



Clinical trial results:

A placebo and active controlled study to assess the longterm safety of once daily QVA149 for 52 weeks in chronic obstructive pulmonary disease (COPD) patients with moderate to severe airflow limitation

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2012-002057-38
Trial protocol	SI HU GB LV EE PL
Global end of trial date	05 February 2015

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	CQVA149A2339
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01610037
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 February 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of QVA149 110/50 µg o.d. compared to placebo in terms of overall (serious adverse event) SAE rate from initiation of study treatment through 30 days post last treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 23
Country: Number of subjects enrolled	Croatia: 45
Country: Number of subjects enrolled	Estonia: 45
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Hungary: 137
Country: Number of subjects enrolled	India: 88
Country: Number of subjects enrolled	Israel: 83
Country: Number of subjects enrolled	Korea, Republic of: 105
Country: Number of subjects enrolled	Latvia: 34
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Panama: 23
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Russian Federation: 114
Country: Number of subjects enrolled	Serbia: 38
Country: Number of subjects enrolled	Slovenia: 38
Country: Number of subjects enrolled	Turkey: 52

Country: Number of subjects enrolled	Argentina: 249
Worldwide total number of subjects	1216
EEA total number of subjects	423

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	614
From 65 to 84 years	594
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2064 patients were screened, of whom 1216 patients were randomized to QVA149 110/50 µg o.d., tiotropium 18 µg o.d., or placebo. Of the 1216, one patient was randomized but not treated. One patient of the 1216 was randomized but did not receive treatment

Period 1

Period 1 title	All Patients (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	QVA149

Arm description:

110/50 µg capsules for inhalation, o.d

Arm type	Experimental
Investigational medicinal product name	indacaterol/glycopyrronium
Investigational medicinal product code	QVA149
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

capsules for oral inhalation

Arm title	Tiotropium
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Arm description:

18 µg capsules for inhalation, o.d

Arm type	Active comparator
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

18 µg capsules for inhalation

Arm title	Placebo
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Arm description:

To match QVA149 capsules for inhalation, o.d To match tiotropium capsules for inhalation, o.d

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Number of subjects in period 1	QVA149	Tiotropium	Placebo
Started	407	405	404
Randomized set (RAN)	407	405	404
Full analysis set (FAS)	407	405	403
Completed	348	354	320
Not completed	59	51	84
Adverse event, serious fatal	4	2	1
Consent withdrawn by subject	12	10	20
Adverse event, non-fatal	27	22	26
Unsatisfactory therapeutic effect	9	8	27
Protocol deviation	4	3	3
Administrative problems	1	4	4
Abnormal laboratory value	1	1	-
Lost to follow-up	1	-	-
Abnormal test procedure result(s)	-	1	3

Baseline characteristics

Reporting groups

Reporting group title	QVA149
Reporting group description: 110/50 µg capsules for inhalation, o.d	
Reporting group title	Tiotropium
Reporting group description: 18 µg capsules for inhalation, o.d	
Reporting group title	Placebo
Reporting group description: To match QVA149 capsules for inhalation, o.d To match tiotropium capsules for inhalation, o.d	

Reporting group values	QVA149	Tiotropium	Placebo
Number of subjects	407	405	404
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	205	215	194
From 65-84 years	199	187	208
85 years and over	3	3	2
Age Continuous Units: Years			
arithmetic mean	64.6	64.1	64.9
standard deviation	± 7.89	± 8.57	± 7.95
Gender, Male/Female Units: Participants			
Female	119	105	94
Male	288	300	310

Reporting group values	Total		
Number of subjects	1216		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	614		

From 65-84 years	594		
85 years and over	8		

Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	318		
Male	898		

End points

End points reporting groups

Reporting group title	QVA149
Reporting group description:	110/50 µg capsules for inhalation, o.d
Reporting group title	Tiotropium
Reporting group description:	18 µg capsules for inhalation, o.d
Reporting group title	Placebo
Reporting group description:	To match QVA149 capsules for inhalation, o.d To match tiotropium capsules for inhalation, o.d

Primary: Number of patients with serious adverse events

End point title	Number of patients with serious adverse events ^[1]
End point description:	The overall rate of serious adverse events reported from initiation through 30 days post last dose. No statistical analysis was planned for this primary outcome.
End point type	Primary
End point timeframe:	Week 52
Notes:	[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this primary outcome

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	403	402	
Units: Participants	55	55	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular (CCV) events.

End point title	Percentage of patients with composite endpoint of all-cause mortality, and serious cardio- and cerebrovascular (CCV) events.
End point description:	The endpoint of all-cause mortality and serious CCV events (composite) was chosen to further characterize any discernible risks. The patients with an event in the analysis were those who had at least one of the 2 events namely, all-cause mortality and serious CCV, during treatment or within 30 days after the date of last dose of study drug.
End point type	Secondary
End point timeframe:	52 weeks

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Percentage of participants				
number (not applicable)	3.9	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Post-hoc analysis: Percentage of patients with composite endpoint of cardiovascular death and MACE

End point title	Post-hoc analysis: Percentage of patients with composite endpoint of cardiovascular death and MACE
End point description: The composite endpoint included all deaths and all serious CCV events, including MACE and events which were not considered MACE. A rigorous post hoc analysis was done on composite endpoint of CV deaths and major adverse cardiovascular events (MACE). The patients with an event in the analysis were those who had at least one of the 2 events namely, CV deaths and MACE, during treatment or within 30 days after the date of last dose of study drug.	
End point type	Secondary
End point timeframe: 52 weeks	

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Percentage of participants				
number (not applicable)	1	0.7	0.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Pre-Dose forced expiratory volume over in second (FEV1)

End point title	Change from baseline in Pre-Dose forced expiratory volume over in second (FEV1)
End point description: Pulmonary function assessments were performed using centralized spirometry according to international standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1.	

End point type	Secondary
End point timeframe:	
Day 22, 43, 85, 183, 274 and 364	

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	379	
Units: Liters				
least squares mean (standard error)				
Day 22 (n=378, 383, 361)	0.1733 (± 0.18537)	0.1018 (± 0.18389)	-0.0148 (± 0.16758)	
Day 43 (n=380, 375, 345)	0.1751 (± 0.208)	0.0961 (± 0.18261)	-0.0196 (± 0.18178)	
Day 85 (n=373, 373, 340)	0.1752 (± 0.20198)	0.0785 (± 0.19606)	-0.0506 (± 0.19369)	
Day 183 (n=356, 358, 314)	0.1557 (± 0.21754)	0.0714 (± 0.20358)	-0.0583 (± 0.20305)	
Day 274 (n=343, 351, 303)	0.1463 (± 0.21424)	0.075 (± 0.21489)	-0.0601 (± 0.20936)	
Day 364 (n=333, 346, 297)	0.1468 (± 0.22933)	0.0559 (± 0.22433)	-0.0826 (± 0.21443)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in health status as measured by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

End point title	Change from baseline in health status as measured by St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
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End point description:

The SGRQ-C contains 40 items divided into two parts covering three aspects of health related to COPD: Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity; Part II covers "Activity" and is concerned with activities that cause or are limited by breathlessness; Part II is also concerned with "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score will be calculated for each of these three subscales and a "Total" score will also be calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

End point type	Secondary
End point timeframe:	
Measurement at day 364	

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	343	349	314	
Units: Score				
arithmetic mean (standard deviation)	-6.79 (± 12.611)	-6.12 (± 13.695)	-2.18 (± 13.311)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Daily, morning and evening symptom scores

End point title	Change from baseline in Daily, morning and evening symptom scores
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End point description:

Patients will be provided with an electronic diary (eDiary) to record daily clinical symptoms, or rescue medication. The patients will be instructed to routinely complete the patient diary twice daily. There are 9 total symptom questions for a total possible score of 27 at each timepoint. A higher score means the patient is reporting more symptoms related to Chronic Obstructive Pulmonary Disease. The mean daily total symptom score, the mean daytime total symptom score and the mean nighttime total symptom score were calculated for each patient over 52 weeks. Diary data recorded during the 14 day run-in period were used to calculate the baseline.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Score				
arithmetic mean (standard deviation)				
Daily total symptom score (n=395, 395, 385)	-1.3478 (± 1.91692)	-1.2283 (± 1.93241)	-0.7683 (± 1.73598)	
Daytime total symptom score (n= 380, 385, 374)	-1.1688 (± 1.9335)	-1.0669 (± 1.90366)	-0.5641 (± 1.62577)	
Nighttime total symptom score (n= 387, 388, 375)	-0.9731 (± 1.96898)	-0.9532 (± 1.78168)	-0.5984 (± 1.73356)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of nights with 'no nighttime awakenings

End point title	Change from baseline in percentage of nights with 'no nighttime awakenings
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End point description:

A night with 'no nighttime awakenings' is defined from diary data as any night where the patient did not wake up due to symptoms.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	387	388	375	
Units: Percentage of nights				
arithmetic mean (standard deviation)	11.34 (± 30.115)	10.66 (± 26.579)	8.21 (± 28.002)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of no daytime symptoms

End point title	Change from baseline in percentage of no daytime symptoms
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End point description:

A day with 'no daytime symptoms' is defined from the diary data as any day where the patient has recorded in the evening no cough, no wheeze, no production of sputum and no feeling of breathlessness (other than when running) during the past 12 hours (approx. 8 am to 8 pm).

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	380	385	374	
Units: Percentage of days				
arithmetic mean (standard deviation)	5.56 (± 19.67)	4.72 (± 15.942)	1.78 (± 15.733)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage of days able to perform usual daily activities.

End point title	Change from baseline in percentage of days able to perform
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usual daily activities.

End point description:

A day able to perform usual daily activities' is defined from diary data as any day where the patient was not prevented from performing their usual daily activities due to respiratory symptoms.

End point type	Secondary
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End point timeframe:

52 weeks

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	380	385	374	
Units: Percentage of days				
arithmetic mean (standard deviation)	10.79 (± 31.006)	6.54 (± 30.215)	1.13 (± 25.039)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 1 hour post-dose Forced vital capacity (FVC) measurements

End point title	Change from baseline in 1 hour post-dose Forced vital capacity (FVC) measurements
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End point description:

Pulmonary function assessments were performed using centralized spirometry according to international standards

End point type	Secondary
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End point timeframe:

Day 1, 22, 43, 85, 183, 274 and 364

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1(n=403, 402, 399)	0.3331 (± 0.30312)	0.2806 (± 0.28293)	0.063 (± 0.22884)	
Day 22 (n=384, 381, 362)	0.3971 (± 0.40009)	0.3123 (± 0.36755)	0.0178 (± 0.33624)	
Day 43 (n=380, 373, 351)	0.4021 (± 0.42797)	0.2966 (± 0.37124)	0.0274 (± 0.35681)	
Day 85 (376, 371, 345)	0.4169 (± 0.42175)	0.2867 (± 0.40131)	0.0035 (± 0.36897)	
Day 183 (n=364, 359, 317)	0.388 (± 0.45342)	0.2822 (± 0.39781)	-0.0283 (± 0.36919)	

Day 274 (n=349, 352, 306)	0.3582 (± 0.43072)	0.2821 (± 0.40546)	-0.0404 (± 0.37777)	
Day 364 (n= 336, 347, 302)	0.3153 (± 0.4656)	0.2224 (± 0.40778)	-0.0498 (± 0.39908)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to premature discontinuation

End point title	Time to premature discontinuation
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End point description:

Time to premature treatment discontinuation for each treatment group was displayed using a Kaplan-Meier curve. The date of last dose of study medication was considered as the event date and also as the censoring date for those patients who did not discontinue treatment early. The range of the 'time to treatment discontinuation' varied from 5-407 days in the Tiotropium group. Hence the model estimated lower limit of the median time to treatment discontinuation is greater than the scheduled treatment period of 52 weeks.

End point type	Secondary
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End point timeframe:

Time varied from 5 - 407 days

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Days				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)	9999 (-9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 1 hour post-dose FEV1 measurements

End point title	Change from baseline in 1 hour post-dose FEV1 measurements
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End point description:

The avg 60 min post dose forced expiratory volume in 1 second (FEV1) at visit 4, 5, 6, 7, 8 and 9 will be analyzed.

End point type	Secondary
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End point timeframe:

Day 1, 22, 43, 85, 183, 274 and 364

End point values	QVA149	Tiotropium	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	407	405	403	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1 (n=403, 402, 399)	0.2064 (± 0.14248)	0.1567 (± 0.13349)	0.0281 (± 0.11123)	
Day 22 (n=384, 381, 362)	0.2883 (± 0.21074)	0.2077 (± 0.20027)	1.5827 (± 15.6999)	
Day 43 (n=380, 373, 351)	0.2904 (± 0.23377)	0.2008 (± 0.20752)	1.6209 (± 16.89209)	
Day 85 (n=376, 371, 345)	0.3026 (± 0.2326)	0.1913 (± 0.23274)	-0.0217 (± 0.20195)	
Day 183 (n=364, 359, 317)	0.286 (± 0.24351)	0.1842 (± 0.22851)	-0.0253 (± 0.21129)	
Day 274 (n=349, 352, 306)	0.2749 (± 0.24314)	0.1681 (± 0.23626)	-0.036 (± 0.21854)	
Day 364 (n= 336, 347, 302)	0.2619 (± 0.25967)	0.1621 (± 0.23922)	-0.0533 (± 0.2156)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Tiotropium 18 µg o.d.
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Reporting group description:

Tiotropium 18 µg o.d.

Reporting group title	QVA149 110/50 µg o.d.
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Reporting group description:

QVA149 110/50 µg o.d.

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	Tiotropium 18 µg o.d.	QVA149 110/50 µg o.d.	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 405 (13.58%)	55 / 407 (13.51%)	50 / 403 (12.41%)
number of deaths (all causes)	5	8	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenolipoma			

subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal cancer			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			

subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant mediastinal neoplasm			
subjects affected / exposed	2 / 405 (0.49%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 405 (0.49%)	2 / 407 (0.49%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 405 (0.00%)	3 / 407 (0.74%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein distension			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Hip arthroplasty			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial disorder			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	18 / 405 (4.44%)	20 / 407 (4.91%)	23 / 403 (5.71%)
occurrences causally related to treatment / all	0 / 19	0 / 23	1 / 31
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cough			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	3 / 405 (0.74%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			

subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 405 (0.25%)	3 / 407 (0.74%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			

subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	2 / 405 (0.49%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 405 (0.00%)	2 / 407 (0.49%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 405 (0.00%)	3 / 407 (0.74%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 405 (0.00%)	2 / 407 (0.49%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 405 (0.00%)	2 / 407 (0.49%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	3 / 405 (0.74%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiopulmonary failure			

subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			

subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculitis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paresis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	2 / 405 (0.49%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatitis haemorrhagic			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	2 / 403 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic mass			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Calculus ureteric			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Synovitis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchitis bacterial			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 405 (0.25%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 405 (0.25%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 405 (0.49%)	0 / 407 (0.00%)	2 / 403 (0.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			

subjects affected / exposed	6 / 405 (1.48%)	3 / 407 (0.74%)	2 / 403 (0.50%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 405 (0.00%)	2 / 407 (0.49%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 405 (0.00%)	0 / 407 (0.00%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	2 / 403 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 405 (0.25%)	2 / 407 (0.49%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 405 (0.49%)	0 / 407 (0.00%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	0 / 405 (0.00%)	2 / 407 (0.49%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	0 / 403 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 405 (0.00%)	1 / 407 (0.25%)	1 / 403 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tiotropium 18 µg o.d.	QVA149 110/50 µg o.d.	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	286 / 405 (70.62%)	285 / 407 (70.02%)	297 / 403 (73.70%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	274 / 405 (67.65%)	269 / 407 (66.09%)	287 / 403 (71.22%)
occurrences (all)	1009	948	1072
Cough			
subjects affected / exposed	21 / 405 (5.19%)	17 / 407 (4.18%)	18 / 403 (4.47%)
occurrences (all)	25	18	21
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	14 / 405 (3.46%)	22 / 407 (5.41%)	19 / 403 (4.71%)
occurrences (all)	18	32	29
Nasopharyngitis			
subjects affected / exposed	31 / 405 (7.65%)	33 / 407 (8.11%)	26 / 403 (6.45%)
occurrences (all)	39	44	34
Upper respiratory tract infection			
subjects affected / exposed	22 / 405 (5.43%)	18 / 407 (4.42%)	18 / 403 (4.47%)
occurrences (all)	28	22	32

Upper respiratory tract infection bacterial			
subjects affected / exposed	28 / 405 (6.91%)	27 / 407 (6.63%)	25 / 403 (6.20%)
occurrences (all)	32	35	30

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: