Clinical trial results:
A 26-week, randomized, double blind, parallel-group multicenter study to assess the efficacy and safety of QVA149 (110/50 mcg o.d.) vs. tiotropium (18 mcg o.d.) + salmeterol/fluticasone propionate FDC (50/500 mcg b.i.d.) in patients with moderate to severe COPD

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	2015-000114-22
Trial protocol	BE EE NL LV LT DE CZ HU DK SK ES AT PL GR HR BG
Global end of trial date	18 July 2017

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	CQVA149A2316

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02603393
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, novartis.email@novartis.com

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	18 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 July 2017
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.) on post-dose trough forced expiratory volume in 1 second (FEV1) versus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) after 26 weeks of treatment in moderate-to-severe COPD patients.

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	20 November 2015
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	Argentina: 106
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 88
Country: Number of subjects enrolled	Germany: 204
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Latvia: 30
Country: Number of subjects enrolled	Lithuania: 25
Country: Number of subjects enrolled	Netherlands: 28

Country: Number of subjects enrolled	Poland: 163
Country: Number of subjects enrolled	Romania: 98
Country: Number of subjects enrolled	Serbia: 59
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Spain: 14
Worldwide total number of subjects	1053
EEA total number of subjects	842

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)	470
From 65 to 84 years	576
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a multicenter, randomized, parallel-group, double-blind, triple-dummy study to assess the efficacy of the 2 active treatment groups in patients with moderate to severe COPD.

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
Arm title	QVA149

Arm description:

110/50 µg capsules o.d. for inhalation

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

Dosage and administration details:

110/50 µg o.d.)

Arm title	Tiotropium + salmeterol/fluticasone

Arm description:

tiotropium (18 µg o.d.), and salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.)

Arm type	Experimental
Investigational medicinal product name	Tiotropium + salmeterol/fluticasone
Investigational medicinal product code	
Other name	FDC 50/500 µg b.i.d
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50/500 µg b.i.d

Number of subjects in period 1	QVA149	Tiotropium + salmeterol/fluticasone
Started	527	526
Completed	456	472
Not completed	71	54
Adverse event, serious fatal	3	4

Physician decision	3	3
Adverse event, non-fatal	17	15
Technical problems	4	7
Protocol deviation	2	3
Non-compliance with study treatment	1	-
Patient/guardian decision	32	18
Lost to follow-up	1	2
Sponsor decision	1	-
Lack of efficacy	7	2

Baseline characteristics

Reporting groups	
Reporting group title	QVA149
Reporting group description:	
110/50 µg capsules o.d. for inhalation	
Reporting group title	Tiotropium + salmeterol/fluticasone
Reporting group description:	
tiotropium (18 µg o.d.), and salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.)	

Reporting group values	QVA149	Tiotropium + salmeterol/fluticasone	Total
Number of subjects	527	526	1053
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)	234	236	470
From 65-84 years	288	288	576
85 years and over	5	2	7
Age Continuous Units: Years			
arithmetic mean	65.4	65.2	
standard deviation	± 7.99	± 7.62	-
Sex: Female, Male Units: Subjects			
Female	149	161	310
Male	378	365	743
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	526	523	1049
More than one race	0	0	0
Unknown or Not Reported	1	0	1

End points

End points reporting groups	
Reporting group title	QVA149
Reporting group description:	
110/50 µg capsules o.d. for inhalation	
Reporting group title	Tiotropium + salmeterol/fluticasone
Reporting group description:	
tiotropium (18 µg o.d.), and salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.)	

Primary: Mean change from baseline in post-dose trough FEV1	
End point title	Mean change from baseline in post-dose trough FEV1
End point description:	
Mean change from baseline in post-dose trough forced expiratory volume in 1 second (FEV1) following 26 weeks of treatment. Trough FEV1 is defined as the mean of the two FEV1 values measured at 23 hr 15 min and 23 hr 45 min after the morning dose taken at site on Day 181. Baseline FEV1 is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1.	
End point type	Primary
End point timeframe:	
26 weeks	

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Liters				
least squares mean (standard error)	-0.029 (± 0.0119)	-0.003 (± 0.0115)		

Statistical analyses

Statistical analysis title	Mean change from baseline in post-dose trough FEV1
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0404 [1]
Method	Mixed Model for Repeated Measures Analys
Confidence interval	
level	95 %

Notes:

[1] - 1 sided

Secondary: Annualized rate of moderate or severe COPD exacerbations

End point title	Annualized rate of moderate or severe COPD exacerbations

End point description:

Moderate or severe COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: COPD exacerbations/year				
number (confidence interval 95%)	0.52 (0.43 to 0.63)	0.48 (0.40 to 0.58)		

Statistical analyses

Statistical analysis title	Annualized rate of COPD exacerbations
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5802 [2]
Method	Generalized Linear Model Analysis
Parameter estimate	Ratio of rates
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.4

Notes:

[2] - 2 sided

Secondary: Annualized Rate of COPD exacerbations requiring treatment with systemic glucocorticosteroids and/or antibiotics, moderate exacerbations only

End point title	Annualized Rate of COPD exacerbations requiring treatment with systemic glucocorticosteroids and/or antibiotics, moderate exacerbations only

End point description:

COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: COPD Exacerbations/year				
number (confidence interval 95%)	0.47 (0.39 to 0.58)	0.44 (0.36 to 0.53)		

Statistical analyses

Statistical analysis title	Annualized Rate of COPD exacerbations
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5651 [3]
Method	Generalized Linear Model Analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.43

Notes:

[3] - 2-sided

Secondary: Annualized Rate of COPD exacerbations requiring hospitalisation

End point title	Annualized Rate of COPD exacerbations requiring hospitalisation

End point description:

COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: COPD Exacerbations/year				
number (confidence interval 95%)	0.001 (0.0 to 9999)	0.001 (0.00 to 9999)		

Statistical analyses

Statistical analysis title	Annualized Rate of COPD exacerbations
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9665 [4]
Method	Generalized Linear Model Analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.34

Notes:

[4] - 2-sided

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

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

End point description:

Trough FEV1 is defined as the average of the pre-dose FEV1 measurements at -45 min and -15 min prior to dosing at each visit except Day 182 which is the average of the post-dose FEV1 measurements at 23h15min and 23h45min after dosing at Day 181. Baseline FEV1 is considered the Day 1 average of pre-dose measurements.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Liters				
least squares mean (standard error)	-0.029 (± 0.0119)	-0.003 (± 0.0115)		

Statistical analyses

Statistical analysis title	Mean change from baseline in pre-dose trough FEV1
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone

Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0573 [5]
Method	Mixed Model for Repeated Measures Analys
Confidence interval	
level	95 %

Notes:

[5] - 2-Sided

Secondary: Mean change from baseline in St. George's Respiratory Questionnaire

End point title	Mean change from baseline in St. George's Respiratory Questionnaire

End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is used to provide the health status measurements in this study. Baseline SGRQ-C is defined as the assessment taken right before the first dose of the double-blind drug on Day 1. Higher values correspond to greater impairment of health status.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Score on a scale				
least squares mean (standard error)	-0.7 (± 0.53)	-2.5 (± 0.51)		

Statistical analyses

Statistical analysis title	St. George's Respiratory Questionnaire
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0022 [6]
Method	Mixed Model for Repeated Measures Analys
Confidence interval	
level	95 %

Notes:

[6] - 2-Sided

Secondary: Mean change from baseline in St. George's Respiratory Questionnaire

End point title	Mean change from baseline in St. George's Respiratory Questionnaire

End point description:

The St. George Respiratory Questionnaire C (SGRQ-C) is used to provide the health status measurements in this study. Baseline SGRQ-C is defined as the assessment taken right before the first dose of the double-blind drug on Day 1. Higher values correspond to greater impairment of health status.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Score on a scale				
least squares mean (standard error)	-1.0 (± 0.54)	-2.5 (± 0.52)		

Statistical analyses

Statistical analysis title	St. George’s Respiratory Questionnaire
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0221 [7]
Method	Mixed Model for Repeated measures Analys
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.6

Notes:

[7] - 2-Sided

Secondary: Transition Dyspnea Index (TDI) score

End point title	Transition Dyspnea Index (TDI) score

End point description:

Transitional Dyspnea Index (TDI) score presents the degree of impairment due to dyspnea. The lower the score the worse the severity of dyspnea.

End point type	Secondary

End point timeframe:

12 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Score on a scale				
least squares mean (standard error)	1.177 (± 0.1558)	1.418 (± 0.1508)		

Statistical analyses

Statistical analysis title	TDI
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1724
Method	Mixed Model for Repeated Measures Analys
Confidence interval	
level	95 %

Secondary: Transition Dyspnea Index (TDI) score

End point title	Transition Dyspnea Index (TDI) score
End point description:	
Transitional Dyspnea Index (TDI) score presents the degree of impairment due to dyspnea. The lower the score the worse the severity of dyspnea.	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Score on a scale				
least squares mean (standard error)	1.382 (± 0.1567)	1.671 (± 0.1519)		

Statistical analyses

Statistical analysis title	TDI
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone

Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1055 [8]
Method	Mixed Model for Repated Measures Analysi
Confidence interval	
level	95 %

Notes:

[8] - 2-Sided

Secondary: Change from baseline in the mean daily number of puffs of rescue medication

End point title	Change from baseline in the mean daily number of puffs of rescue medication

End point description:

Change from baseline in mean daily number of puffs of rescue medication (number of puffs taken in the previous 12 hours) over 26 weeks of treatment.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Number of puffs per day				
least squares mean (standard error)	-0.307 (± 0.1006)	-0.484 (± 0.0983)		

Statistical analyses

Statistical analysis title	Rescue medication
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0641 [9]
Method	Linear Mixed Model Analysis
Confidence interval	
level	95 %

Notes:

[9] - 2-Sided

Secondary: Mean change From baseline in Forced Vital Capacity (FVC)

End point title	Mean change From baseline in Forced Vital Capacity (FVC)

End point description:

Change from baseline in forced vital capacity following 26 weeks of treatment. Trough FVC is defined as the average of the pre-dose FVC measurements at -45 min and -15 min prior to dosing at each visit except Day 182 which is the average of the post-dose FVC measurements at 23h15min and 23h45min after dosing at Day 181. Baseline is considered the Day 1 average of pre-dose measurements.

End point type	Secondary

End point timeframe:

26 weeks

End point values	QVA149	Tiotropium + salmeterol/fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	527	526		
Units: Liters				
least squares mean (standard error)	-0.030 (± 0.0192)	-0.048 (± 0.0186)		

Statistical analyses

Statistical analysis title	FVC
Comparison groups	QVA149 v Tiotropium + salmeterol/fluticasone
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4107 [10]
Method	Mixed Model for Repeated Measures Analys
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.061

Notes:

[10] - 2-Sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The study consists of four epochs: screening (1 week), run-in (4 weeks), blinded treatment (26 weeks) and follow-up (4 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	QVA149
Reporting group description:	
QVA149	
Reporting group title	Tio+Salm/flut
Reporting group description:	
Tio+Salm/flut	

Serious adverse events	QVA149	Tio+Salm/flut	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 527 (6.07%)	34 / 526 (6.46%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			

subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 527 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pituitary tumour benign			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic aneurysm rupture			

subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic dissection			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	12 / 527 (2.28%)	13 / 526 (2.47%)	
occurrences causally related to treatment / all	1 / 14	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 527 (0.38%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 527 (0.19%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac tamponade			

subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 527 (0.38%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Duodenal ulcer			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			

subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 527 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 527 (0.76%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 527 (0.19%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	QVA149	Tio+Salm/flut	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	398 / 527 (75.52%)	392 / 526 (74.52%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	26 / 527 (4.93%)	24 / 526 (4.56%)	
occurrences (all)	29	24	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 527 (1.33%)	10 / 526 (1.90%)	
occurrences (all)	8	10	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 527 (0.19%)	6 / 526 (1.14%)	
occurrences (all)	1	6	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 527 (1.33%)	13 / 526 (2.47%)	
occurrences (all)	12	14	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	3 / 527 (0.57%)	6 / 526 (1.14%)	
occurrences (all)	4	6	
Oedema peripheral			
subjects affected / exposed	7 / 527 (1.33%)	3 / 526 (0.57%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 527 (0.57%)	6 / 526 (1.14%)	
occurrences (all)	3	6	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	370 / 527 (70.21%)	353 / 526 (67.11%)	
occurrences (all)	1024	1014	
Cough			
subjects affected / exposed	24 / 527 (4.55%)	15 / 526 (2.85%)	
occurrences (all)	27	17	
Oropharyngeal pain			
subjects affected / exposed	7 / 527 (1.33%)	7 / 526 (1.33%)	
occurrences (all)	7	7	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 527 (1.52%)	9 / 526 (1.71%)	
occurrences (all)	9	9	
Pain in extremity			
subjects affected / exposed	2 / 527 (0.38%)	6 / 526 (1.14%)	
occurrences (all)	2	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 527 (2.47%)	5 / 526 (0.95%)	
occurrences (all)	13	6	
Influenza			
subjects affected / exposed	6 / 527 (1.14%)	6 / 526 (1.14%)	
occurrences (all)	8	6	
Oral candidiasis			
subjects affected / exposed	12 / 527 (2.28%)	18 / 526 (3.42%)	
occurrences (all)	16	25	
Oropharyngeal candidiasis			
subjects affected / exposed	6 / 527 (1.14%)	7 / 526 (1.33%)	
occurrences (all)	7	7	
Pneumonia			
subjects affected / exposed	2 / 527 (0.38%)	6 / 526 (1.14%)	
occurrences (all)	2	6	
Respiratory tract infection viral			
subjects affected / exposed	1 / 527 (0.19%)	6 / 526 (1.14%)	
occurrences (all)	1	6	
Upper respiratory tract infection			

bacterial			
subjects affected / exposed	2 / 527 (0.38%)	6 / 526 (1.14%)	
occurrences (all)	2	6	
Urinary tract infection			
subjects affected / exposed	7 / 527 (1.33%)	1 / 526 (0.19%)	
occurrences (all)	7	1	
Viral upper respiratory tract infection			
subjects affected / exposed	57 / 527 (10.82%)	59 / 526 (11.22%)	
occurrences (all)	65	73	

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.novfor complete trial results

Notes: