



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 standard deviation | 1.3987 ± 0.37266 | - | |
| Percent Predicted FEV1 0 Minutes Pre Inhalation Units: Percent arithmetic mean standard deviation | 43.90 ± 10.873 | - | |
| Percent Predicted FEV1 60 Minutes Post Inhalation Units: Percent arithmetic mean standard deviation | 53.10 ± 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 standard deviation | 2.7426 ± 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 standard deviation | 3.0781 ± 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 standard deviation | 42.968 ± 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 standard deviation | 46.365 ± 8.8240 | - | |
| Reversibility | | | |
| Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation | | | |
| Units: Liter arithmetic mean standard deviation | 0.2403 ± 0.12994 | - | |
| Reversibility | | | |
| Reversibility = FEV1 post-inhalation - FEV1 pre-inhalation | | | |
| Units: Percent arithmetic mean standard deviation | 9.19 ± 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 | 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. |

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 | |

| 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: