3)	9 (1.9)	6 (1.3)	1 (0.2)	5 (2.2)
Ear and labyrinth disorders	5 (1.1)	6 (1.3)	4 (0.8)	4 (0.8)	1 (0.4)
Investigations	3 (0.6)	10 (2.1)	9 (1.9)	4 (0.8)	7 (3.0)
Blood and lymphatic system disorders	3 (0.6)	5 (1.1)	3 (0.6)	4 (0.8)	1 (0.4)
Endocrine disorders	3 (0.6)	0	1 (0.2)	1 (0.2)	0
Immune system disorders	2 (0.4)	2 (0.4)	3 (0.6)	0	2 (0.9)
Reproductive system and breast disorders	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)	2 (0.9)
Congenital, familial and genetic disorders	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Hepatobiliary disorders	0	3 (0.6)	3 (0.6)	4 (0.8)	1 (0.4)
Surgical and medical procedures	0	0	1 (0.2)	0	0

Primary system organ classes are sorted in descending order of frequency in the QVA149 treatment group.
A patient with multiple AEs is counted only once in the any AE row.
A patient with multiple AEs within a primary system organ class is counted only once for that SOC.
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 Frequently Reported AEs Overall by Preferred Term n (%)

	QVA149 N = 474	QAB149 N = 476	NVA237 N = 473	Tio N = 480	Pbo N = 232
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any AE (s)	261 (55.1)	291 (61.1)	290 (61.3)	275 (57.3)	134 (57.8)
Preferred term					
Chronic obstructive pulmonary disease	137 (28.9)	153 (32.1)	150 (31.7)	138 (28.8)	91 (39.2)
Nasopharyngitis	31 (6.5)	35 (7.4)	46 (9.7)	40 (8.3)	23 (9.9)
Cough	26 (5.5)	38 (8.0)	18 (3.8)	21 (4.4)	8 (3.4)
Upper respiratory tract infection	20 (4.2)	32 (6.7)	20 (4.2)	24 (5.0)	13 (5.6)
Oropharyngeal pain	17 (3.6)	7 (1.5)	10 (2.1)	10 (2.1)	7 (3.0)
Viral upper respiratory tract infection	15 (3.2)	11 (2.3)	13 (2.7)	12 (2.5)	7 (3.0)
Headache	13 (2.7)	13 (2.7)	10 (2.1)	11 (2.3)	3 (1.3)
Bronchitis	11 (2.3)	12 (2.5)	11 (2.3)	8 (1.7)	7 (3.0)
Upper respiratory tract infection bacterial	10 (2.1)	13 (2.7)	15 (3.2)	22 (4.6)	13 (5.6)
Urinary tract infection	10 (2.1)	7 (1.5)	6 (1.3)	3 (0.6)	1 (0.4)
Hypertension	9 (1.9)	8 (1.7)	9 (1.9)	9 (1.9)	2 (0.9)
Lower respiratory tract infection	9 (1.9)	15 (3.2)	7 (1.5)	12 (2.5)	5 (2.2)
Non-cardiac chest pain	9 (1.9)	3 (0.6)	2 (0.4)	2 (0.4)	1 (0.4)
Back pain	8 (1.7)	11 (2.3)	17 (3.6)	8 (1.7)	5 (2.2)
Pharyngitis	7 (1.5)	2 (0.4)	8 (1.7)	6 (1.3)	1 (0.4)
Pyrexia	7 (1.5)	13 (2.7)	7 (1.5)	3 (0.6)	4 (1.7)
Dyspnea	6 (1.3)	10 (2.1)	13 (2.7)	10 (2.1)	1 (0.4)
Influenza	6 (1.3)	7 (1.5)	9 (1.9)	8 (1.7)	2 (0.9)
Constipation	5 (1.1)	8 (1.7)	7 (1.5)	4 (0.8)	1 (0.4)
Gastrooesophageal reflux disease	5 (1.1)	6 (1.3)	5 (1.1)	4 (0.8)	1 (0.4)
Musculoskeletal pain	5 (1.1)	3 (0.6)	0	2 (0.4)	1 (0.4)
Nausea	5 (1.1)	7 (1.5)	3 (0.6)	5 (1.0)	1 (0.4)
Respiratory tract infection viral	5 (1.1)	4 (0.8)	2 (0.4)	1 (0.2)	1 (0.4)
Arthralgia	4 (0.8)	5 (1.1)	3 (0.6)	5 (1.0)	3 (1.3)
Diarrhoea	4 (0.8)	6 (1.3)	6 (1.3)	2 (0.4)	7 (3.0)
Dry mouth	4 (0.8)	2 (0.4)	4 (0.8)	5 (1.0)	1 (0.4)
Pneumonia	4 (0.8)	3 (0.6)	4 (0.8)	6 (1.3)	3 (1.3)
Productive cough	4 (0.8)	2 (0.4)	1 (0.2)	5 (1.0)	2 (0.9)
Fatigue	3 (0.6)	0	5 (1.1)	4 (0.8)	0
Pain in extremity	3 (0.6)	5 (1.1)	4 (0.8)	4 (0.8)	1 (0.4)
Sputum increased	3 (0.6)	3 (0.6)	6 (1.3)	1 (0.2)	1 (0.4)
Vomiting	3 (0.6)	3 (0.6)	2 (0.4)	5 (1.0)	3 (1.3)
Abdominal pain	2 (0.4)	4 (0.8)	5 (1.1)	2 (0.4)	1 (0.4)
Muscle spasms	2 (0.4)	6 (1.3)	3 (0.6)	3 (0.6)	0
Cataract	1 (0.2)	2 (0.4)	2 (0.4)	5 (1.0)	0
Gastroenteritis	1 (0.2)	5 (1.1)	2 (0.4)	3 (0.6)	2 (0.9)
Palpitations	1 (0.2)	0	1 (0.2)	2 (0.4)	3 (1.3)
Rhinitis	1 (0.2)	7 (1.5)	4 (0.8)	3 (0.6)	1 (0.4)

	QVA149 N = 474 n (%)	QAB149 N = 476 n (%)	NVA237 N = 473 n (%)	Tio N = 480 n (%)	Pbo N = 232 n (%)
Sinusitis	0	8 (1.7)	4 (0.8)	6 (1.3)	1 (0.4)
Wheezing	0	3 (0.6)	4 (0.8)	5 (1.0)	1 (0.4)

Preferred terms are sorted in descending order of frequency in the QVA149 treatment group.
A patient with multiple AEs is counted only once in the any AE row.
A patient with multiple AEs within a preferred term is counted only once for that preferred term.
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.
Source: PT-Table 14.3.1-1.1

Serious Adverse Events and Deaths

	QVA149 N = 474 n (%)	QAB149 N = 476 n (%)	NVA237 N = 473 n (%)	Tio N = 480 n (%)	Pbo N = 232 n (%)
Patients with any AE(s)	261 (55.1)	291 (61.1)	290 (61.3)	275 (57.3)	134 (57.8)
Serious AEs or AE discontinuations					
Death*	1 (0.2)	2 (0.4)	1 (0.2)	3 (0.6)	0
Death**	0	1 (0.2)	1 (0.2)	0	0
SAE(s)	22 (4.6)	26 (5.5)	29 (6.1)	19 (4.0)	13 (5.6)
Discontinued due to AE(s)	6 (1.3)	24 (5.0)	14 (3.0)	10 (2.1)	10 (4.3)
Discontinued due to SAE(s)	3 (0.6)	11 (2.3)	6 (1.3)	5 (1.0)	3 (1.3)
Discontinued due to non-SAE(s)	3 (0.6)	13 (2.7)	8 (1.7)	5 (1.0)	7 (3.0)

A patient could have discontinued study treatment due to both a SAE and a non-SAE.
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.
Death* = deaths between a patient's first treatment and within 30 days of the last dose of study drug.
Death** = death occurred more than 30 days after last dose of study drug but before the end of the follow-up visit

Number (%) of patients with newly occurring or worsening notable QTc values (according to Fridericia's formula) and maximum increase from baseline on study treatment

According to Fridericia's formula	QVA149 N=474 n/N' (%)	QAB149 N=476 n/N' (%)	NVA237 N=473 n/N' (%)	Tio N=480 n/N' (%)	Pbo N=232 n/N' (%)
QTc >450 ms	22/455 (4.8)	24/453 (5.3)	21/446 (4.7)	18/458 (3.9)	12/207 (5.8)
QTc >480 ms	2/455 (0.4)	0/453	2/446 (0.4)	2/458 (0.4)	0/207
QTc >500 ms	1/455 (0.2)	0/453	0/446	0/458	0/207
Maximum increase from baseline					
30 - 60 ms	43/455 (9.5)	43/453 (9.5)	23/446 (5.2)	26/458 (5.7)	20/207 (9.7)
>60 ms	1/455 (0.2)	0/453	2/446 (0.4)	2/458 (0.4)	0/207

N'= Number of patients with data during treatment period.
QTc was calculated using Fridericia's formula: QTc = QT (ms) / cube root RR (s).

Number (%) of patients with worsening of ventricular ectopies (VEs) after baseline (Holter monitoring subgroup)

Baseline finding	Worsening of VEs after baseline	QVA149 N=59 N'=48 n (%)	QAB149 N=52 N'=46 n (%)	NVA237 N=55 N'=42 n (%)	Pbo N=24 N'=23 n (%)
0 VEs/hour	> 30 VEs/hour	0	0	0	0
> 0 - 100 VEs/hour	≥10 fold increase in VEs	6 (12.5)	3 (6.5)	5 (11.9)	4 (17.4)
> 100 VEs/hour	≥ 3 fold increase in VEs	0	0	0	0
VE run events > 0	≥ 10 fold increase in VE run events	0	0	0	0
VE run events = 0	VE run events > 3 or at least one with > 5 beats	0	1 (2.2)	1 (2.4)	1 (4.3)
Total	Any worsening of VEs after baseline	6 (12.5)	4 (8.7)	6 (14.3)	4 (17.4)

Data with less than 18 hours of acceptable quality recording time out of each 24 hourly recording are included in this analysis.
Patients are counted as having a worsening of ventricular ectopies after baseline if they experienced an increase of total VEs or VE run events at any post-baseline visit.
N' = Total number of patients with evaluable holter measurements at baseline and at least one post-baseline visit.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

06-Jul-2012

Date Inclusion on Novartis Clinical Trial Results Database

07-Feb-2013

Date of Latest Update

Not applicable