Clinical trial results:
A multicenter, 4-week crossover (total duration 12 weeks), placebo-controlled, double-blind study to determine the impact of QVA149 (indacaterol/glycopyrronium) 85/43 g on nocturnal oxygen levels in Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2013-005573-51
Trial protocol	DK SE
Global end of trial date	22 June 2016

Results information

Result version number	v1 (current)
This version publication date	06 July 2017
First version publication date	06 July 2017

Trial information

Trial identification

Sponsor protocol code	CQVA149ANO01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02233543
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
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	22 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the level of improvement in mean night time SpO2 following 4 weeks of administration of QVA149 compared to placebo.

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 November 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	Norway: 14
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Denmark: 11
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	9
From 65 to 84 years	29

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	First QVA149 (indacaterol/glycopyrronium), then Placebo

Arm description:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Arm type	Experimental
Investigational medicinal product name	Indacaterol/glycpyrronium
Investigational medicinal product code	QVA149
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Arm title	First Placebo, then QVA149 (indacaterol/glycopyrronium)

Arm description:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

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

Dosage and administration details:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Investigational medicinal product name	Indacaterol/glycopyrronium
Investigational medicinal product code	QVA149
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Number of subjects in period 1	First QVA149 (indacaterol/glycopyrronium), then Placebo	First Placebo, then QVA149 (indacaterol/glycopyrronium)
Started	22	16
Completed	19	13
Not completed	3	3
Consent withdrawn by subject	1	-
Participants required other treatment.	2	3

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	First QVA149 (indacaterol/glycopyrronium), then Placebo

Arm description:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

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

Dosage and administration details:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Arm title	First Placebo, then QVA149 (indacaterol/glycopyrronium)

Arm description:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

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

Dosage and administration details:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day

Number of subjects in period 2	First QVA149 (indacaterol/glycopyrronium), then Placebo	First Placebo, then QVA149 (indacaterol/glycopyrronium)
Started	19	13
Completed	17	12
Not completed	2	1
Adverse event, non-fatal	1	-
COPD exacerbation	1	-
Participant required other treatment.	-	1

Baseline characteristics

Reporting groups

Reporting group title	Period 1

Reporting group description: -

Reporting group values	Period 1	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	29	29	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	68.4		
standard deviation	± 6.2	-	
Gender, Male/Female Units: Subjects			
Female	14	14	
Male	24	24	

Subject analysis sets

Subject analysis set title	All participants (QVA149/Placebo)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received 4 weeks of QVA149 and 4 weeks of placebo according to either of the following sequences: QVA149 first and then placebo, or placebo first and then QVA149.

Subject analysis set title	QVA149 (indacaterol/glycopyrronium)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.

Reporting group values	All participants (QVA149/Placebo)	QVA149 (indacaterol/glycopyrronium)	Placebo
Number of subjects	38	35	34
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	68.4		
standard deviation	± 6.2	±	±
Gender, Male/Female Units: Subjects			
Female	14		
Male	24		

End points

End points reporting groups

Reporting group title	First QVA149 (indacaterol/glycopyrronium), then Placebo
Reporting group description:	
Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	
Reporting group title	First Placebo, then QVA149 (indacaterol/glycopyrronium)
Reporting group description:	
Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	
Reporting group title	First QVA149 (indacaterol/glycopyrronium), then Placebo
Reporting group description:	
Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	
Reporting group title	First Placebo, then QVA149 (indacaterol/glycopyrronium)
Reporting group description:	
Participants received 4 weeks of placebo once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day followed by 2 weeks washout. Then participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	
Subject analysis set title	All participants (QVA149/Placebo)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 4 weeks of QVA149 and 4 weeks of placebo according to either of the following sequences: QVA149 first and then placebo, or placebo first and then QVA149.	
Subject analysis set title	QVA149 (indacaterol/glycopyrronium)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received 4 weeks of QVA149 85/43 µg delivered dose once daily in the morning between 08:00 and 11:00 AM at approximately the same time every day.	

Primary: Mean night-time blood oxygenation

End point title	Mean night-time blood oxygenation
End point description:	
The mean night-time blood oxygenation following 4 weeks administration of QVA149 compared to placebo was assessed. Night time oxygenation (SpO2) was measured using polygraphy.	
End point type	Primary
End point timeframe:	
Post 4 weeks administration of QVA149, post 4 weeks administration of placebo	

End point values	QVA149 (indacaterol/glycopyrronium)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	34		
Units: Percent				
least squares mean (standard error)	89.59 (± 0.3)	90.04 (± 0.28)		

Statistical analyses

Statistical analysis title	Mean night-time blood oxygenation
Comparison groups	QVA149 (indacaterol/glycopyrronium) v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2419
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.32

Secondary: Time during the night spent below 90 % in blood oxygen saturation

End point title	Time during the night spent below 90 % in blood oxygen saturation

End point description:

The time during the night spent below 90 % in blood oxygen saturation following 4 weeks administration of QVA149 compared to placebo was assessed. Night time oxygenation (SpO2) was measured using polygraphy.

End point type	Secondary

End point timeframe:

Post 4 weeks administration of QVA149, post 4 weeks administration of placebo

End point values	QVA149 (indacaterol/glycopyrronium)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	34		
Units: Percent				
least squares mean (standard error)	44.37 (± 5.09)	36.58 (± 4.84)		

Statistical analyses

Statistical analysis title	Time during the night spent below 90% blood oxygen
Comparison groups	QVA149 (indacaterol/glycopyrronium) v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2016
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	7.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.51
upper limit	20.08

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	17.0

Reporting groups	
Reporting group title	QVA149
Reporting group description:	
QVA149	
Reporting group title	PLACEBO
Reporting group description:	
PLACEBO	

Serious adverse events	QVA149	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 35 (2.86%)	1 / 34 (2.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 35 (2.86%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	QVA149	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 35 (40.00%)	12 / 34 (35.29%)	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 35 (2.86%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 35 (5.71%)	3 / 34 (8.82%)	
occurrences (all)	2	3	
Cough			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	5 / 35 (14.29%)	4 / 34 (11.76%)	
occurrences (all)	5	4	
Laryngospasm			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	3 / 35 (8.57%)	2 / 34 (5.88%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2014	The procedures for keeping the treatment codes blinded and the responsibilities of the unblinded pharmacist/trained site staff were clarified; The procedures for unblinding the study medication in case of emergency situations were clarified; Sponsor contact details in case of medical emergency situations were added; Inclusion criterion number 5 was modified to specify the criteria for COPD diagnosis; Exclusion criterion number 18 was modified to specify that hypersensitivity relates to the investigational therapy; Non-selective beta blockers (including eye drops) and anticholinergic medications (except for study treatment) were added to the list of prohibited medications. Two new exclusion criteria (number 20 and number 21) specifying this were added; The procedures for archiving of essential documents were clarified; Corrections of typos and some additional clarifications to the text were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported