



## Clinical trial results:

**A multi-center, randomized, double-blind, 52-week study to assess the safety of QVA149 compared to QAB149 in patients with chronic obstructive pulmonary disease (COPD) who have 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> for complete trial results.**

## Summary

EudraCT number	2012-001998-93
Trial protocol	HU FI BG
Global end of trial date	30 June 2014

## Results information

Result version number	v1 (current)
This version publication date	25 July 2018
First version publication date	25 July 2018

## Trial information

### Trial identification

Sponsor protocol code	QVA149A2340
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01682863
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	30 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

### General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d. in terms of adverse event (AE) reporting rate in patients with COPD with moderate to severe airflow limitation during 52 weeks of 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	26 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	Finland: 27
Country: Number of subjects enrolled	Hungary: 96
Country: Number of subjects enrolled	Romania: 97
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	United States: 266
Country: Number of subjects enrolled	Bulgaria: 67
Worldwide total number of subjects	615
EEA total number of subjects	349

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)	334
From 65 to 84 years	281
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were randomized to each treatment arm in 1:1:1 ratio.

### Pre-assignment

Screening details:

Six hundred fifteen patients were randomized. One patient was randomized but did not receive treatment due to an adverse event. In the safety set, patients were analyzed according to the treatment received.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	QVA149 27.5/12.5 ug bid
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Arm description:

QVA149

Arm type	Experimental
Investigational medicinal product name	indacaterol maleate-glycopyrronium bromide
Investigational medicinal product code	QVA149
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

27.5/12.5 ug bid

<b>Arm title</b>	QVA149 27.5/25 ug bid
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	QVA149
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

27.5/25

<b>Arm title</b>	QAB149 75 ug od
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	QVA149
Investigational medicinal product code	QAB149
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Inhalation capsule

<b>Number of subjects in period 1</b>	QVA149 27.5/12.5 ug bid	QVA149 27.5/25 ug bid	QAB149 75 ug od
Started	204	204	207
Safety set	204	204	206
Randomized set	204	204	207
Full analysis set (FAS)	204	204	206
Completed	177	187	183
Not completed	27	17	24
Adverse event, serious fatal	1	3	4
Physician decision	-	-	1
Technical problems	1	-	-
Adverse event, non-fatal	-	1	2
Protocol deviation	1	-	1
Lost to follow-up	5	1	6
Subject/guardian decision	19	12	10

## Baseline characteristics

<b>Reporting groups</b>	
Reporting group title	QVA149 27.5/12.5 ug bid
Reporting group description: QVA149	
Reporting group title	QVA149 27.5/25 ug bid
Reporting group description: -	
Reporting group title	QAB149 75 ug od
Reporting group description: -	

<b>Reporting group values</b>	QVA149 27.5/12.5 ug bid	QVA149 27.5/25 ug bid	QAB149 75 ug od
Number of subjects	204	204	207
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)	113	104	117
From 65-84 years	91	100	90
85 years and over	0	0	0
Age Continuous   Units: Years			
arithmetic mean	64	63.9	62.8
standard deviation	± 7.9	± 8.5	± 8.52
Gender, Male/Female Units: Participants			
Female	73	81	58
Male	131	123	149

<b>Reporting group values</b>	Total		
Number of subjects	615		
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)	334		
From 65-84 years	281		
85 years and over	0		

Age Continuous   Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	212		
Male	403		

## End points

### End points reporting groups

Reporting group title	QVA149 27.5/12.5 ug bid
Reporting group description:	QVA149
Reporting group title	QVA149 27.5/25 ug bid
Reporting group description:	-
Reporting group title	QAB149 75 ug od
Reporting group description:	-

### Primary: Percent of patients with adverse events, serious adverse events, and death

End point title	Percent of patients with adverse events, serious adverse events, and death <sup>[1]</sup>
End point description:	The overall rate of adverse events reported from initiation through 30 days post last dose. No statistical analysis was specified for this outcome measure.
End point type	Primary
End point timeframe:	56 weeks

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 specified for this outcome measure.

End point values	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	204	206	
Units: percent				
number (not applicable)				
Patients with at least one SAEs	12.7	12.3	11.7	
Patients with at least one AE	68.1	69.6	67.5	
Death	0.5	1.5	2.4	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to premature discontinuation of treatment

End point title	Time to premature discontinuation of treatment
End point description:	Time is calculated at the end of the specified weeks by the Kaplan Meier method
End point type	Secondary
End point timeframe:	52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204 <sup>[2]</sup>	204 <sup>[3]</sup>	206 <sup>[4]</sup>	
Units: Days				
median (confidence interval 95%)	384 (384 to 99999)	9999 (999 to 99999)	9999 (999 to 99999)	

Notes:

[2] - 99999 value is a place holder in the Eudract sytem for which can't handle the term(NE)not estimable

[3] - 99999 value is a place holder in the Eudract sytem for which can't handle the term(NE)not estimable

[4] - 99999 value is a place holder in the Eudract sytem for which can't handle the term(NE)not estimable

### Statistical analyses

No statistical analyses for this end point

### Secondary: change from baseline in pre-dose trough FEV1

End point title	change from baseline in pre-dose trough FEV1
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End point description:

Pulmonary function assessments were performed using centralized spirometry according to ATS/ERS standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, baseline FEV1 \* visit interaction, airflow limitation severity and visit, treatment \* visit interaction.

End point type	Secondary
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End point timeframe:

Baseline, 52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	196	199	
Units: Liters				
least squares mean (standard error)	0.116 (± 0.0169)	0.116 (± 0.0167)	0.037 (± 0.0169)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in FEV1 measurements at all post-baseline time points

End point title	Change from baseline in FEV1 measurements at all post-
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End point description:

Pulmonary function assessments were performed using centralized spirometry according to ATS/ERS standards. Baseline FEV1 was defined as the average of the pre-dose FEV1 measured at -45 minutes (min) and -15 min at day 1. A mixed model for repeated measures (MMRM), used for this analysis, included terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline inhaled corticosteroid (ICS) use, region, baseline FEV1 \* visit interaction, and visit, treatment \* visit interaction.

End point type

Secondary

End point timeframe:

52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	202	202	
Units: Liters				
least squares mean (standard error)				
Day 1	0.166 (± 0.0088)	0.178 (± 0.0088)	0.122 (± 0.0089)	
Day 29	0.257 (± 0.0152)	0.287 (± 0.0151)	0.173 (± 0.0151)	
Day 57	0.267 (± 0.0157)	0.302 (± 0.0155)	0.173 (± 0.0154)	
Day 85	0.269 (± 0.0164)	0.301 (± 0.0162)	0.17 (± 0.0162)	
Day 141	0.268 (± 0.0182)	0.288 (± 0.0179)	0.17 (± 0.0181)	
Day 197	0.229 (± 0.0178)	0.278 (± 0.0175)	0.157 (± 0.0177)	
Day 253	0.231 (± 0.0178)	0.24 (± 0.0175)	0.14 (± 0.0176)	
Day 309	0.199 (± 0.017)	0.222 (± 0.0169)	0.125 (± 0.017)	
Day 365	0.212 (± 0.0175)	0.221 (± 0.0173)	0.104 (± 0.0174)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in FVC measurement at all post-baseline time points

End point title

Change from baseline in FVC measurement at all post-baseline time points

End point description:

Pulmonary function assessments were performed using centralized spirometry according to ATS/ERS standards.

End point type

Secondary

End point timeframe:

Baseline, 52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	200	202	202	
Units: Liters				
least squares mean (standard error)				
Day 1	0.316 (± 0.0201)	0.349 (± 0.02)	0.248 (± 0.0203)	
Day 29	0.375 (± 0.0274)	0.44 (± 0.0271)	0.28 (± 0.0272)	
Day 57	0.39 (± 0.0274)	0.439 (± 0.0271)	0.279 (± 0.0271)	
Day 85	0.388 (± 0.0287)	0.432 (± 0.0283)	0.268 (± 0.0284)	
Day 141	0.382 (± 0.0297)	0.403 (± 0.0292)	0.235 (± 0.0295)	
Day 197	0.313 (± 0.0288)	0.4 (± 0.0284)	0.22 (± 0.0288)	
Day 253	0.31 (± 0.0303)	0.365 (± 0.0298)	0.205 (± 0.0301)	
Day 309	0.272 (± 0.0284)	0.334 (± 0.0281)	0.185 (± 0.0285)	
Day 365	0.312 (± 0.0286)	0.323 (± 0.0282)	0.139 (± 0.0286)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants experiencing moderate or severe COPD exacerbation

End point title	Percentage of participants experiencing moderate or severe COPD exacerbation
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End point description:

Percentage of participants experiencing moderate or severe Chronic Obstructive Pulmonary Disease (COPD)

End point type	Secondary
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End point timeframe:

52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	204	206	
Units: Percentage of participants				
number (not applicable)	23.5	24.9	27	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in mean total daily symptom scores

End point title | Change from baseline in mean total daily symptom scores

End point description:

The participant recorded symptom scores twice daily in the eDiary. The daily clinical symptoms included: cough, wheezing, shortness of breath, sputum volume, sputum color, and night time awakening. A negative change from baseline indicated improvement.

End point type | Secondary

End point timeframe:

52 weeks

End point values	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	199	198	
Units: Score				
least squares mean (standard error)	-1.57 (± 0.133)	-1.56 (± 0.133)	-1.31 (± 0.135)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in the daily number of puffs of rescue medication over the 52 week period

End point title | Change from baseline in the daily number of puffs of rescue medication over the 52 week period

End point description:

Participants completed an electronic diary (eDiary) twice daily at the same time in the morning and evening to record the number of puffs of rescue medication taken in the previous 12 hours.

End point type | Secondary

End point timeframe:

52 weeks

<b>End point values</b>	QVA149 27.5/12.5 ug	QVA149 27.5/25 ug bid	QAB149 75 ug od	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	199	198	
Units: Number of puffs				
least squares mean (standard error)	-1.89 (± 0.164)	-1.62 (± 0.164)	-1.73 (± 0.166)	

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	QVA149 27.5/12.5 bid
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Reporting group description:

QVA149 27.5/12.5 bid

Reporting group title	QVA149 27.5/25 bid
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Reporting group description:

QVA149 27.5/25 bid

Reporting group title	QAB149 75 od
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Reporting group description:

QAB149 75 od

<b>Serious adverse events</b>	QVA149 27.5/12.5 bid	QVA149 27.5/25 bid	QAB149 75 od
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 204 (12.75%)	25 / 204 (12.25%)	24 / 206 (11.65%)
number of deaths (all causes)	1	3	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE CANCER			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COLON CANCER			

subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>KAPOSI'S SARCOMA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>LUNG NEOPLASM MALIGNANT</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>METASTASES TO LUNG</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>METASTASES TO PERITONEUM</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>METASTASES TO SPINE</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>NON-SMALL CELL LUNG CANCER STAGE IV</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>PROSTATE CANCER</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>RENAL CELL CARCINOMA</b>			

subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SQUAMOUS CELL CARCINOMA</b>			
subjects affected / exposed	1 / 204 (0.49%)	1 / 204 (0.49%)	0 / 206 (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
<b>SQUAMOUS CELL CARCINOMA OF LUNG</b>			
subjects affected / exposed	1 / 204 (0.49%)	1 / 204 (0.49%)	0 / 206 (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
<b>Vascular disorders</b>			
<b>AORTIC DISSECTION</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>HAEMATOMA</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>HYPOTENSION</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>General disorders and administration site conditions</b>			
<b>FACIAL PAIN</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>NON-CARDIAC CHEST PAIN</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	8 / 204 (3.92%)	5 / 204 (2.45%)	10 / 206 (4.85%)
occurrences causally related to treatment / all	2 / 9	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HAEMOTHORAX			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
PLEURAL EFFUSION			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY MASS			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
PANIC ATTACK			

subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SUICIDE ATTEMPT</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>Injury, poisoning and procedural complications</b>			
<b>BRAIN HERNIATION</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>RIB FRACTURE</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SKULL FRACTURED BASE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>SUBDURAL HAEMORRHAGE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>Congenital, familial and genetic disorders</b>			
<b>ASPLENIA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>Cardiac disorders</b>			
<b>ACUTE MYOCARDIAL INFARCTION</b>			

subjects affected / exposed	2 / 204 (0.98%)	0 / 204 (0.00%)	0 / 206 (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
<b>ANGINA UNSTABLE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>ATRIAL FIBRILLATION</b>			
subjects affected / exposed	1 / 204 (0.49%)	1 / 204 (0.49%)	0 / 206 (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
<b>ATRIAL FLUTTER</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ATRIOVENTRICULAR BLOCK SECOND DEGREE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>BRADYCARDIA</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>CARDIAC FAILURE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>CARDIAC FAILURE ACUTE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>CARDIAC TAMPONADE</b>			

subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>CARDIO-RESPIRATORY ARREST</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
<b>CARDIOGENIC SHOCK</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>CORONARY ARTERY OCCLUSION</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>MYOCARDIAL ISCHAEMIA</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>PERICARDIAL EFFUSION</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SILENT MYOCARDIAL INFARCTION</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>Nervous system disorders</b>			
<b>BRAIN OEDEMA</b>			

subjects affected / exposed	0 / 204 (0.00%)	2 / 204 (0.98%)	0 / 206 (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
<b>CEREBRAL ISCHAEMIA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SUBARACHNOID HAEMORRHAGE</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>TRANSIENT ISCHAEMIC ATTACK</b>			
subjects affected / exposed	1 / 204 (0.49%)	1 / 204 (0.49%)	0 / 206 (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
<b>Blood and lymphatic system disorders</b>			
<b>ANAEMIA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>Gastrointestinal disorders</b>			
<b>ABDOMINAL PAIN</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>HIATUS HERNIA</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>INGUINAL HERNIA</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>INGUINAL HERNIA STRANGULATED</b>			

subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>INTESTINAL OBSTRUCTION</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>LARGE INTESTINE PERFORATION</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>ORAL PAIN</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
<b>RENAL FAILURE ACUTE</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>RENAL IMPAIRMENT</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>Musculoskeletal and connective tissue disorders</b>			
<b>INTERVERTEBRAL DISC PROTRUSION</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
<b>ARTHRITIS INFECTIVE</b>			

subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BRONCHITIS</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>BRONCHOPNEUMONIA</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DIVERTICULITIS</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>ERYSIPELAS</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>H1N1 INFLUENZA</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>LOWER RESPIRATORY TRACT INFECTION</b>			
subjects affected / exposed	1 / 204 (0.49%)	1 / 204 (0.49%)	0 / 206 (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
<b>LUNG INFECTION</b>			
subjects affected / exposed	0 / 204 (0.00%)	0 / 204 (0.00%)	1 / 206 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>MENINGITIS</b>			

subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>PNEUMONIA</b>			
subjects affected / exposed	4 / 204 (1.96%)	1 / 204 (0.49%)	2 / 206 (0.97%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PYELONEPHRITIS</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>PYELONEPHRITIS ACUTE</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SEPSIS</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>SINUSITIS</b>			
subjects affected / exposed	0 / 204 (0.00%)	1 / 204 (0.49%)	0 / 206 (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
<b>UPPER RESPIRATORY TRACT INFECTION BACTERIAL</b>			
subjects affected / exposed	2 / 204 (0.98%)	0 / 204 (0.00%)	0 / 206 (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
<b>URINARY TRACT INFECTION</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>Metabolism and nutrition disorders</b>			
<b>DEHYDRATION</b>			

subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>HYPERGLYCAEMIA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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
<b>HYPOGLYCAEMIA</b>			
subjects affected / exposed	1 / 204 (0.49%)	0 / 204 (0.00%)	0 / 206 (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

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

<b>Non-serious adverse events</b>	QVA149 27.5/12.5 bid	QVA149 27.5/25 bid	QAB149 75 od
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 204 (40.20%)	86 / 204 (42.16%)	88 / 206 (42.72%)
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</b>			
subjects affected / exposed	70 / 204 (34.31%)	64 / 204 (31.37%)	71 / 206 (34.47%)
occurrences (all)	129	154	138
<b>COUGH</b>			
subjects affected / exposed	3 / 204 (1.47%)	13 / 204 (6.37%)	7 / 206 (3.40%)
occurrences (all)	5	16	7
<b>Infections and infestations</b>			
<b>NASOPHARYNGITIS</b>			
subjects affected / exposed	19 / 204 (9.31%)	18 / 204 (8.82%)	22 / 206 (10.68%)
occurrences (all)	22	21	27
<b>UPPER RESPIRATORY TRACT INFECTION BACTERIAL</b>			
subjects affected / exposed	10 / 204 (4.90%)	14 / 204 (6.86%)	13 / 206 (6.31%)
occurrences (all)	11	18	16

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.novfor> for complete trial results.

Notes: