



Clinical trial results:

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results

Summary

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

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 25 July 2018 |
| First version publication date | 25 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CQVA149A2316 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02603393 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 18 July 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 July 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of QVA149 (110/50 µg o.d.) on post-dose trough forced expiratory volume in 1 second (FEV1) versus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) after 26 weeks of treatment in moderate-to-severe COPD patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 20 November 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 470 |
| From 65 to 84 years | 576 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | QVA149 |

Arm description:

110/50 µg capsules o.d. for inhalation

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

Dosage and administration details:

110/50 µg o.d.)

| | |
|------------------|-------------------------------------|
| Arm title | Tiotropium + salmeterol/fluticasone |
|------------------|-------------------------------------|

Arm description:

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

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

Dosage and administration details:

50/500 µg b.i.d

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

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | QVA149 |
|-----------------------|--------|

Reporting group description:

110/50 µg capsules o.d. for inhalation

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Tiotropium + salmeterol/fluticasone |
|-----------------------|-------------------------------------|

Reporting group description:

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

| Reporting group values | QVA149 | Tiotropium + salmeterol/fluticasone | Total |
|--|--------|-------------------------------------|-------|
| Number of subjects | 527 | 526 | 1053 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 234 | 236 | 470 |
| From 65-84 years | 288 | 288 | 576 |
| 85 years and over | 5 | 2 | 7 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 65.4 | 65.2 | |
| standard deviation | ± 7.99 | ± 7.62 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 149 | 161 | 310 |
| Male | 378 | 365 | 743 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 3 | 3 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 526 | 523 | 1049 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |

End points

End points reporting groups

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

Primary: Mean change from baseline in post-dose trough FEV1

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

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

Statistical analyses

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

Notes:

[1] - 1 sided

Secondary: Annualized rate of moderate or severe COPD exacerbations

| | |
|---|--|
| End point title | Annualized rate of moderate or severe COPD exacerbations |
| End point description: Moderate or severe COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event. | |
| End point type | Secondary |
| End point timeframe: 26 weeks | |

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

Statistical analyses

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

Notes:

[2] - 2 sided

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

| | |
|---|--|
| End point title | Annualized Rate of COPD exacerbations requiring treatment with systemic glucocorticosteroids and/or antibiotics, moderate exacerbations only |
| End point description: COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event | |
| End point type | Secondary |
| End point timeframe: 26 weeks | |

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

Statistical analyses

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

Notes:

[3] - 2-sided

Secondary: Annualized Rate of COPD exacerbations requiring hospitalisation

| | |
|------------------------|--|
| End point title | Annualized Rate of COPD exacerbations requiring hospitalisation |
| End point description: | COPD exacerbations starting between first dose and one day after last treatment are included. COPD exacerbations that occurred within 7 days of each other are collapsed as one event. |
| End point type | Secondary |
| End point timeframe: | 26 weeks |

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

Statistical analyses

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

Notes:

[4] - 2-sided

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

| | |
|---|---|
| End point title | Mean change from baseline in pre-dose trough FEV1 |
| End point description: | |
| Trough FEV1 is defined as the average of the pre-dose FEV1 measurements at -45 min and -15 min prior to dosing at each visit except Day 182 which is the average of the post-dose FEV1 measurements at 23h15min and 23h45min after dosing at Day 181. Baseline FEV1 is considered the Day 1 average of pre-dose measurements. | |
| End point type | Secondary |
| End point timeframe: | |
| 26 weeks | |

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

Statistical analyses

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

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

Notes:

[5] - 2-Sided

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

| | |
|---|---|
| End point title | Mean change from baseline in St. George's Respiratory Questionnaire |
| End point description: | |
| The St. George Respiratory Questionnaire C (SGRQ-C) is used to provide the health status measurements in this study. Baseline SGRQ-C is defined as the assessment taken right before the first dose of the double-blind drug on Day 1. Higher values correspond to greater impairment of health status. | |
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks | |

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

Statistical analyses

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

Notes:

[6] - 2-Sided

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

26 weeks

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

Statistical analyses

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

Notes:

[7] - 2-Sided

Secondary: Transition Dyspnea Index (TDI) score

| | |
|-----------------|--------------------------------------|
| End point title | Transition Dyspnea Index (TDI) score |
|-----------------|--------------------------------------|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 weeks

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

Statistical analyses

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

Secondary: Transition Dyspnea Index (TDI) score

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

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

Statistical analyses

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

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

Notes:

[8] - 2-Sided

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

| | |
|--|---|
| End point title | Change from baseline in the mean daily number of puffs of rescue medication |
| End point description: Change from baseline in mean daily number of puffs of rescue medication (number of puffs taken in the previous 12 hours) over 26 weeks of treatment. | |
| End point type | Secondary |
| End point timeframe: 26 weeks | |

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

Statistical analyses

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

Notes:

[9] - 2-Sided

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

26 weeks

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

Statistical analyses

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

Notes:

[10] - 2-Sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | QVA149 |
|-----------------------|--------|

Reporting group description:

QVA149

| | |
|-----------------------|---------------|
| Reporting group title | Tio+Salm/flut |
|-----------------------|---------------|

Reporting group description:

Tio+Salm/flut

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results |
|--|

Notes: