Clinical trial results:
A randomized, multicenter, open-label, cross-over study to assess lung function and patient preference after a 4 week treatment each with QVA149 vs. tiotropium in patients with stable chronic obstructive pulmonary disease (COPD) and moderate to severe airflow limitation who are on a tiotropium therapy (FAVOR study).

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2013-004223-37
Trial protocol	DE
Global end of trial date	12 January 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	CQVA149ADE04
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02125734
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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of QVA149 (100/50 µg o.d.) as compared to tiotropium (18 µg o.d.) in terms of FEV1 1 h post-inhalation after 4 weeks of treatment in patients with stable COPD and moderate to severe airflow limitation still having symptoms (COPD Assessment Test [CAT] score of at least 10) despite treatment with tiotropium.

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	24 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	49
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

119 patients were screened for study participation, 88 were randomized and all of them were exposed to treatment. 43 patients (43/88, 48.9%) were randomized into the QVA149, then tiotropium group (further referred to as QVA-Tio) and 45 patients (45/88, 51.1%) were randomized into the tiotropium, then QVA149 group (further referred to as Tio- QVA)

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment sequence 1

Arm description:

QVA149 from day 1 to day 28 and tiotropium from day 29 to day 56

Arm type	Experimental
Investigational medicinal product name	QVA149 from day 1 to day 28 and tiotropium from day 29 to day 56
Investigational medicinal product code	QVA149
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

QVA149 capsules 110/50 µg for inhalation

Arm title	Treatment sequence 2

Arm description:

Tiotropium from day 1 to day 28 and QVA149 from day 29 to day 56

Arm type	Experimental
Investigational medicinal product name	Tiotropium from day 1 to day 28 and QVA149 from day 29 to day 56
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 18 µg capsules for inhalation via HandiHaler

Number of subjects in period 1	Treatment sequence 1	Treatment sequence 2
Started	40	48
Completed	40	47
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment sequence 1
Reporting group description:	
QVA149 from day 1 to day 28 and tiotropium from day 29 to day 56	
Reporting group title	Treatment sequence 2
Reporting group description:	
Tiotropium from day 1 to day 28 and QVA149 from day 29 to day 56	

Reporting group values	Treatment sequence 1	Treatment sequence 2	Total
Number of subjects	40	48	88
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)	23	26	49
From 65-84 years	16	22	38
85 years and over	1	0	1
Age Continuous | Units: Years			
arithmetic mean	63.9	66	
standard deviation	± 9.83	± 9.31	-
Gender, Male/Female Units: Participants			
Female	15	16	31
Male	25	32	57

End points

End points reporting groups

Reporting group title	Treatment sequence 1
Reporting group description:	
QVA149 from day 1 to day 28 and tiotropium from day 29 to day 56	
Reporting group title	Treatment sequence 2
Reporting group description:	
Tiotropium from day 1 to day 28 and QVA149 from day 29 to day 56	
Subject analysis set title	QVA149
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who applied at least one dose of study medication during at least one study period	
Subject analysis set title	Tiotropium
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who applied at least one dose of study medication during at least one study period	
Subject analysis set title	QVA149
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who applied at least one dose of study medication during at least one study period	
Subject analysis set title	Tiotropium
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who applied at least one dose of study medication during at least one study period	
Subject analysis set title	Tiotropium
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who applied at least one dose of study medication during at least one study period	

Primary: Forced Expiratory Volume in one second (FEV1) at 1 h post-inhalation

End point title	Forced Expiratory Volume in one second (FEV1) at 1 h post-inhalation
End point description:	
Forced Expiratory Volume in one second (FEV1) will be calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.	
End point type	Primary
End point timeframe:	
week 4	

End point values	QVA149	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	88		
Units: Liters				
least squares mean (confidence interval 95%)	1.676 (1.635 to 1.716)	1.595 (1.555 to 1.634)		

Statistical analyses

Statistical analysis title	Comparision of FEV1 between QVA149 and Tiotropium
Comparison groups	QVA149 v Tiotropium
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0017
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.13

Secondary: Patient preference after experiencing both treatments was assessed at the end of treatment period 2 with a Patient Preference Questionnaire.

End point title	Patient preference after experiencing both treatments was assessed at the end of treatment period 2 with a Patient Preference Questionnaire.

End point description:

Patient preference after experiencing both treatments. The patient’s preference questionnaire was a two-choice question (preference for QVA149 OR Tiotropium.

End point type	Secondary

End point timeframe:

8 weeks

End point values	QVA149	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: Participants	59	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator preference per patient after experiencing both treatments for future suggestions.

End point title	Investigator preference per patient after experiencing both treatments for future suggestions.

End point description:

The investigator preference for future treatment suggestion after experiencing both treatments was assessed at the end of treatment period 2 with the Investigator Preference Questionnaire

End point type	Secondary

End point timeframe:

8 weeks

End point values	QVA149	Tiotropium		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	87		
Units: Participants	71	16		

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	QVA149
Reporting group description:	
QVA149	
Reporting group title	Tiotropium
Reporting group description:	
Tiotropium	

Serious adverse events	QVA149	Tiotropium	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (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	Tiotropium	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 88 (31.82%)	21 / 88 (23.86%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	12 / 88 (13.64%)	4 / 88 (4.55%)	
occurrences (all)	15	4	
Dysphonia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	2	
Increased viscosity of bronchial secretion			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 88 (0.00%)	2 / 88 (2.27%)	
occurrences (all)	0	3	
Nasal discomfort			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	3 / 88 (3.41%)	0 / 88 (0.00%)	
occurrences (all)	3	0	
Rhinorrhoea			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	2 / 88 (2.27%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Escherichia test positive			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	

Wound			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	2 / 88 (2.27%)	0 / 88 (0.00%)	
occurrences (all)	4	0	
Arrhythmia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 88 (2.27%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	4 / 88 (4.55%)	2 / 88 (2.27%)	
occurrences (all)	5	3	
Hypotonia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Nerve compression			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 88 (3.41%)	0 / 88 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	

Flatulence			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 88 (1.14%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 88 (3.41%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Herpes zoster			

subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 88 (1.14%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2014	The protocol was amended to correct the exact time-point when the Physician Preference Questionnaire was supposed to be filled in at Visit 6. Furthermore, minor inconsistencies and corrections were made.

Notes:

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, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: