Clinical trial results:
A randomized, double-blind, placebo-controlled, two-period crossover study to assess the effect of inhaled QVA149 on global and regional lung function and gas exchange in patients with moderate to severe COPD.

Summary

EudraCT number	2013-004461-13
Trial protocol	GB
Global end of trial date	26 September 2017

Results information

Result version number	v1 (current)
This version publication date	11 October 2018
First version publication date	11 October 2018

Trial information

Trial identification

Sponsor protocol code	CQVA149A2325

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02634983
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 612241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 612241111, 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	26 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2017
Global end of trial reached?	Yes
Global end of trial date	26 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess global ventilated lung volume after treatment with QVA149 compared to placebo. Secondary objectives included assessment of regional lung ventilated volume, evaluation of physiologic measures of lung function and assessment of small airway function after treatment with QVA149 compared to placebo.

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.

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	03 June 2016
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	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	13
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study took place in 3 clinical sites in United-Kingdom

Pre-assignment

Screening details:

31 patients were randomized, all of whom were included in the safety set and PD analysis sets (primary population of interest)

Period 1

Period 1 title	Period One (First treatment, 8-10 days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients were assigned to one of the following two treatment arms in a ratio of 1:1 (active: placebo)

Arms

Are arms mutually exclusive?	Yes
Arm title	QVA149 110/50 mcg then Matching placebo

Arm description:

QVA149, followed by matching placebo. Each treatment 8-10 days.

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:

Single daily dose of 110/50 mcg QVA149 for 8-10 days.

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

Dosage and administration details:

Single daily dose of matching placebo for 8-10 days

Arm title	Matching placebo then QVA149 110/50 mcg

Arm description:

Matching placebo, followed by QVA149. Each treatment 8-10 days.

Arm type	Placebo
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:

Single daily dose of 110/50 mcg QVA149 for 8-10 days.

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

Dosage and administration details:

Single daily dose of matching placebo for 8-10 days

Number of subjects in period 1	QVA149 110/50 mcg then Matching placebo	Matching placebo then QVA149 110/50 mcg
Started	16	15
Completed	16	15

Period 2

Period 2 title	Washout (approximately 7-14 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients were assigned to one of the following two treatment arms in a ratio of 1:1 (active: placebo)

Arms

Are arms mutually exclusive?	Yes
Arm title	QVA149 110/50 mcg then Matching placebo

Arm description:

QVA149, followed by matching placebo. Each treatment 8-10 days.

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:

Single daily dose of 110/50 mcg QVA149 for 8-10 days.

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

Dosage and administration details:

Single daily dose of matching placebo for 8-10 days

Arm title	Matching placebo then QVA149 110/50 mcg

Arm description:	
Matching placebo, followed by QVA149. Each treatment 8-10 days.	
Arm type	Placebo
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:	
Single daily dose of 110/50 mcg QVA149 for 8-10 days.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details:	
Single daily dose of matching placebo for 8-10 days	

Number of subjects in period 2	QVA149 110/50 mcg then Matching placebo	Matching placebo then QVA149 110/50 mcg
Started	16	15
Completed	16	15

Period 3	
Period 3 title	Period 2 (Second treatment, 8-10 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator
Blinding implementation details:	
Patients were assigned to one of the following two treatment arms in a ratio of 1:1 (active: placebo)	

Arms	
Are arms mutually exclusive?	Yes
Arm title	QVA149 110/50 mcg then Matching placebo
Arm description:	
QVA149, followed by matching placebo. Each treatment 8-10 days.	
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: Single daily dose of 110/50 mcg QVA149 for 8-10 days.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details: Single daily dose of matching placebo for 8-10 days	
Arm title	Matching placebo then QVA149 110/50 mcg
Arm description: Matching placebo, followed by QVA149. Each treatment 8-10 days.	
Arm type	Placebo
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: Single daily dose of 110/50 mcg QVA149 for 8-10 days.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details: Single daily dose of matching placebo for 8-10 days	

Number of subjects in period 3	QVA149 110/50 mcg then Matching placebo	Matching placebo then QVA149 110/50 mcg
Started	16	15
Completed	14	15
Not completed	2	0
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups

Reporting group title	Period One (First treatment, 8-10 days)

Reporting group description: -

Reporting group values	Period One (First treatment, 8-10 days)	Total	
Number of subjects	31	31	
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)	13	13	
From 65-84 years	18	18	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	65.9		
standard deviation	± 6.31	-	
Sex: Female, Male			
Units: Subjects			
Female	15	15	
Male	16	16	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	31	31	
More than one race	0	0	
Unknown or Not Reported	0	0	
Forced Expiratory Volume in 1 Second|0 Minutes Pre Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter			
arithmetic mean	1.1584		
standard deviation	± 0.35206	-	
Forced Expiratory Volume in 1 Second|60 Minutes Post Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			

Units: Liter			
arithmetic mean	1.3987		
standard deviation	± 0.37266	-	
Percent Predicted FEV1|0 Minutes Pre Inhalation|			
Units: Percent			
arithmetic mean	43.90		
standard deviation	± 10.873	-	
Percent Predicted FEV1|60 Minutes Post Inhalation|			
Units: Percent			
arithmetic mean	53.10		
standard deviation	± 11.680	-	
Forced Vital Capacity|0 Minutes Pre Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter			
arithmetic mean	2.7426		
standard deviation	± 0.73932	-	
Forced Vital Capacity|60 Minutes Post Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter			
arithmetic mean	3.0781		
standard deviation	± 0.81113	-	
FEV1/FVC ratio|0 Minutes Pre Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent			
arithmetic mean	42.968		
standard deviation	± 8.9797	-	
FEV1/FVC ratio|60 Minutes Post Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent			
arithmetic mean	46.365		
standard deviation	± 8.8240	-	
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Liter			
arithmetic mean	0.2403		
standard deviation	± 0.12994	-	
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Percent			
arithmetic mean	9.19		
standard deviation	± 4.743	-	

Subject analysis sets	
Subject analysis set title	All Study Participants
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who were randomized to receive either QVA149 110/50 mcg or Placebo matching QVA149 110/50 mcg	
Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of 110/50 µg QVA149 for 8-10 days.	
Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of matching placebo for 8-10 days.	
Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of 110/50 µg QVA149 for 8-10 days.	
Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of matching placebo for 8-10 days.	
Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of matching placebo for 8-10 days.	
Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis
Subject analysis set description:	
Single daily dose of 110/50 µg QVA149 for 8-10 days.	

Reporting group values	All Study Participants	QVA149 110/50 mcg	Matching placebo
Number of subjects	31	31	28
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)	13	0	0
From 65-84 years	18	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	65.9		
standard deviation	± 6.31	±	±

Sex: Female, Male Units: Subjects			
Female	15		
Male	16		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	31		
More than one race	0		
Unknown or Not Reported	0		
Forced Expiratory Volume in 1 Second|0 Minutes Pre Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter			
arithmetic mean	1.1584		
standard deviation	± 0.35206	±	±
Forced Expiratory Volume in 1 Second|60 Minutes Post Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter			
arithmetic mean	1.3987		
standard deviation	± 0.37266	±	±
Percent Predicted FEV1|0 Minutes Pre Inhalation|			
Units: Percent			
arithmetic mean	43.90		
standard deviation	± 10.873	±	±
Percent Predicted FEV1|60 Minutes Post Inhalation|			
Units: Percent			
arithmetic mean	53.10		
standard deviation	± 11.680	±	±
Forced Vital Capacity|0 Minutes Pre Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter			
arithmetic mean	2.7426		
standard deviation	± 0.73932	±	±
Forced Vital Capacity|60 Minutes Post Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter			
arithmetic mean	3.0781		
standard deviation	± 0.81113	±	±
FEV1/FVC ratio|0 Minutes Pre Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			

Units: Percent			
arithmetic mean	42.968		
standard deviation	± 8.9797	±	±
FEV1/FVC ratio|60 Minutes Post Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent			
arithmetic mean	46.365		
standard deviation	± 8.8240	±	±
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Liter			
arithmetic mean	0.2403		
standard deviation	± 0.12994	±	±
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Percent			
arithmetic mean	9.19		
standard deviation	± 4.743	±	±

Reporting group values	QVA149 110/50 mcg	Matching placebo	Matching placebo
Number of subjects	27	26	31
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	±	±	±
Sex: Female, Male			
Units: Subjects			
Female			
Male			
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			

Unknown or Not Reported			

Forced Expiratory Volume in 1 Second|0 Minutes Pre Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter arithmetic mean standard deviation	±	±	±
Forced Expiratory Volume in 1 Second|60 Minutes Post Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter arithmetic mean standard deviation	±	±	±
Percent Predicted FEV1|0 Minutes Pre Inhalation| Units: Percent arithmetic mean standard deviation	±	±	±
Percent Predicted FEV1|60 Minutes Post Inhalation| Units: Percent arithmetic mean standard deviation	±	±	±
Forced Vital Capacity|0 Minutes Pre Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter arithmetic mean standard deviation	±	±	±
Forced Vital Capacity|60 Minutes Post Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter arithmetic mean standard deviation	±	±	±
FEV1/FVC ratio|0 Minutes Pre Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent arithmetic mean standard deviation	±	±	±
FEV1/FVC ratio|60 Minutes Post Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent arithmetic mean standard deviation	±	±	±
Reversibility			

Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Liter			
arithmetic mean			
standard deviation	±	±	±
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Percent			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	QVA149 110/50 mcg		
Number of subjects	29		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	±		
Sex: Female, Male			
Units: Subjects			
Female			
Male			
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			
Forced Expiratory Volume in 1 Second|0 Minutes Pre Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			
Units: Liter			
arithmetic mean			
standard deviation	±		
Forced Expiratory Volume in 1 Second|60 Minutes Post Inhalation|			
The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.			

Units: Liter arithmetic mean standard deviation	±		
Percent Predicted FEV1|0 Minutes Pre Inhalation| Units: Percent arithmetic mean standard deviation	±		
Percent Predicted FEV1|60 Minutes Post Inhalation| Units: Percent arithmetic mean standard deviation	±		
Forced Vital Capacity|0 Minutes Pre Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter arithmetic mean standard deviation	±		
Forced Vital Capacity|60 Minutes Post Inhalation|			
Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry.			
Units: Liter arithmetic mean standard deviation	±		
FEV1/FVC ratio|0 Minutes Pre Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent arithmetic mean standard deviation	±		
FEV1/FVC ratio|60 Minutes Post Inhalation|			
The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).			
Units: Percent arithmetic mean standard deviation	±		
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Liter arithmetic mean standard deviation	±		
Reversibility			
Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation			
Units: Percent arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	QVA149 110/50 mcg then Matching placebo

Reporting group description:

QVA149, followed by matching placebo. Each treatment 8-10 days.

Reporting group title	Matching placebo then QVA149 110/50 mcg

Reporting group description:

Matching placebo, followed by QVA149. Each treatment 8-10 days.

Reporting group title	QVA149 110/50 mcg then Matching placebo

Reporting group description:

QVA149, followed by matching placebo. Each treatment 8-10 days.

Reporting group title	Matching placebo then QVA149 110/50 mcg

Reporting group description:

Matching placebo, followed by QVA149. Each treatment 8-10 days.

Reporting group title	QVA149 110/50 mcg then Matching placebo

Reporting group description:

QVA149, followed by matching placebo. Each treatment 8-10 days.

Reporting group title	Matching placebo then QVA149 110/50 mcg

Reporting group description:

Matching placebo, followed by QVA149. Each treatment 8-10 days.

Subject analysis set title	All Study Participants
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomized to receive either QVA149 110/50 mcg or Placebo matching QVA149 110/50 mcg

Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of 110/50 µg QVA149 for 8-10 days.

Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of matching placebo for 8-10 days.

Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of 110/50 µg QVA149 for 8-10 days.

Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of matching placebo for 8-10 days.

Subject analysis set title	Matching placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of matching placebo for 8-10 days.

Subject analysis set title	QVA149 110/50 mcg
Subject analysis set type	Full analysis

Subject analysis set description:

Single daily dose of 110/50 µg QVA149 for 8-10 days.

Primary: Global Ventilated Lung Volume

End point title	Global Ventilated Lung Volume

End point description:

The global distribution of inhaled gas within the lung was assessed using an inhaled gaseous contrast agent, Hyperpolarized Helium (3He) Lung Imaging. The Global Ventilated Lung Volume was expressed in percentage (%VV) of total lung volume.

End point type	Primary

End point timeframe:

Day 8 to Day 10 (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	28		
Units: Percentage of total lung volume				
least squares mean (confidence interval 90%)	61.73 (56.16 to 67.30)	56.73 (51.07 to 62.39)		

Statistical analyses

Statistical analysis title	Global Ventilated Lung Volume
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0254
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.4
upper limit	8.6
Variability estimate	Standard error of the mean
Dispersion value	2.11

Secondary: Regional Ventilated Lung Volume

End point title	Regional Ventilated Lung Volume

End point description:

The regional distribution of inhaled gas within the lung was assessed using an inhaled gaseous contrast agent, Hyperpolarized Helium (3He) Lung Imaging. The Regional Ventilated Lung Volume was expressed in percentage (% VDV) of total lung volume for each lobar region.

End point type	Secondary

End point timeframe:
Day 8 to Day 10 (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	28		
Units: Percentage of total lung volume				
least squares mean (confidence interval 90%)				
Lung, Left Ventilation|	61.94 (56.04 to 67.83)	57.16 (51.17 to 63.15)		
Lung, Left Lower Lobe Ventilation|	58.97 (52.63 to 65.31)	54.01 (47.52 to 60.49)		
Lung, Left Upper Lobe Ventilation|	64.17 (57.95 to 70.39)	59.20 (52.87 to 65.53)		
Lung, Right Ventilation|	61.63 (55.90 to 67.36)	56.24 (50.40 to 62.08)		
Lung, Right Lower Lobe Ventilation|	60.92 (54.62 to 67.21)	57.65 (51.26 to 64.04)		
Lung, Right Middle Lobe Ventilation|	59.59 (52.85 to 66.34)	53.98 (47.01 to 60.95)		
Lung, Right Upper Lobe Ventilation|	63.25 (56.71 to 69.79)	55.53 (48.85 to 62.20)		

Statistical analyses

Statistical analysis title	Lung, Left Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.035
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.77
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.11
upper limit	8.44
Variability estimate	Standard error of the mean
Dispersion value	2.15

Statistical analysis title	Lung, Left Lower Lobe Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0946
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.08
upper limit	9.84
Variability estimate	Standard error of the mean
Dispersion value	2.86

Statistical analysis title	Lung, Left Upper Lobe Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0486
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	9.07
Variability estimate	Standard error of the mean
Dispersion value	2.41

Statistical analysis title	Lung, Right Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0286
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.42
upper limit	9.35

Variability estimate	Standard error of the mean
Dispersion value	2.33

Statistical analysis title	Lung, Right Lower Lobe Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.165
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.63
upper limit	7.17
Variability estimate	Standard error of the mean
Dispersion value	2.29

Statistical analysis title	Lung, Right Middle Lobe Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1421
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5.61
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.71
upper limit	11.94
Variability estimate	Standard error of the mean
Dispersion value	3.71

Statistical analysis title	Lung, Right Upper Lobe Ventilation
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0099
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	7.73
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.98
upper limit	12.47
Variability estimate	Standard error of the mean
Dispersion value	2.78

Secondary: Pulmonary Perfusion

End point title	Pulmonary Perfusion

End point description:

Lung Perfusion Imaging, or MR perfusion imaging of the lung with gadolinium contrast agent, was performed to determine whether vascular abnormalities producing perfusion deficits corresponded to abnormalities in ventilation (hypoxic vasoconstriction). Pulmonary Perfusion was expressed in ml/100 g lung tissue/min of each lobar region.

End point type	Secondary

End point timeframe:

Day 8 to Day 10 (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: ml/100 g lung tissue/min				
least squares mean (confidence interval 90%)				
Lung Perfusion|	13.96 (12.50 to 15.41)	13.03 (11.56 to 14.50)		
Lung, Left Perfusion|	14.42 (12.94 to 15.90)	13.08 (11.58 to 14.57)		
Lung, Left Lower Lobe Perfusion|	13.48 (11.91 to 15.06)	12.79 (11.20 to 14.38)		
Lung, Left Upper Lobe Perfusion|	15.35 (13.69 to 17.01)	13.45 (11.77 to 15.12)		
Lung, Right Perfusion|	13.54 (12.07 to 15.01)	12.97 (11.49 to 14.46)		
Lung, Right Lower Lobe Perfusion|	13.26 (11.74 to 14.79)	13.25 (11.71 to 14.79)		
Lung, Right Middle Lobe Perfusion|	14.86 (12.72 to 17.00)	13.36 (11.19 to 15.53)		
Lung, Right Upper Lobe Perfusion|	13.57 (11.91 to 15.23)	12.70 (11.03 to 14.37)		

Statistical analyses

Statistical analysis title	Lung Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.323
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.64
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	0.92

Statistical analysis title	Lung, Left Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1717
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.34
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.29
upper limit	2.97
Variability estimate	Standard error of the mean
Dispersion value	0.95

Statistical analysis title	Lung, Left Lower Lobe Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5031
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.05
upper limit	2.43
Variability estimate	Standard error of the mean
Dispersion value	1.02

Statistical analysis title	Lung, Left Upper Lobe Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.076
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.15
upper limit	3.65
Variability estimate	Standard error of the mean
Dispersion value	1.03

Statistical analysis title	Lung, Right Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5465
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.57
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.02
upper limit	2.16

Variability estimate	Standard error of the mean
Dispersion value	0.93

Statistical analysis title	Lung, Right Lower Lobe Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9913
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.85
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	1.08

Statistical analysis title	Lung, Right Middle Lobe Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3837
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.39
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	1.7

Statistical analysis title	Lung, Right Upper Lobe Perfusion
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3624
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.73
upper limit	2.48
Variability estimate	Standard error of the mean
Dispersion value	0.94

Secondary: Forced Expiratory Volume in 1 second (FEV1)

End point title	Forced Expiratory Volume in 1 second (FEV1)

End point description:

The Forced Expiratory Volume in one second (FEV1) was calculated as the volume of air forcibly exhaled in one second as measured by a spirometer.

End point type	Secondary

End point timeframe:

Day 1 (0.25, 1 and 2 hours post-dose), Day 8 (-0.75, -0.25, 0.25, 1 and 2 hours post-dose) (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	31		
Units: Liter				
least squares mean (confidence interval 90%)				
FEV1 Day 1 (0.25 hrs post-dose) (n=31, 29)|	1.27 (1.25 to 1.30)	1.13 (1.10 to 1.15)		
FEV1 Day 1 (1 hrs post-dose) (n=31,28)|	1.32 (1.29 to 1.36)	1.12 (1.09 to 1.16)		
FEV1 Day 1 (2 hrs post-dose) (n=31,30)|	1.34 (1.30 to 1.38)	1.15 (1.11 to 1.19)		
FEV1 Day 8 (-0.75 hrs post-dose) (n=31,28)|	1.30 (1.26 to 1.34)	1.09 (1.05 to 1.13)		
FEV1 Day 8 (-0.25 hrs post-dose) (n=30,27)|	1.33 (1.29 to 1.37)	1.11 (1.07 to 1.15)		
FEV1 Day 8 (0.25 hrs post-dose) (n=31,28)|	1.38 (1.35 to 1.42)	1.10 (1.06 to 1.14)		
FEV1 Day 8 (1 hrs post-dose) (n=30, 26)|	1.45 (1.41 to 1.49)	1.13 (1.09 to 1.17)		
FEV1 Day 8 (2 hrs post-dose) (n=31,28)|	1.43 (1.39 to 1.47)	1.11 (1.07 to 1.15)		

Statistical analyses

Statistical analysis title	FEV1 Day 1 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.11
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	FEV1 Day 1 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.15
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 1 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.13
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 8 (-0.75 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.16
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 8 (-0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.16
upper limit	0.28

Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 8 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.23
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 8 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	FEV1 Day 8 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Forced Vital Capacity (FVC)

End point title	Forced Vital Capacity (FVC)

End point description:

Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC was assessed via spirometry. An increase in FVC indicates improvement in lung function.

End point type	Secondary

End point timeframe:

Day 1 (0.25, 1 and 2 hours post-dose), Day 8 (-0.75, -0.25, 0.25, 1 and 2 hours post-dose) (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	31		
Units: Liter				
least squares mean (confidence interval 90%)				
FVC Day 1 (0.25 hrs post-dose) (n=31,29)|	2.92 (2.85 to 2.98)	2.68 (2.61 to 2.74)		
FVC Day 1 (1 hrs post-dose) (n=31,28)|	2.99 (2.91 to 3.06)	2.63 (2.56 to 2.71)		
FVC Day 1 (2 hrs post-dose) (n=31,30)|	2.99 (2.91 to 3.07)	2.68 (2.59 to 2.76)		
FVC Day 8 (-0.75 hrs post-dose) (n=31,29)|	2.91 (2.84 to 2.98)	2.56 (2.49 to 2.64)		
FVC Day 8 (-0.25 hrs post-dose) (n=30,27)|	2.91 (2.84 to 2.98)	2.63 (2.56 to 2.70)		
FVC Day 8 (0.25 hrs post-dose) (n=31,28)|	3.02 (2.95 to 3.09)	2.59 (2.51 to 2.66)		
FVC Day 8 (1 hrs post-dose) (n=30,26)|	3.10 (3.04 to 3.17)	2.65 (2.58 to 2.72)		
FVC Day 8 (2 hrs post-dose) (n=31,28)|	3.06 (2.98 to 3.13)	2.62 (2.54 to 2.70)		

Statistical analyses

Statistical analysis title	FVC Day 1 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.15
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.05

Statistical analysis title	FVC Day 1 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	FVC Day 1 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2
upper limit	0.42
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	FVC Day 8 (-0.75 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	FVC Day 8 (-0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.19
upper limit	0.37

Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	FVC Day 8 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.33
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	FVC Day 8 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.36
upper limit	0.54
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	FVC Day 8 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.33
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.06

Secondary: FEV1/FVC ratio

End point title	FEV1/FVC ratio

End point description:

The FEV1/FVC ratio is the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC). The result of this ratio is expressed as FEV1%.

End point type	Secondary

End point timeframe:

Day 1 (0.25, 1 and 2 hours post-dose), Day 8 (-0.75, -0.25, 0.25, 1 and 2 hours post-dose) (each treatment period)

End point values	QVA149 110/50 mcg	Matching placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	31		
Units: FEV1 Percentage				
least squares mean (confidence interval 90%)				
FEV1/FVC Day 1 (0.25 hrs post-dose) (n=31,29)|	44.31 (43.59 to 45.02)	42.14 (41.39 to 42.89)		
FEV1/FVC Day 1 (1 hrs post-dose) (n=31,28)|	44.97 (44.05 to 45.88)	42.91 (41.95 to 43.87)		
FEV1/FVC Day 1 (2 hrs post-dose) (n=31,30)|	45.25 (44.42 to 46.08)	42.93 (42.08 to 43.79)		
FEV1/FVC Day 8 (-0.75 hrs post-dose) (n=31,28)|	45.05 (44.05 to 46.05)	42.23 (41.16 to 43.30)		
FEV1/FVC Day 8 (-0.25 hrs post-dose) (n=30,27)|	45.97 (45.05 to 46.89)	42.17 (41.19 to 43.15)		
FEV1/FVC Day 8 (0.25 hrs post-dose) (n=31,28)|	46.34 (45.43 to 47.26)	42.60 (41.63 to 43.58)		
FEV1/FVC Day 8 (1 hrs post-dose) (n=30,26)|	47.32 (46.31 to 48.33)	42.72 (41.64 to 43.80)		
FEV1/FVC Day 8 (2 hrs post-dose) (n=31,28)|	47.39 (46.39 to 48.40)	42.42 (41.35 to 43.48)		

Statistical analyses

Statistical analysis title	FEV1/FVC Day 1 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.21
upper limit	3.12
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	FEV1/FVC Day 1 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0106
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	3.33
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	FEV1/FVC Day 1 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2
upper limit	3.44
Variability estimate	Standard error of the mean
Dispersion value	0.66

Statistical analysis title	FEV1/FVC Day 8 (-0.75 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0017
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.41
upper limit	4.23
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	FEV1/FVC Day 8 (-0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.51
upper limit	5.09

Variability estimate	Standard error of the mean
Dispersion value	0.76

Statistical analysis title	FEV1/FVC Day 8 (0.25 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.45
upper limit	5.02
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	FEV1/FVC Day 8 (1 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.16
upper limit	6.03
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	FEV1/FVC Day 8 (2 hrs post-dose)
Comparison groups	QVA149 110/50 mcg v Matching placebo

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.56
upper limit	6.39
Variability estimate	Standard error of the mean
Dispersion value	0.83

Secondary: Lung Clearance Index by Multiple Breath Nitrogen Washout (MBNW)

End point title	Lung Clearance Index by Multiple Breath Nitrogen Washout (MBNW)

End point description:

Multiple Breath Nitrogen Washout (MBNW) was performed after 2 hours post-dose spirometry assessments using a multiple breath inert gas washout technique. The device provides the global index of ventilation inhomogeneity assessment (LCI = Cumulative Expired Volume/Functional Residual Capacity).

End point type	Secondary

End point timeframe:

Day 8 (each treatment period)

End point values	Matching placebo	QVA149 110/50 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	29		
Units: Ratio				
least squares mean (confidence interval 90%)	10.81 (10.20 to 11.41)	10.80 (10.22 to 11.37)		

Statistical analyses

Statistical analysis title	Lung Clearance Index
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.982
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.01

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.62
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.36

Secondary: Diffusing capacity of the lung for carbon monoxide (DLCO)

End point title	Diffusing capacity of the lung for carbon monoxide (DLCO)

End point description:

The diffusing capacity of the lung for carbon monoxide (DLCO) is a measure of how easily carbon monoxide (CO) molecules transfer from the alveolar gas to the hemoglobin of the red cells in the pulmonary circulation. To measure the DLCO, the patient inhales a single breath containing a minute amount of CO and holds it for 10 seconds. The breath is then exhaled and the exhaled breath is analyzed for CO. The change in the concentration of the CO is then multiplied by the single breath TLC to calculate the DLCO.

End point type	Secondary

End point timeframe:

Day 8 (each treatment period)

End point values	Matching placebo	QVA149 110/50 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	29		
Units: mL/min/mmHg				
least squares mean (confidence interval 90%)	15.73 (14.10 to 17.35)	16.38 (14.77 to 18.00)		

Statistical analyses

Statistical analysis title	Diffusion Capacity of Lung for CO
Comparison groups	QVA149 110/50 mcg v Matching placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0821
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.04
upper limit	1.27

Variability estimate	Standard error of the mean
Dispersion value	0.36

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 1 year.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events fields "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

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	QVA149 110/50 mcg

Reporting group description:

QVA149 110/50 mcg

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	QVA149 110/50 mcg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	QVA149 110/50 mcg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)	3 / 31 (9.68%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			

Pain in extremity subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 31 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2016	The primary purpose of this protocol amendment was to modify the required rescue medication to be used by patients for the entire duration of the trial. At the time of the protocol amendment, no patients were randomized. In addition, this amendment served to correct Exclusion Criteria #6 as this criterion was inadvertently combined with a separate exclusion criteria relating to patients taking prohibited medications prior to dosing. Exclusion Criteria #3 was further defined to allow for clinical judgement on COPD exacerbations and ensure consistency with the protocol. Exclusion Criteria #16, 17, and 18 were revised and aligned with Section 5 of the protocol regarding prohibited treatments. For the MRI assessments, the analysis related to collateral ventilation with regional mapping was moved from a secondary objective to an exploratory objective. Finally, this amendment served to clarify and expand upon Section 5.2 and the minimum cessation for prohibited medications.
17 February 2017	The primary purpose of this protocol amendment was to update the assessment schedule to clarify that all patients would receive HbA1c testing at screening to confirm if patients met the HbA1c exclusion criterion. In addition, this amendment clarified the definition of randomization and corrected typographical errors throughout the document.

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: