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Trial record **1 of 1** for: CQVA149A2304

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Effect of QVA149 Versus NVA237 and Tiotropium on Chronic Obstructive Pulmonary Disorder (COPD) Exacerbations (SPARK)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01120691

First received: May 5, 2010
Last updated: October 29, 2013
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History of Changes

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Results First Received: July 9, 2013

Study Type:	Interventional
Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition:	Chronic Obstructive Pulmonary Disease
Interventions:	Drug: QVA149 Drug: NVA237 Drug: tiotropium

	Drug: Salbutamol/albuterol

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
A total of 3865 participants were screened of whom 2224 were randomized to 1 of the 3 treatment groups (QVA149, NVA237 or tiotropium) in a 1:1:1 ratio for at least 64 weeks (maximum 76 weeks) of treatment period.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
5 (QVA149), 2 (NVA237) and 3 (tiotropium) participants were randomized but did not receive study drug.

Reporting Groups

	Description
QVA149	QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period. Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period. Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Participant Flow: Overall Study

	QVA149	NVA237	Open-label Tiotropium
STARTED	**741**	**741**	**742**

Full Analysis Set (FAS)	**736**	**739**	**739**
Safety Set (SAF)	**736**	**740**	**739**
Modified Safety Set (mSAF)	**729**	**740**	**737**
Modified Full Analysis Set (mFAS)	**729**	**739**	**737**
COMPLETED	**570**	**538**	**559**
NOT COMPLETED	**171**	**203**	**183**
Adverse Event	**59**	**67**	**47**
Subject withdrew consent	**33**	**50**	**44**
Death	**21**	**22**	**24**
Unsatisfactory therapeutic effect	**18**	**32**	**38**
Administrative problems	**15**	**8**	**9**
Protocol deviation	**13**	**12**	**12**
Lost to Follow-up	**5**	**6**	**4**
Abnormal test procedure result(s)	**3**	**2**	**1**
Patient's inability to use the device	**3**	**1**	**0**
Abnormal laboratory value(s)	**1**	**3**	**4**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

The modified safety set (mSAF set) includes all patients in the safety set except patients from a site who had major GCP issues.

Reporting Groups

	Description
QVA149	QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period. Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period. Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Total	Total of all reporting groups

Baseline Measures

	QVA149	NVA237	Open-label Tiotropium	Total
Number of Participants [units: participants]	**729**	**740**	**737**	**2206**
Age [units: years] Mean (Standard Deviation)	**63.1 (8.07)**	**63.1 (7.98)**	**63.6 (7.79)**	**63.3 (7.95)**
Gender [units: participants]				
Female	**173**	**198**	**184**	**555**
Male	**556**	**542**	**553**	**1651**

Outcome Measures

Hide All Outcome Measures

1. Primary: Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and NVA237 Treatment Arms During the Treatment Period. [Time Frame: 64 weeks]

Measure Type	Primary
Measure Title	Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and NVA237 Treatment Arms During the Treatment Period.
Measure Description	A Chronic Obstructive Pulmonary Disease (COPD) exacerbation was defined as a worsening of two or more of the following major symptoms for at least 2 consecutive days: dyspnea, sputum volume or sputum purulence OR a worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, cough or wheezing. A COPD exacerbation was considered of moderate severity if treatment with systemic glucocorticosteroids or antibiotics or both was required and severe if hospitalization was required. An emergency room (ER) visit of longer than 24 hours was considered a hospitalization. Rate of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site , which had major issues with Good Clinical Practice (GCP) compliance.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for

	at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237
Number of Participants Analyzed [units: participants]	**729**	**739**
Number of Moderate to Severe COPD Exacerbation Analyzed [units: Moderate to Severe COPD Exacerbation]	**812**	**900**
Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and NVA237 Treatment Arms During the Treatment Period. [units: Exacerbations per year]	**0.94**	**1.07**

No statistical analysis provided for Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and NVA237 Treatment Arms During the Treatment Period.

2. Secondary: Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and Open-label Tiotropium Treatment Arms During the Treatment Period. [Time Frame: 76 weeks]

Measure Type	Secondary
Measure Title	Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and Open-label Tiotropium Treatment Arms During the Treatment Period.
Measure Description	A Chronic Obstructive Pulmonary Disease (COPD) exacerbation was defined as a worsening of two or more of the following major symptoms for at least 2 consecutive days: dyspnea, sputum volume or sputum purulence OR a

	worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, cough or wheezing. A COPD exacerbation was considered of moderate severity if treatment with systemic glucocorticosteroids or antibiotics or both was required and severe if hospitalization was required. An emergency room (ER) visit of longer than 24 hours was considered a hospitalization. Rate of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years
Time Frame	76 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site, which had major issues with GCP compliance.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	**Open-label Tiotropium**
Number of Participants Analyzed		

[units: participants]	**729**	**737**
Number of Moderate to Severe COPD Exacerbation Analyzed [units: Moderate to Severe COPD Exacerbation]	**812**	**898**
Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and Open-label Tiotropium Treatment Arms During the Treatment Period. [units: Exacerbations per year]	**0.94**	**1.06**

No statistical analysis provided for Rate of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in QVA149 and Open-label Tiotropium Treatment Arms During the Treatment Period.

3. Secondary: Time to First Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Between QVA149, NVA237 and Open Label Tiotropium During the Treatment Period [Time Frame: 64 weeks]

Measure Type	Secondary
Measure Title	Time to First Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Between QVA149, NVA237 and Open Label Tiotropium During the Treatment Period
Measure Description	A Chronic Obstructive Pulmonary Disease (COPD) exacerbation was defined as a worsening of two or more of the following major symptoms for at least 2 consecutive days: dyspnea, sputum volume or sputum purulence OR a worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, cough or wheezing. A COPD exacerbation was considered of moderate severity if treatment with systemic glucocorticosteroids or antibiotics or both was required and severe if hospitalization was required. An emergency room (ER) visit of longer than 24 hours was considered a hospitalization. Rate of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site, which had major issues with GCP compliance. Only patients with a moderate or severe COPD exacerbation were included in this analysis.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	**NVA237**	**Open-label Tiotropium**
Number of Participants Analyzed **[units: participants]**	**419**	**426**	**402**
Time to First Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Between QVA149, NVA237 and Open Label Tiotropium During the Treatment Period **[units: days]** **Median (95% Confidence Interval)**	**296** **(267 to 358)**	**287** **(255 to 325)**	**331** **(280 to 390)**

No statistical analysis provided for Time to First Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbation Between QVA149, NVA237 and Open Label Tiotropium During the Treatment Period

4. Secondary: Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Requiring the Use of Both Systemic Glucocorticosteroids and Antibiotics [Time Frame: 64 weeks]

Measure Type	Secondary
Measure Title	Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Requiring the Use of Both Systemic Glucocorticosteroids and Antibiotics
Measure Description	Rate of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site, which had major issues with GCP compliance. The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study drug and data was available for analysis.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least

	64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed [units: participants]	**729**	**739**	**737**
Number of exacerbations Analyzed [units: exacerbations]	**403**	**491**	**461**
Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Requiring the Use of Both Systemic Glucocorticosteroids and Antibiotics [units: exacerbations per year]	**0.46**	**0.58**	**0.54**

No statistical analysis provided for Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Requiring the Use of Both Systemic Glucocorticosteroids and Antibiotics

5. Secondary: Number of Days With Moderate or Severe Exacerbation That Required Treatment With Systemic Corticosteroids and Antibiotics [Time Frame: 64 weeks]

Measure Type	Secondary
Measure Title	Number of Days With Moderate or Severe Exacerbation That Required Treatment With Systemic Corticosteroids and Antibiotics
Measure Description	The number of exacerbation days is defined as the sum of the duration of days recorded as an exacerbation for all exacerbations recorded per patient.
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site with GCP non-compliance. This is a sub-group analysis with mutually exclusive population in each category for analysis.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	**NVA237**	**Open-label Tiotropium**
Number of Participants Analyzed **[units: participants]**	**528**	**575**	**556**
Number of Days With Moderate or Severe Exacerbation That Required Treatment With Systemic Corticosteroids and Antibiotics **[units: Days]** **Mean (Standard Deviation)**			
systemic corticosteroids [n= 97, 108, 109]	**20.49 (25.426)**	**25.22 (42.674)**	**17.57 (17.797)**

antibiotics [n= 195, 177, 177]	**25.08 (47.035)**	**18.10 (21.790)**	**25.94 (50.007)**
corticosteroids and antibiotic [n= 266, 290, 270]	**22.10 (49.999)**	**26.18 (52.336)**	**22.03 (42.513)**

No statistical analysis provided for Number of Days With Moderate or Severe Exacerbation That Required Treatment With Systemic Corticosteroids and Antibiotics

6. Secondary: 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. [Time Frame: 64 weeks]

Measure Type	Secondary
Measure Title	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.
Measure Description	Time to Study Withdrawal or Premature Discontinuation for Any Reason was analyzed for each treatment group using a Kaplan-Meier estimation for the modified safety set. Patients who did not discontinue early were censored at the final visit of the treatment phase.
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified safety set (mSAF set) includes all patients in the safety set except patients from a site who had major GCP issues. The Safety set includes all patients who received at least one dose of study drug whether or not being randomized. Analysis population included patients with study withdrawal or premature discontinuation for any reason.

Reporting Groups

	Description

QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed **[units: participants]**	**159**	**202**	**178**
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. **[units: days]** **Median (95% Confidence Interval)**	**NA** [1]	**NA** [1]	**NA** [1]

[1] Less than 50% of patients had withdrawn from the study or prematurely discontinued for any reason.

No statistical analysis provided for 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.

7. Secondary: 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 [Time Frame: 64 weeks]

Measure Type	Secondary

Measure Title	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
Measure Description	Percentage of Patients With Study Withdrawal or Premature Discontinuation for Any Reason was analyzed for each treatment group using a Kaplan-Meier estimation for the modified safety set. Patients who did not discontinue early were censored at the final visit of the treatment phase.
Time Frame	64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified safety set (mSAF set) includes all patients in the safety set except patients from a site who had major GCP issues. The Safety set includes all patients who received at least one dose of study drug whether or not being randomized

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	**NVA237**	**Open-label Tiotropium**

Number of Participants Analyzed [units: participants]	**729**	**740**	**737**
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 [units: percentage of participants]	**21.8**	**27.3**	**24.2**

No statistical analysis provided for 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

8. Secondary: Cumulative Rates of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations for Multiple COPD Exacerbation at Different Time Points [Time Frame: 26, 52, 64, 76 weeks]

Measure Type	Secondary
Measure Title	Cumulative Rates of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations for Multiple COPD Exacerbation at Different Time Points
Measure Description	Cumulative rates were estimated using Anderson and Gill method. Chronic Obstructive Pulmonary Disease (COPD) exacerbations are considered to be moderate if treatment with systemic corticosteroids and/or antibiotics was required. COPD exacerbations are considered to be severe if treatment for moderate severity and hospitalization were required. Rate of moderate or severe exacerbations per year = total number of moderate or severe exacerbations / total number of treatment years
Time Frame	26, 52, 64, 76 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set(mFAS) included all patients in the Full Analysis Set (FAS) except patients from a site, which had major issues with

GCP compliance. FAS include all randomized patients who received at least one dose of study drug and data was available for analysis.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks.Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed [units: participants]	**729**	**739**	**737**
Number of Moderate or Severe COPD Exacerbations Analyzed [units: Moderate or Severe COPD Exacerbations]	**831**	**926**	**897**
Cumulative Rates of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations for Multiple COPD Exacerbation at Different Time Points [units: exacerbations per year] Number (95% Confidence Interval)			
26 weeks	**0.57 (0.51 to 0.62)**	**0.65 (0.58 to 0.71)**	**0.63 (0.56 to 0.70)**
	0.99	**1.13**	**1.11**

52 weeks	**(0.91 to 1.09)**	**(1.03 to 1.25)**	**(1.00 to 1.23)**
64 weeks	**1.19 (1.08 to 1.30)**	**1.36 (1.24 to 1.49)**	**1.31 (1.19 to 1.46)**
76 weeks	**1.39 (1.27 to 1.53)**	**1.59 (1.45 to 1.74)**	**1.55 (1.40 to 1.71)**

No statistical analysis provided for Cumulative Rates of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations for Multiple COPD Exacerbation at Different Time Points

9. Secondary: Pre-dose 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 [Time Frame: 4, 12, 26, 38, 52 and 64 weeks]

Measure Type	Secondary
Measure Title	Pre-dose 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
Measure Description	Pulmonary function assessments were performed using centralized spirometry. The spirometer was customized and programmed according to the requirements of the study protocol in accordance with American Thoracic Society (ATS) standards. Spirometry measurements taken were FEV1 at -45 minutes and -15 minutes pre-dose. Three acceptable maneuvers had to be performed for each time point. The FEV1 values recorded had to be the highest values measured irrespective of whether or not they occurred on the same curve. The mixed model for analysis contained treatment as a fixed effect with average of the 45 minutes and 15 minutes pre dose FEV1 measurements at day 1 as the baseline measurement, FEV1 prior to inhalation and FEV1 60 minutes post inhalation of two short acting bronchodilators (components of reversibility at -14 Day) as covariates.
Time Frame	4, 12, 26, 38, 52 and 64 weeks

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set(mFAS) included all patients in the Full Analysis Set (FAS) except patients from a site, which had major issues with GCP compliance. FAS include all randomized patients who received at least one dose of study drug and data was available for analysis. Each category has patients with assessable data at that particular time.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed **[units: participants]**	**729**	**739**	**737**
Pre-dose 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 **[units: L (liters)]** **Least Squares Mean (Standard Error)**			

predose FEV1 Week 4 (n= 656,654,630)	**1.08 (0.009)**	**0.99 (0.009)**	**1.00 (0.009)**
predose FEV1 Week 12 (n= 666,663,653)	**1.08 (0.010)**	**1.01 (0.009)**	**1.01 (0.009)**
predose FEV1 Week 26 (n= 604,577,599)	**1.07 (0.010)**	**0.99 (0.010)**	**1.00 (0.010)**
predose FEV1 Week 38 (n= 593,549,583)	**1.08 (0.011)**	**1.00 (0.011)**	**1.00 (0.011)**
predose FEV1 Week 52 (n= 557,538,548)	**1.05 (0.011)**	**0.98 (0.011)**	**0.99 (0.011)**
predose FEV1 Week 64 (n= 549,504,530)	**1.05 (0.011)**	**0.98 (0.011)**	**0.99 (0.011)**

No statistical analysis provided for Pre-dose 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

10. Secondary: Pre-dose Forced Vital Capacity (FVC)After 4, 12, 26, 38, 52 and 64 Weeks of Treatment Between QVA149, NVA237 and Open Label Tiotropium [Time Frame: 4, 12, 26, 38, 52 and 64 weeks]

Measure Type	Secondary
Measure Title	Pre-dose Forced Vital Capacity (FVC)After 4, 12, 26, 38, 52 and 64 Weeks of Treatment Between QVA149, NVA237 and Open Label Tiotropium
Measure Description	Pulmonary function assessments were performed using centralized spirometry. The spirometer was customized and programmed according to the requirements of the study protocol in accordance with American Thoracic Society (ATS)

	standards. Pre-dose Forced Vital Capacity (FVC) is defined as the average of the -15 minutes and the -45 minutes FVC values. Baseline is defined as the average of the -45 minutes and -15 minutes 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
Time Frame	4, 12, 26, 38, 52 and 64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set(mFAS) included all patients in the Full Analysis Set (FAS) except patients from a site, which had major issues with GCP compliance. FAS include all randomized patients who received at least one dose of study drug and data was available for analysis. Each category has patients with assessable data at that particular time.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	**NVA237**	**Open-label Tiotropium**

Number of Participants Analyzed [units: participants]	**729**	**739**	**737**
Pre-dose Forced Vital Capacity (FVC)After 4, 12, 26, 38, 52 and 64 Weeks of Treatment Between QVA149, NVA237 and Open Label Tiotropium [units: L (liters)] Least Squares Mean (Standard Error)			
predose FVC Week 4 (n= 656,654,630)	**2.74 (0.020)**	**2.59 (0.019)**	**2.60 (0.019)**
predose FVC Week 12 (n= 623,621,619)	**2.77 (0.021)**	**2.63 (0.021)**	**2.65 (0.021)**
predose FVC Week 26 (n= 604,577,599)	**2.73 (0.023)**	**2.60 (0.022)**	**2.61 (0.022)**
predose FVC Week 38 (n= 592,548,580)	**2.76 (0.025)**	**2.65 (0.025)**	**2.63 (0.025)**
predose FVC Week 52 (n= 557,538,547)	**2.68 (0.025)**	**2.58 (0.025)**	**2.58 (0.025)**
predose FVC Week 64 (n= 549,502,526)	**2.67 (0.025)**	**2.57 (0.025)**	**2.59 (0.025)**

No statistical analysis provided for Pre-dose Forced Vital Capacity (FVC)After 4, 12, 26, 38, 52 and 64 Weeks of Treatment Between QVA149, NVA237 and Open Label Tiotropium

11. Secondary: Change in Mean Daily Use (Number of Puffs) of Rescue Therapy Between QVA149, NVA237 and Open Label Tiotropium From Baseling Over the 64 Week Treatment Period [Time Frame: Baseline (14 day run-in), 64 weeks]

Measure Type	Secondary
Measure Title	Change in Mean Daily Use (Number of Puffs) of Rescue Therapy Between QVA149, NVA237 and Open Label Tiotropium From Baseling Over the 64 Week Treatment Period
Measure Description	The severe or less FEV1 % predicted (post bronchodilator)>=30%; very severe=> FEV1 % predicted(the post

	bronchodilator)<30%.Number of puffs of rescue medication taken in the previous 12 hours was recorded in patient diary in the morning and in the evening for 26 weeks.The total number of puffs per day was calculated and divided by the number of days with data to determine the mean daily number of puffs of rescue medication for each patient.Rescue medication data recorded during the 14 day run-in was used to calculate the baseline.A negative change from baseline indicates improvement. A mixed model was used with treatment as a fixed effect with baseline number of puffs and FEV1 prior to inhalation and FEV1 60 minutes post inhalation of two short acting bronchodilators (components of reversibility at Day -14) as covariates.
Time Frame	Baseline (14 day run-in), 64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set mFAS included all patients in the Full analysis set except patients from a site,which had major issues with GCP compliance. The Full Analysis Set includes all randomized patients who received at least one dose of study drug and data was available for analysis. Patients with evaluable data were included in this analysis

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

			Open-label

	QVA149	NVA237	Tiotropium
Number of Participants Analyzed [units: participants]	**708**	**724**	**709**
Change in Mean Daily Use (Number of Puffs) of Rescue Therapy Between QVA149, NVA237 and Open Label Tiotropium From Baseling Over the 64 Week Treatment Period [units: # puffs] Least Squares Mean (Standard Error)			
Mean Daily # puffs Severe or Less(n=565,575,561)	**-2.3 (0.137)**	**-1.5 (0.135)**	**-1.6 (0.136)**
Mean Daily # puffs Very Severe (n=143,149,148)	**-2.1 (0.234)**	**-1.1 (0.228)**	**-1.0 (0.228)**

No statistical analysis provided for Change in Mean Daily Use (Number of Puffs) of Rescue Therapy Between QVA149, NVA237 and Open Label Tiotropium From Baseling Over the 64 Week Treatment Period

12. Secondary: Change From Baseline of Percentage of Days Without Rescue Therapy Use Between QVA149,NVA237 and Open Label Tiotropium Over the 64 Week Treatment Period [Time Frame: Baseline (14 day run-in), 64 weeks]

Measure Type	Secondary
Measure Title	Change From Baseline of Percentage of Days Without Rescue Therapy Use Between QVA149,NVA237 and Open Label Tiotropium Over the 64 Week Treatment Period
Measure Description	A day with no rescue medication use is defined from the diary data as any day where the patient recorded no rescue medicine use during the previous 12 hours. The percentage of days is calculated by the number of days with no rescue medicine use/total number of days with evaluable data X 100. A mixed model was used with treatment as a fixed effect with baseline number of puffs 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.

Time Frame	Baseline (14 day run-in), 64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set(mFAS)included all patients in the Full analysis set except patients from a site,which had major issues with GCP compliance. The Full Analysis Set includes all randomized patients who received at least one dose of study drug and data was available for analysis. Patients with evaluable data were included in this analysis

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed [units: participants]	**701**	**720**	**703**
Change From Baseline of Percentage of Days Without Rescue Therapy Use Between QVA149,NVA237 and Open Label Tiotropium Over the 64 Week Treatment Period	**29.36**	**21.65**	**23.86 (1.422)**

[units: percentage of days] **Least Squares Mean (Standard Error)**	**(1.445)**	**(1.410)**	

No statistical analysis provided for Change From Baseline of Percentage of Days Without Rescue Therapy Use Between QVA149,NVA237 and Open Label Tiotropium Over the 64 Week Treatment Period

13. Secondary: St. George's Respiratory Questionnaire (SGRQ) Scores Between QVA149, NVA237 and Open Label Tiotropium Over 12, 26, 38, 52 and 64 Weeks of Treatment [Time Frame: 12, 26, 38, 52 and 64 weeks]

Measure Type	Secondary
Measure Title	St. George's Respiratory Questionnaire (SGRQ) Scores Between QVA149, NVA237 and Open Label Tiotropium Over 12, 26, 38, 52 and 64 Weeks of Treatment
Measure Description	St. George's Respiratory Questionnaire (SGRQ) is a health related quality of life questionnaire consisting of 51 items in three components: symptoms, activity, and impacts. The lowest possible value is zero and the highest 100. Higher values correspond to greater impairment in quality of life. Mixed model used baseline SGRQ, baseline inhaled corticosteroid (ICS) use, Forced Expiratory Volume in 1 Second (FEV1) prior to inhalation of short acting beta-agonist (SABA), and FEV1 45 minutes post-inhalation of SABA as covariates. SGRQ total score is the sum of the scores from the three components; symptoms, activity and impacts.
Time Frame	12, 26, 38, 52 and 64 weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Modified Full Analysis Set (mFAS) included all patients in the Full analysis set except patients from a site, which had major issues with GCP compliance. The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study drug and data was available for analysis.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI)for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Measured Values

	QVA149	NVA237	Open-label Tiotropium
Number of Participants Analyzed [units: participants]	**729**	**739**	**737**
St. George's Respiratory Questionnaire (SGRQ) Scores Between QVA149, NVA237 and Open Label Tiotropium Over 12, 26, 38, 52 and 64 Weeks of Treatment [units: units on a scale] Least Squares Mean (Standard Error)			
Week 12 (n= 694,694,676)	**44.69 (0.612)**	**47.13 (0.603)**	**47.62 (0.607)**
Week 26 (n= 684,677,658)	**44.06 (0.655)**	**45.93 (0.647)**	**45.77 (0.651)**
Week 38 (n= 648,626,635)	**42.72 (0.667)**	**45.53 (0.663)**	**45.86 (0.660)**
Week 52 (n= 625,593,613)	**43.38 (0.722)**	**45.96 (0.723)**	**46.21 (0.714)**
Week 64 (n= 600,564,579)	**43.39**	**45.46**	**46.08 (0.778)**

	(0.778)	(0.780)	

No statistical analysis provided for St. George's Respiratory Questionnaire (SGRQ) Scores Between QVA149, NVA237 and Open Label Tiotropium Over 12, 26, 38, 52 and 64 Weeks of Treatment

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	Modified safety set (mSAF set) includes all patients in the safety set except patients from a site who had major GCP issues. The Safety set includes all patients who received at least one dose of study drug whether or not being randomized. Analysis population included patients with study withdrawal or premature discontinuation for any reason.

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device. for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Serious Adverse Events

	QVA149	NVA237	Open-label Tiotropium

Total, serious adverse events			
# participants affected / at risk	**167/729 (22.91%)**	**179/740 (24.19%)**	**165/737 (22.39%)**
Blood and lymphatic system disorders			
Anaemia † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Idiopathic thrombocytopenic purpura † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cardiac disorders			
Acute coronary syndrome † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Acute myocardial infarction † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**4/740 (0.54%)**	**2/737 (0.27%)**
Angina pectoris † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**3/740 (0.41%)**	**1/737 (0.14%)**
Angina unstable † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Arteriosclerosis coronary artery † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Atrial fibrillation † [1]			
# participants affected / at risk	**6/729 (0.82%)**	**3/740 (0.41%)**	**4/737 (0.54%)**
Atrial flutter † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**1/737 (0.14%)**
Cardiac arrest † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**4/740 (0.54%)**	**2/737 (0.27%)**
Cardiac failure † [1]			

# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**4/737 (0.54%)**
Cardiac failure acute † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cardiac failure chronic † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cardiac failure congestive † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cardio-respiratory arrest † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**3/740 (0.41%)**	**3/737 (0.41%)**
Cardiopulmonary failure † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cor pulmonale † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**3/740 (0.41%)**	**0/737 (0.00%)**
Cor pulmonale chronic † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Coronary artery disease † [1]			
# participants affected / at risk	**3/729 (0.41%)**	**2/740 (0.27%)**	**1/737 (0.14%)**
Ischaemic cardiomyopathy † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Left ventricular dysfunction † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Left ventricular hypertrophy † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Mitral valve incompetence † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**

Myocardial infarction † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**3/740 (0.41%)**	**4/737 (0.54%)**
Myocardial ischaemia † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pericardial effusion † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pericarditis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Right ventricular failure † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Supraventricular tachyarrhythmia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Tachycardia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Congenital, familial and genetic disorders			
Congenital laryngeal stridor † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Phimosis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Ear and labyrinth disorders			
Acute vestibular syndrome † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Vertigo † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Endocrine disorders			

Goitre † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Eye disorders			
Angle closure glaucoma † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cataract † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Retinal detachment † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Vision blurred † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Gastrointestinal disorders			
Abdominal distension † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Abdominal pain † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Abdominal pain upper † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Colitis ulcerative † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Constipation † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Diarrhoea † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Duodenal ulcer † [1]			

# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Duodenal ulcer perforation † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Enteritis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Food poisoning † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Gastric disorder † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Gastric ulcer † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Gastritis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Gastrointestinal haemorrhage † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Gastrooesophageal reflux disease † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Haemorrhoids † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Hiatus hernia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Inguinal hernia † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Intestinal congestion † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Intestinal obstruction † [1]			

# participants affected / at risk	0/729 (0.00%)	2/740 (0.27%)	0/737 (0.00%)
Intestinal polyp † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Nausea † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Oesophageal ulcer haemorrhage † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Pancreatic mass † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Pancreatitis † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Peptic ulcer haemorrhage † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Small intestinal obstruction † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	1/737 (0.14%)
General disorders			
Adverse drug reaction † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Chills † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Cyst † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Death † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Generalised oedema † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)

Multi-organ failure † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Non-cardiac chest pain † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**2/740 (0.27%)**	**3/737 (0.41%)**
Oedema peripheral † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pyrexia † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**1/740 (0.14%)**	**2/737 (0.27%)**
Sudden cardiac death † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Sudden death † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Thrombosis in device † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Hepatobiliary disorders			
Bile duct obstruction † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cholecystitis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cholecystitis acute † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Cholelithiasis † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Hepatitis alcoholic † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**

Immune system disorders			
Allergy to arthropod sting † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Infections and infestations			
Abscess † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Abscess intestinal † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Abscess rupture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Anal abscess † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Appendicitis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**2/740 (0.27%)**	**1/737 (0.14%)**
Appendicitis perforated † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Bronchitis † [1]			
# participants affected / at risk	**4/729 (0.55%)**	**2/740 (0.27%)**	**5/737 (0.68%)**
Bronchopneumonia † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cellulitis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cholecystitis infective † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Haemophilus infection † [1]			

# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Herpes zoster † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Kidney infection † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Laryngitis † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Lobar pneumonia † [1]			
# participants affected / at risk	4/729 (0.55%)	2/740 (0.27%)	0/737 (0.00%)
Lower respiratory tract infection † [1]			
# participants affected / at risk	14/729 (1.92%)	24/740 (3.24%)	13/737 (1.76%)
Lower respiratory tract infection bacterial † [1]			
# participants affected / at risk	2/729 (0.27%)	5/740 (0.68%)	1/737 (0.14%)
Lower respiratory tract infection fungal † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Lower respiratory tract infection viral † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Lung infection † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Lung infection pseudomonal † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Nasopharyngitis † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Oral candidiasis † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)

Oropharyngeal candidiasis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Otitis media acute † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Otitis media chronic † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Perineal abscess † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Peritonitis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pneumonia † [1]			
# participants affected / at risk	**23/729 (3.16%)**	**25/740 (3.38%)**	**24/737 (3.26%)**
Pneumonia bacterial † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pneumonia legionella † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Pneumonia primary atypical † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pneumonia staphylococcal † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pulmonary tuberculosis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Rabies † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Respiratory tract infection † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**2/740 (0.27%)**	**0/737 (0.00%)**

Respiratory tract infection bacterial † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**2/737 (0.27%)**
Respiratory tract infection viral † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Scrotal abscess † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Sepsis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**3/740 (0.41%)**	**0/737 (0.00%)**
Septic shock † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Subcutaneous abscess † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Upper respiratory tract infection † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Upper respiratory tract infection bacterial † [1]			
# participants affected / at risk	**20/729 (2.74%)**	**20/740 (2.70%)**	**10/737 (1.36%)**
Urinary tract infection † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Viral upper respiratory tract infection † [1]			
# participants affected / at risk	**6/729 (0.82%)**	**5/740 (0.68%)**	**3/737 (0.41%)**
Injury, poisoning and procedural complications			
Alcohol poisoning † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Animal bite † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**

Cervical vertebral fracture † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Clavicle fracture † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Contusion † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Fall † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Femur fracture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Head injury † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Hip fracture † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Incisional hernia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Lower limb fracture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Meniscus lesion † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Muscle rupture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pneumothorax traumatic † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Postoperative ileus † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**

Rib fracture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Spinal fracture † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Tendon rupture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Wound dehiscence † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Wrist fracture † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Investigations			
Blood pressure increased † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Electrocardiogram abnormal † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Intraocular pressure increased † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Metabolism and nutrition disorders			
Cachexia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Decreased appetite † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Dehydration † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Hyperglycaemia † [1]			

# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Hyperkalaemia † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Hypokalaemia † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Hyponatraemia † [1]			
# participants affected / at risk	3/729 (0.41%)	1/740 (0.14%)	1/737 (0.14%)
Malnutrition † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Type 2 diabetes mellitus † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	1/737 (0.14%)
Musculoskeletal and connective tissue disorders			
Arthralgia † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Arthritis † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Back pain † [1]			
# participants affected / at risk	1/729 (0.14%)	1/740 (0.14%)	1/737 (0.14%)
Bursitis † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Compartment syndrome † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Intervertebral disc protrusion † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Musculoskeletal pain † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	1/737 (0.14%)

Osteoarthritis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Osteochondritis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Rhabdomyolysis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Spinal column stenosis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Adrenal neoplasm † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
B-cell lymphoma † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Bladder cancer † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Bladder neoplasm † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Breast cancer † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Breast cancer recurrent † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Bronchial carcinoma † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**2/737 (0.27%)**

Carcinoid tumour of the caecum † 1			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Colon adenoma † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Colon cancer † 1			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Gliosarcoma † 1			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Laryngeal cancer † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**2/737 (0.27%)**
Laryngeal cancer stage 0 † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Lung neoplasm † 1			
# participants affected / at risk	**1/729 (0.14%)**	**2/740 (0.27%)**	**0/737 (0.00%)**
Lung neoplasm malignant † 1			
# participants affected / at risk	**3/729 (0.41%)**	**0/740 (0.00%)**	**4/737 (0.54%)**
Lung squamous cell carcinoma stage unspecified † 1			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Mediastinum neoplasm † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Metastases to bone † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Metastases to central nervous system † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Metastases to liver † 1			

# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Metastases to lung † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Non-small cell lung cancer † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Oesophageal carcinoma † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Oesophageal squamous cell carcinoma † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Pancreatic neoplasm † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Prostate cancer † [1]			
# participants affected / at risk	0/729 (0.00%)	2/740 (0.27%)	0/737 (0.00%)
Prostatic adenoma † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Rectal cancer † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	2/737 (0.27%)
Renal cancer † [1]			
# participants affected / at risk	1/729 (0.14%)	1/740 (0.14%)	0/737 (0.00%)
Small cell lung cancer metastatic † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Small intestine carcinoma † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Squamous cell carcinoma † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Nervous system disorders			

Ataxia † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cerebellar syndrome † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cerebral haemorrhage † 1			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Cerebral infarction † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cerebral ischaemia † 1			
# participants affected / at risk	**2/729 (0.27%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Cerebrovascular accident † 1			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**3/737 (0.41%)**
Cerebrovascular disorder † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Cerebrovascular insufficiency † 1			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Cervicobrachial syndrome † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Convulsion † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Epilepsy † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Grand mal convulsion † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Headache † 1			

# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Ischaemic stroke † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Lethargy † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Loss of consciousness † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Monoparesis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Movement disorder † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Neuropathy peripheral † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Syncope † [1]			
# participants affected / at risk	**3/729 (0.41%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Transient ischaemic attack † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Psychiatric disorders			
Alcohol withdrawal syndrome † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Completed suicide † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Confusional state † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Delirium † [1]			

# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Depression † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Hallucination † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Major depression † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Mental status changes † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Psychotic disorder † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Renal and urinary disorders			
Acute prerenal failure † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Bladder dysfunction † [1]			
# participants affected / at risk	0/729 (0.00%)	0/740 (0.00%)	1/737 (0.14%)
Calculus ureteric † [1]			
# participants affected / at risk	0/729 (0.00%)	2/740 (0.27%)	0/737 (0.00%)
Nephrolithiasis † [1]			
# participants affected / at risk	2/729 (0.27%)	0/740 (0.00%)	0/737 (0.00%)
Renal colic † [1]			
# participants affected / at risk	1/729 (0.14%)	0/740 (0.00%)	0/737 (0.00%)
Urinary retention † [1]			
# participants affected / at risk	0/729 (0.00%)	1/740 (0.14%)	0/737 (0.00%)
Reproductive system and breast disorders			

Benign prostatic hyperplasia † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Epididymitis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Acute respiratory failure † [1]			
# participants affected / at risk	**7/729 (0.96%)**	**6/740 (0.81%)**	**1/737 (0.14%)**
Atelectasis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Chronic obstructive pulmonary disease † [1]			
# participants affected / at risk	**107/729 (14.68%)**	**116/740 (15.68%)**	**87/737 (11.80%)**
Chronic respiratory failure † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Cough † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Dyspnoea † [1]			
# participants affected / at risk	**5/729 (0.69%)**	**2/740 (0.27%)**	**3/737 (0.41%)**
Epistaxis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Foreign body aspiration † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Haemoptysis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**2/740 (0.27%)**	**1/737 (0.14%)**

Hydrothorax † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Hypercapnia † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**3/740 (0.41%)**	**1/737 (0.14%)**
Hypoxia † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Lung consolidation † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Lung disorder † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Oropharyngeal pain † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Pleural effusion † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pleurisy † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**1/737 (0.14%)**
Pneumothorax † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**5/740 (0.68%)**	**1/737 (0.14%)**
Productive cough † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pulmonary air leakage † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Pulmonary congestion † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pulmonary embolism † [1]			
# participants affected / at risk	**3/729 (0.41%)**	**3/740 (0.41%)**	**1/737 (0.14%)**

Pulmonary hypertension † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Pulmonary mass † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**2/737 (0.27%)**
Respiratory distress † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Respiratory failure † [1]			
# participants affected / at risk	**5/729 (0.69%)**	**7/740 (0.95%)**	**6/737 (0.81%)**
Sleep apnoea syndrome † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Sputum increased † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Vocal cord inflammation † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Wheezing † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Skin and subcutaneous tissue disorders			
Angioedema † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Dermal cyst † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Social circumstances			
Pollution † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Surgical and medical procedures			

Coronary arterial stent insertion † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Vascular disorders			
Aortic aneurysm † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Aortic aneurysm rupture † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Arterial occlusive disease † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**2/737 (0.27%)**
Arterial stenosis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**1/740 (0.14%)**	**0/737 (0.00%)**
Arteriosclerosis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Deep vein thrombosis † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Hypertension † [1]			
# participants affected / at risk	**2/729 (0.27%)**	**2/740 (0.27%)**	**2/737 (0.27%)**
Hypotension † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Iliac artery stenosis † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Peripheral arterial occlusive disease † [1]			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Peripheral artery aneurysm † [1]			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**

Peripheral ischaemia † 1			
# participants affected / at risk	**0/729 (0.00%)**	**0/740 (0.00%)**	**1/737 (0.14%)**
Phlebitis deep † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**
Shock haemorrhagic † 1			
# participants affected / at risk	**1/729 (0.14%)**	**0/740 (0.00%)**	**0/737 (0.00%)**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	Modified safety set (mSAF set) includes all patients in the safety set except patients from a site who had major GCP issues. The Safety set includes all patients who received at least one dose of study drug whether or not being randomized. Analysis population included patients with study withdrawal or premature discontinuation for any reason.

Frequency Threshold

Threshold above which other adverse events are reported	1%

Reporting Groups

	Description
QVA149	QVA149 : QVA149 110/50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler (SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
NVA237	NVA237 : NVA237 50 µg capsules for inhalation, once daily delivered via Novartis Single Dose Dry Powder Inhaler

	(SDDPI) for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.
Open-label Tiotropium	Open-label tiotropium bromide 18 µg capsules for inhalation once daily delivered via HandiHaler® device. for at least 64 weeks of double blind treatment period (study duration was up to 76 weeks). Salbutamol/albuterol was available for rescue medication use throughout the study.

Other Adverse Events

	QVA149	NVA237	Open-label Tiotropium
Total, other (not including serious) adverse events			
# participants affected / at risk	**656/729 (89.99%)**	**671/740 (90.68%)**	**666/737 (90.37%)**
Cardiac disorders			
Tachycardia † [1]			
# participants affected / at risk	**3/729 (0.41%)**	**8/740 (1.08%)**	**3/737 (0.41%)**
Gastrointestinal disorders			
Abdominal pain † [1]			
# participants affected / at risk	**6/729 (0.82%)**	**11/740 (1.49%)**	**9/737 (1.22%)**
Abdominal pain upper † [1]			
# participants affected / at risk	**7/729 (0.96%)**	**7/740 (0.95%)**	**8/737 (1.09%)**
Constipation † [1]			
# participants affected / at risk	**8/729 (1.10%)**	**11/740 (1.49%)**	**4/737 (0.54%)**
Diarrhoea † [1]			
# participants affected / at risk	**21/729 (2.88%)**	**11/740 (1.49%)**	**15/737 (2.04%)**
Dry mouth † [1]			
# participants affected / at risk	**4/729 (0.55%)**	**13/740 (1.76%)**	**16/737 (2.17%)**
Dyspepsia † [1]			
# participants affected / at risk	**13/729 (1.78%)**	**10/740 (1.35%)**	**15/737 (2.04%)**

Gastritis † [1]			
# participants affected / at risk	12/729 (1.65%)	5/740 (0.68%)	12/737 (1.63%)
Gastrooesophageal reflux disease † [1]			
# participants affected / at risk	9/729 (1.23%)	4/740 (0.54%)	9/737 (1.22%)
Nausea † [1]			
# participants affected / at risk	9/729 (1.23%)	12/740 (1.62%)	4/737 (0.54%)
Toothache † [1]			
# participants affected / at risk	9/729 (1.23%)	4/740 (0.54%)	6/737 (0.81%)
General disorders			
Fatigue † [1]			
# participants affected / at risk	4/729 (0.55%)	8/740 (1.08%)	3/737 (0.41%)
Non-cardiac chest pain † [1]			
# participants affected / at risk	14/729 (1.92%)	11/740 (1.49%)	9/737 (1.22%)
Oedema peripheral † [1]			
# participants affected / at risk	22/729 (3.02%)	18/740 (2.43%)	16/737 (2.17%)
Pyrexia † [1]			
# participants affected / at risk	26/729 (3.57%)	24/740 (3.24%)	22/737 (2.99%)
Infections and infestations			
Bronchitis † [1]			
# participants affected / at risk	32/729 (4.39%)	36/740 (4.86%)	26/737 (3.53%)
Influenza † [1]			
# participants affected / at risk	23/729 (3.16%)	22/740 (2.97%)	19/737 (2.58%)
Lower respiratory tract infection † [1]			
# participants affected / at risk	49/729 (6.72%)	68/740 (9.19%)	69/737 (9.36%)
Lower respiratory tract infection bacterial † [1]			

# participants affected / at risk	6/729 (0.82%)	8/740 (1.08%)	4/737 (0.54%)
Nasopharyngitis † [1]			
# participants affected / at risk	98/729 (13.44%)	81/740 (10.95%)	90/737 (12.21%)
Oral candidiasis † [1]			
# participants affected / at risk	11/729 (1.51%)	10/740 (1.35%)	12/737 (1.63%)
Pharyngitis † [1]			
# participants affected / at risk	17/729 (2.33%)	11/740 (1.49%)	10/737 (1.36%)
Pneumonia † [1]			
# participants affected / at risk	11/729 (1.51%)	13/740 (1.76%)	10/737 (1.36%)
Rhinitis † [1]			
# participants affected / at risk	9/729 (1.23%)	10/740 (1.35%)	6/737 (0.81%)
Sinusitis † [1]			
# participants affected / at risk	12/729 (1.65%)	20/740 (2.70%)	21/737 (2.85%)
Upper respiratory tract infection † [1]			
# participants affected / at risk	26/729 (3.57%)	25/740 (3.38%)	28/737 (3.80%)
Upper respiratory tract infection bacterial † [1]			
# participants affected / at risk	119/729 (16.32%)	123/740 (16.62%)	109/737 (14.79%)
Urinary tract infection † [1]			
# participants affected / at risk	27/729 (3.70%)	19/740 (2.57%)	15/737 (2.04%)
Viral upper respiratory tract infection † [1]			
# participants affected / at risk	70/729 (9.60%)	75/740 (10.14%)	72/737 (9.77%)
Injury, poisoning and procedural complications			
Contusion † [1]			
# participants affected / at risk	9/729 (1.23%)	4/740 (0.54%)	4/737 (0.54%)
Metabolism and nutrition disorders			

Hypercholesterolaemia † [1]			
# participants affected / at risk	14/729 (1.92%)	11/740 (1.49%)	11/737 (1.49%)
Hyperlipidaemia † [1]			
# participants affected / at risk	9/729 (1.23%)	4/740 (0.54%)	7/737 (0.95%)
Type 2 diabetes mellitus † [1]			
# participants affected / at risk	12/729 (1.65%)	9/740 (1.22%)	5/737 (0.68%)
Musculoskeletal and connective tissue disorders			
Arthralgia † [1]			
# participants affected / at risk	12/729 (1.65%)	10/740 (1.35%)	10/737 (1.36%)
Back pain † [1]			
# participants affected / at risk	24/729 (3.29%)	33/740 (4.46%)	36/737 (4.88%)
Muscle spasms † [1]			
# participants affected / at risk	5/729 (0.69%)	9/740 (1.22%)	9/737 (1.22%)
Musculoskeletal pain † [1]			
# participants affected / at risk	12/729 (1.65%)	9/740 (1.22%)	6/737 (0.81%)
Pain in extremity † [1]			
# participants affected / at risk	9/729 (1.23%)	8/740 (1.08%)	5/737 (0.68%)
Nervous system disorders			
Dizziness † [1]			
# participants affected / at risk	13/729 (1.78%)	12/740 (1.62%)	8/737 (1.09%)
Headache † [1]			
# participants affected / at risk	30/729 (4.12%)	33/740 (4.46%)	39/737 (5.29%)
Psychiatric disorders			
Depression † [1]			
# participants affected / at risk	4/729 (0.55%)	2/740 (0.27%)	9/737 (1.22%)

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease † 1			
# participants affected / at risk	**618/729 (84.77%)**	**639/740 (86.35%)**	**629/737 (85.35%)**
Cough † 1			
# participants affected / at risk	**40/729 (5.49%)**	**39/740 (5.27%)**	**25/737 (3.39%)**
Dysphonia † 1			
# participants affected / at risk	**2/729 (0.27%)**	**5/740 (0.68%)**	**9/737 (1.22%)**
Dyspnoea † 1			
# participants affected / at risk	**21/729 (2.88%)**	**42/740 (5.68%)**	**32/737 (4.34%)**
Oropharyngeal pain † 1			
# participants affected / at risk	**25/729 (3.43%)**	**32/740 (4.32%)**	**29/737 (3.93%)**
Sputum increased † 1			
# participants affected / at risk	**7/729 (0.96%)**	**13/740 (1.76%)**	**8/737 (1.09%)**
Wheezing † 1			
# participants affected / at risk	**5/729 (0.69%)**	**9/740 (1.22%)**	**3/737 (0.41%)**
Vascular disorders			
Hypertension † 1			
# participants affected / at risk	**30/729 (4.12%)**	**20/740 (2.70%)**	**24/737 (3.26%)**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data

No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☑ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Restriction Description: The terms and conditions of Novartis' agreements with its investigators may vary. However, Novartis does not prohibit any investigator from publishing. Any publications from a single-site are postponed until the publication of the pooled data (i.e., data from all sites) in the clinical trial or disclosure of trial results in their entirety.

Results Point of Contact:

Name/Title: Study Director
Organization: Novartis Pharmaceuticals
phone: 862-778-8300
e-mail: trialandresults.registries@novartis.com

No publications provided by Novartis

Publications automatically indexed to this study:

Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandström T, Taylor AF, D'Andrea P, Arrasate C, Chen H, Banerji D. 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. Lancet Respir Med. 2013 May;1(3):199-209. doi: 10.1016/S2213-2600(13)70052-3. Epub 2013 Apr 23.

Responsible Party:	Novartis (Novartis Pharmaceuticals)
ClinicalTrials.gov Identifier:	NCT01120691 History of Changes
Other Study ID Numbers:	**CQVA149A2304**
	2009-013256-69 (EudraCT Number)
Study First Received:	May 5, 2010
Results First Received:	July 9, 2013
Last Updated:	October 29, 2013
Health Authority:	United States: Food and Drug Administration
	Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica
	Australia: Department of Health and Ageing Therapeutic Goods Administration
	Belgium: Federal Agency for Medicinal Products and Health Products
	Brazil: National Health Surveillance Agency
	Canada: Health Canada
	Chile: Comisión Nacional de Investigación Científica y Tecnológica
	Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos
	Czech Republic: State Institute for Drug Control
	Denmark: Danish Medicines Agency
	Estonia: The State Agency of Medicine
	Finland: Finnish Medicines Agency
	France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)
	Germany: Federal Institute for Drugs and Medical Devices
	Greece: National Organization of Medicines
	Guatemala: Ministry of Public Health and Social Assistance
	Hungary: National Institute of Pharmacy
	India: Drugs Controller General of India
	Ireland: Irish Medicines Board
	Israel: Ministry of Health
	Italy: The Italian Medicines Agency
	Korea: Food and Drug Administration

Malaysia: Ministry of Health
Mexico: Ministry of Health
Netherlands: Medicines Evaluation Board (MEB)
New Zealand: Food Safety Authority
Norway: Norwegian Medicines Agency
Peru: Ministry of Health
Philippines: Bureau of Food and Drugs
Poland: Ministry of Health
Romania: National Medicines Agency
Russia: Ministry of Health of the Russian Federation
Singapore: Health Sciences Authority
South Africa: Department of Health
Spain: Spanish Agency of Medicines
Thailand: Food and Drug Administration
Turkey: Ministry of Health
Ukraine: Ministry of Health
United Kingdom: Medicines and Healthcare Products Regulatory Agency